Source: GUIPCAR Group. In: Clinical practice guideline for the management of rheumatoid arthritis. Madrid: Spanish Society of Rheumatology; 2001. 146 p.

GUIPCAR
CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS

- Translated from the Spanish

Contents

Rheumatoid arthritis (RA) is a highly prevalent disease in Spain, and its management consumes a large amount of health and social resources. The disease often has serious repercussions on the quality of life of those affected, provoking chronic pain, limitations in the activities of daily living, and work disability. Although there is currently no cure for the disease, its symptoms can be controlled by early detection and the initiation of appropriate treatment. In recent years, however, the appearance of new drugs, new forms of combined treatment, and a plethora of studies on the efficacy of different therapeutic modalities means that the clinician is not always sure which treatment strategy to follow for a particular patient.

Faced with this explosion of new information, it is not surprising that there is large variability in the treatment of patients with RA, which cannot always be explained by characteristics of the disease. Thus, the Spanish Society of Rheumatology (SER), aware of the difficulties involved in making decisions about the management of RA, decided to develop this Clinical Practice Guideline for the Management of Rheumatoid Arthritis in Spain *(Guía de Práctica Clínica para el manejo de Artritis Reumatoide en España - GUIPCAR).* The aim of the guideline is to help clinicians make decisions about their patients. The guideline recommendations are based on the best available scientific evidence and, when this is lacking, on the work of an expert panel that developed a series of detailed recommendations on the diagnosis, management, and treatment of patients with RA. The recommendations on disease-modifying antirheumatic drugs (DMARDs) are the result of an exhaustive

review and synthesis of the published randomized clinical trials meeting strict methodological criteria for these types of studies.

Clinical practice guidelines are one of the most appropriate tools for improving the quality of care and decreasing unnecessary variability in clinical practice. Their objective is to offer systematically developed recommendations to aid the physician and patient in decision making. Although these recommendations aim to include most patients who would present to a physician, there may be particular circumstances in which they do not apply.

With this work, the SER hopes to offer the clinician a practical tool that will prove useful in daily clinical practice. We hope the information included here will be of assistance to physicians, will help improve the quality of care, and, above all, will help patients who suffer from RA. Should this be so, we will have achieved an important objective for the year 2001, designated by the Society as the "Year of Rheumatoid Arthritis."

Armando Laffón Roca
Emilio Martín Mola

PARTICIPATING INSTITUTIONS

This guideline is an initiative of the Spanish Society of Rheumatology. A number of institutions have collaborated in carrying out this initiative:

Spanish Society of Rheumatology *(Sociedad Española de Reumatología - SER).* The SER promoted the idea for this guideline, chose the research group to develop it, helped select the panel of experts, sponsored its development, and presented the project to the financing organization.

Health Services Research Unit *(Unidad de Investigación en Servicios de Salud - UISS).* When the SER decided to produce the guideline in late 1998, the Society proposed that it be developed by the UISS. At that time the UISS was a research unit within the Carlos III Health Institute (ISCIII). The UISS began to develop the guideline, but organizational changes in the ISCIII took place at the end of 2000. The UISS then became a private company with the name of TAISS, part of whose research staff came from the UISS.

Ignacio de Mercado Foundation *(Fundación Ignacio de Mercado - FIdeM)* for research and education in the health services. The FIdeM contracted project personnel who were not on the staff of the UISS.

Advanced Research Techniques in the Health Services *(Técnicas Avanzadas de Investigación en Servicios de Salud, S.L. - TAISS).* TAISS is a company devoted to producing knowledge to improve decision making in the health sector at the macro (policy) level, as well as at the meso (management) and micro (physician-patient) levels. Its research staff came from the UISS. All the investigators who participated in the project at its inception have continued to work on it.

Novartis. Novartis is the organization that financed the development of this guideline. It also oversaw each project activity and, together with the SER, monitored project tasks to ensure they were carried out in a correct and timely fashion.

Abbott. This English-language version of GUIPCAR was made possible thanks to Abbott, which provided financing for the translation.

HOW TO CITE THIS GUIDELINE

The following format is suggested for citation of this guideline:

GUIPCAR Group. Clinical Practice Guideline for the Management of Rheumatoid Arthritis in Spain. Spanish Society of Rheumatology. Madrid, 2001.

GUIPCAR GROUP

The following persons are members of the GUIPCAR Group, which authored this guideline:

1. Principal Investigator

***Pablo Lázaro y de Mercado,* Director of TAISS.** Founder and director of the Health Services Research Unit (UISS) of the Carlos III Health Institute (1993-2000). Vice-Director General of Health and Technological Evaluation of the Ministry of Health and Consumer Affairs (1997-98). University graduate in Medicine (Complutense University of Madrid, 1973). Doctor of Medicine (Autonomous University of Madrid, 1989). Specialist in Internal Medicine and in Respiratory Diseases (1977). Residency in Respiratory Diseases at the 12 de Octubre Hospital in Madrid (1974-77), and associate in Respiratory Diseases at the Ramón y Cajal Hospital in Madrid (1978-86). Master of Business Administration from the IESE (1989). Post-doctoral studies in health policy analysis at the RAND/UCLA Center for Health Policy Analysis, Santa Monica, California (USA), where he helped develop clinical practice guidelines (1990-93). His areas of expertise include research in the health services, socioeconomic evaluation, medical technology evaluation, development of clinical practice guidelines, and development of appropriateness criteria for clinical procedures.

2. Expert Panel

The experts who developed the recommendations in this guideline, listed in alphabetical order, are:

***José Luis Andréu Sánchez,* rheumatologist, Clínica Puerta de Hierro, Madrid.**
University graduate in Medicine and Surgery (Autonomous University of Madrid, 1983), specialist in Rheumatology via the MIR (Puerta de Hierro Clinic, Madrid, 1984-87) and Doctor of Medicine with special honors (Autonomous University of Madrid, 1990). Has participated in different research projects related with Immunology at the Center of Molecular Biology (Professor Martínez-Alonso) and has been a member of various expert groups (e.g., the Strategic Plan of the Spanish Society of Rheumatology and the Consensus Conference on the use of biological therapies in rheumatoid arthritis) sponsored by the Spanish Society of Rheumatology, of which he was Secretary (1998-2000). Formerly or currently serving on the editorial boards of various clinical journals such as *Annals of the Rheumatic Diseases, Revista Española de Reumatología and Revista Clínica Española.* Has published over 100 book chapters, 54 articles in national scientific journals, and 30 articles in the most prestigious international journals such as *Nature, Journal of Experimental Medicine, and Arthritis and Rheumatism.* Editor of 8 books. Has given over 40 post-graduate seminars on different subjects related with his speciality. Currently works as a rheumatologist at the Puerta de Hierro Clinic in Madrid, is honorary professor of Rheumatology at the Faculty of Medicine of the Autonomous University of Madrid and the Hospital for Rheumatic Diseases of Barcelona, and is President of the Society of Rheumatology of the Community of Madrid.

***Enrique Batlle Gualda,* rheumatologist, University Hospital General of Alicante, Alicante.** University graduate in Medicine and Surgery by the Autonomous University of Barcelona (1978), specialist in Rheumatology via the MIR (1984), Doctor of Medicine (University of Alicante, 1992), and University Specialist in Health Economics and Management of Health and Social Services (University of Alicante, 1993). Trained in epidemiology and statistics. Experienced as a teacher, evaluator, and advisor for different agencies, organizations, and research groups. Research experience in brucelar arthritis and clinical epidemiology in the evaluation of health-related quality of life, clinical methodology, and clinical trials. Currently associate in the Rheumatology Section and Secretary of the Clinical Research Ethics Committee of the General University Hospital of Alicante, and Associate Professor of the Miguel Hernández University.

***Loreto Carmona Ortells,* rheumatologist and epidemiologist, Spanish Society of Rheumatology, Madrid.**
University graduate in Medicine and Surgery (Autonomous University of Madrid, 1990) and specialist in Rheumatology via the MIR (La Princesa Hospital, Madrid, 1991-94). Carried out the project "Clinical Epidemiology and Application to the Study of Rheumatic Diseases" (FIS BAE grant 96/5485 and 97/5090) in the Arthritis Research Group (directed by Edward Yelin) and the Departments of Rheumatology and Epidemiology and Biostatistics of the University of California in San Francisco. Has worked in the Spanish Medicines Agency (grant FC1 1999- 2000) as technical evaluator for various recently developed drugs in rheumatology. Coordinator since 1998 for various epidemiological projects of the Spanish Society of Rheumatology. Currently contracted as investigator of the Health Research Fund in the Research Unit of La Princesa Hospital to develop a line of Research in Rheumatic Diseases and coordinate the installation of a Cochrane Centre in Madrid for the diffusion of Evidence-Based Medicine.

***Federico Díaz González,* rheumatologist, University Hospital of the Canary Islands, Santa Cruz de Tenerife.**
University graduate in Medicine and Surgery (La Laguna University, 1986), specialist in Rheumatology via the MIR (La Princesa Hospital, 1991), and Doctor of Medicine from the Autonomous University of Madrid (1994). Post-doctoral training under grants from the Ministry of Health and the Spanish Ministry of Education and Science at the Laboratory of Dr. Mark H. Ginsberg in the Department of Vascular Biology of the Scripps Research Institute, La Jolla, California. Has published 28 articles in Spanish and international journals, has authored 2 book chapters and has wide experience in research. Formerly, specialist in the Rheumatology Department of La Princesa Hospital of Madrid, and currently occupies the same position in the University Hospital of the Canary Islands.

***Juan José Domínguez Reboiras,* orthopedist, La Paz University Hospital, Madrid.**
University graduate in Medicine and Surgery by the Santiago de Compostela University (1968); Doctor of Medicine and Surgery from the Autonomous University of Madrid (1974); specialist in Orthopedic Surgery and Traumatology, in Physical Education and Sports Medicine and in Occupational Medicine, and Advanced Degree in the Management of Health Institutions. Tenured Professor in Anatomy and Physiology in the La Paz University School of Nursing. Formerly, Chief of the Orthopedic Surgery and Traumatology Department in the Xeral Cies Hospital of Vigo. Currently, Chief of the Shoulder and Elbow Diseases Unit in the La Paz University Hospital of Madrid.

***Ángel Elena Ibáñez,* rheumatologist, San Millán-San Pedro Hospital, Logroño.**
University graduate in Medicine and Surgery (Autonomous University of Madrid 1979), specialist in Rheumatology via the MIR (Ramón y Cajal Hospital, Madrid, 1980-1984), and Doctor in Medicine and Surgery (Autonomous University of Madrid, 1994). Area specialist of the Rheumatology Section, San Millán-San Pedro Hospital of La Rioja, since 1987. Degree in Clinical Research (Autonomous University of Madrid, 1997 and National School of Health, 1999). Formerly responsible for the Clinical-Epidemiological Research Unit of La Rioja from 1995 to 1999. Currently working

in the Rheumatology Section of the San Millán-San Pedro Hospital of La Rioja, Logroño.

***Juan Gómez-Reino Carnota,* rheumatologist, University Clinical Hospital, Santiago de Compostela.**
Residency in Medicine and Fellowship in Rheumatology at the State University of New York at Stony Brook (USA). Previously Chief of Section of Rheumatology and Director of the Research Centre of the 12 de Octubre University Hospital of Madrid. Formerly responsible for the Area of Biomedicine at the National Agency of Planning and Evaluation (ANEP) and member of evaluation committees for national and international research. Has published numerous articles in speciality journals in the area of autoimmune diseases and inflammation. Currently, Chief of the Rheumatology Department in the Santiago University Clinical Hospital.

***Agustún Gómez de la Cámara,* epidemiologist, Research Unit, 12 de Octubre Hospital, Madrid.**
Doctor in Medicine and Surgery from the Autonomous University of Madrid. Currently, Chief of the Clinical Epidemiology Unit of the Research Unit in the 12 de Octubre Hospital. His training in clinical epidemiology was received, among other centres, at the Houston Medical Center, University of Texas (USA). Has worked mainly in teaching and research in the Health Research Fund, Carlos III Health Institute, and 12 de Octubre Hospital in diagnostic, prognostic, and therapeutic research areas from the perspective of clinical epidemiology. Actively promotes the use and development of Evidence-Based Medicine and has translated its basic texts. Technical advisor to the Health Research Fund and ANEP, and member of the Spanish Medicines Agency as advisor to the Committee on Drug Safety.

***Nuria Guañabens Gay,* rheumatologist, Clinical and Provincial Hospital, Barcelona.**
University graduate in Medicine and Surgery (1978), specialist in Rheumatology (Clinical Hospital, Barcelona, 1979-1984), and Doctor of Medicine (University of Barcelona, 1987). Responsible for the Bone Metabolic Disease Team of the Agust Pi I Sunyer Biomedical Research Institute (IDIBAPS), Clinical Hospital, Barcelona. Currently, medical rheumatology adviser at the Clinical Hospital and Associate Professor of Medicine of the University of Barcelona.

***César Hernández García,* rheumatologist, San Carlos Clinical Hospital, Madrid.**
University graduate in Medicine and Surgery (Complutense University of Madrid, 1987), Doctor of Medicine (Complutense University of Madrid, 1996, special honors), and specialist in Rheumatology via the MIR (San Carlos Clinical Hospital, Madrid, 1988-91). Visiting Fellow at the Division of Arthritis and Rheumatism, Oregon Health Sciences University. FIS fellow (1992-94) at the San Carlos Clinical Hospital, Madrid, and Area Specialist in the Rheumatology Department of that hospital since 1994. Current major research area is rheumatoid arthritis, involving both clinical research and health services projects.

***Mª Victoria Irigoyen Oyarzábal,* rheumatologist, Carlos Haya General Hospital, Málaga.**
University graduate in Medicine and Surgery (University of Malaga, 1979) and specialist in Rheumatology via the MIR (Ramón y Cajal Hospital, Madrid 1981-1984). One year of specialization via the MIR in Anesthesiology (Carlos Haya Hospital, Malaga 1980). Area specialist in Rheumatology (Hospital of Navarra, Pamplona 1987-1992) and area specialist in Rheumatology (Carlos Haya Hospital, Malaga, Connective Tissue Diseases Unit, from 1992 to present).

***José Luis Marenco de la Fuente,* rheumatologist, Hospital Universitario de Valme, Sevilla.**
University graduate in Medicine and Surgery (University of Sevilla,1974-80), specialist in Rheumatology via the MIR (Puerto de Hierro Clinic, Autonomous University of Madrid, 1981-84). Doctorate *cum laude* in 1986 for the thesis "Synoviorthesis with yttrium-90 in knees. Long-term results" (directed by Professor Noguera Hernando). Responsible for the creation of the Rheumatology Section in the Hospitals of Jerez (1987-91) and Valme of Sevilla (1992) and Chief of Rheumatology Section in the latter hospital since 1994. Associate Professor of Rheumatology in the Faculty of Medicine of Sevilla.

***Víctor Manuel Martínez Taboada,* rheumatologist, Marqués de Valdecilla University Hospital, Santander.**
University graduate in Medicine and Surgery (University of Zaragoza, 1988) and specialist in Rheumatology via the MIR (Marqués de Valdecilla University Hospital, Santander, 1992). Completed clinical and research training in the Lupus Research Unit (The Rayne Institute, St. Thomas Hospital) in London (UK) and in the Rheumatology Research Unit (Mayo Clinic) of Rochester, Minnesota (USA). Doctor of Medicine from the University of Cantabria (1998). Since 1994, associate physician of the Rheumatology Department at the Marqués de Valdecilla University Hospital in Santander.

***Cristina Riera Riezu,* rehabilitation therapist, Germans Trias i Pujol Hospital of Badalona, Barcelona.**
University graduate in Medicine and Surgery (Central University of Barcelona, 1983), specialist in Physical Therapy and Rehabilitation via the MIR (Germans Trias i Pujol University Hospital, 1989), and Doctor of Medicine (Autonomous University of Barcelona, 2000). Member of the Medical Commission of the International Para-Olympics Committee and of the Catalan and Spanish Sports Federations for the Physically Handicapped. Member of the Catalan Society of Rheumatology; received first prize from the Catalan Society of Rehabilitation Therapy for her work "Rehabilitation therapy in rheumatoid arthritis: protocol for action." Has published 12 articles in national journals and 8 in international journals, in addition to 93 conference contributions. Worked as associate physician for the Department of Rehabilitation Therapy at the General Hospital of Cataluña (1990-91), and is currently associate physician for the Department of Rehabilitation Therapy at the Germans Trias i Pujol University Hospital, where she is responsible for the Rheumatological Rehabilitation Unit.

***José María Salazar Vallinas,* rheumatologist, Infanta Cristina Hospital, Badajoz.**
University graduate in Medicine and Surgery (Autonomous University of Madrid,1977), specialist in Rheumatology via the MIR (Ramón y Cajal Hospital, Madrid 1980-83), and in Family and

Community Medicine (Ministry of Education and Science, 1987). Master of Public Health (National School of Health, Madrid, 1986). Formerly, President and Founding Member of the Rheumatological Association of Extremadura and spokesperson for the Spanish Society of Rheumatology, and responsible for residency training in Family and Community Medicine and member of the Teaching Commission (1988-95) and the Clinical Chart Commission (1990-1996) of the Infanta Cristina de Badajoz University Regional Hospital. Also Associate Professor of the Health Sciences in the Department of Human Clinical Pathology, Area of Medicine/Rheumatology, of the University of Extremadura.

3. Investigators

The research team, originally from the UISS (most of whom currently work at TAISS), that was responsible for designing the study methodology, coordinating the work of the expert panel, carrying out the synthesis of the scientific evidence, and producing the final guideline document, was made up of the following persons:

Setefilla Luengo Matos (UISS). **Design of the synthesis of the evidence.**
Doctor of Medicine (Autonomous University of Madrid, 1990) and specialist in Preventive Medicine and Public Health (La Paz Hospital, 1985). Master of Public Health (National School of Health). Area Chief at the Agency for Health Technology Evaluation, Carlos III Health Institute, Madrid.

José Manuel Estrada Lorenzo **(TAISS). Bibliographic search.**
University graduate in Geography and History from the Complutense University of Madrid (1986), specializing in documentation in the Health Sciences.

Santiago Alonso Corral **(UISS). Database design.**
University graduate in Medicine and Surgery (University of Salamanca, 1987) and specialist in Preventive Medicine and Public Health (San Carlos Clinical Hospital, Madrid, 2001). Master of Public Health (National School of Health, 1997). Specialist in Health Information Systems (Complutense University of Madrid, 1994) and Master in Applied Electronics (School of Industrial Organisation, 1992).

Miguel Ángel Abad Hernández **(FIdeM). Analysis of the scientific evidence.**
University graduate in Medicine (Complutense University of Madrid, 1991) and specialist in Rheumatology via the MIR (Gregorio Marañón University General Hospital of Madrid, 1997).

Hildegarda Godoy Tundidor **(FIdeM). Analysis of the scientific evidence.**
University graduate in Medicine (Complutense University of Madrid 1994) and specialist in Rheumatology via the MIR (Gregorio Marañón University General Hospital of Madrid, 1998).

Sandra García Armesto **(UISS). Analysis of the scientific evidence.**
University graduate in Medicine (Autonomous University of Madrid) and Master of Public Health, specializing in Health Services Management and Evaluation, from the University Center of Public Health (CUSP) in Madrid.

Yesenia Tordecillas Echenique **(FIdeM). Analysis of the scientific evidence.**
University graduate in Medicine (University of Cartagena, Colombia, 1997). Has participated in various research projects in Colombian hospitals. Trained in the methodology of scientific research and the critical review of medical literature.

Yira Tordecillas Echenique **(FIdeM). Analysis of the scientific evidence.**
University graduate in Medicine (University of Cartagena, Colombia, 1996). Has participated in various research projects in Colombian hospitals. Trained in the methodology of scientific research and the critical review of medical literature.

Milena Gobbo Montoya **(TAISS). General coordinator and editor of GUIPCAR.**
University graduate in Psychology (Autonomous University of Madrid, 1984). Previous training and experience related with the practice of clinical psychology and the administration and management of hospital units.

ACKNOWLEDGEMENTS

This guideline is the fruit of collaboration among a number of institutions and persons, all of whom have helped to make it possible.

The **SER,** for its initiative in promoting the development of this guideline, monitoring activities, and providing the meeting ground for strategic discussions.

Novartis should receive special thanks, not only for its sensitivity in sponsoring the guideline, but also for not influencing its content or development except to ensure its timely completion. The investigators and panelists can thus confirm that their freedom of opinion and criteria was preserved so that this guideline is free of financing bias.

The **ISCIII** made a significant contribution to making this guideline possible, both by carrying out research activities in the UISS, and for generously allowing the use of its installations for various research meetings, including those of the panel.

TAISS, which assumed responsibility from the UISS for producing the guideline, contracted the UISS investigators to continue its development, and provided the site for various research meetings, including the last meeting of the panel.

FIdeM, for handling the contracting of non-UISS staff.

The **panelists,** who so generously dedicated their time, energy, and knowledge to producing this guideline, are responsible for developing the key parts of the guideline.

The **investigators,** who overcame difficult moments and maintained their enthusiasm throughout all phases of the project, from its initial design, to the synthesis of the evidence, and the final assemblage of the pieces that make up this guideline.

María Dolores Aguilar and Kathy Fitch, who provided suggestions in previous versions of the guideline, and Ignacio Lázaro, for his silent miracles in solving computer-related mysteries.

The librarians at the National Library of the Health Sciences and at the libraries of the *12 de Octubre* and the *Ramón y Cajal* Hospitals, who helped locate the documents necessary for the synthesis of the evidence.

SUMMARY

Rheumatoid arthritis (RA) affects some 200,000 persons in Spain, with 20,000 new cases emerging each year. RA reduces quality of life and functional capacity, produces work disability, and increases mortality. It has been estimated that the annual social cost of RA in Spain exceeds 200 billion pesetas (US$1.04 billion), of which 65 billion pesetas ($338.5 million) are devoted to health expenditures. There is evidence of large variability in the management of RA in Spain; this variability depends not only on patient or disease characteristics, but also on characteristics of the hospital, department, or physician providing patient care. These facts suggest that some diagnostic or therapeutic procedures are overused, while others may be underused.

For these reasons, in 1998 the Spanish Society of Rheumatology (SER) decided to develop a clinical practice guideline for the management of rheumatoid arthritis (GUIPCAR) to help physicians make decisions about the diagnosis and treatment of patients with RA. The objective of GUIPCAR is to develop standards of quality for the treatment of RA and to reduce the variability that does not depend on patient characteristics.

This guideline, aimed at rheumatologists, describes the diagnostic and management strategies for the evaluation and treatment of patients with RA. It focuses on RA in adults (excluding juvenile RA) and includes diagnosis, evaluation, prognosis, and treatments such as drugs, rehabilitation, and surgery. It does not cover other treatments such as acupuncture, and only briefly treats extra-articular complications of RA such as amyloidosis, anemia, or Sjögren's syndrome.

The guideline begins with a description of its origin and justification in the preface and an explanation of its objectives. The methodology followed to develop the recommendations is then described. The recommendations for treatment with disease-modifying antirheumatic drugs (DMARDs) in this guideline are based on a synthesis of the best available scientific evidence, after making a systematic review of the clinical trials and meta-analyses that have been published. A total of 2,281 articles was identified, 103 of which met the inclusion criteria for this review. The rest of the recommendations or considerations are based on scientific evidence obtained without a systematic literature review, or on the opinions of the expert panel. The experts were chosen by the SER, applying a series of criteria designed to support their validity at the national level and to avoid conflicts of interest. The guideline describes how it can be used, its contents, and its limitations.

Chapter 1 focuses on the diagnosis of RA, chapter 2 on the initial evaluation, based on which, in chapter 3, patients are classified according to the number of swollen joints and the presence of erosions. The classification is further broken down by acute phase reactants, the health assessment questionnaire (HAQ), and rheumatoid factor (RF). The recommendations on medical treatment are presented in chapter 4, the criteria for response to treatment in chapter 5, and the adverse effects of medical treatment in chapter 6. Surgical, rehabilitative, and local treatments are covered in chapter 7. Chapter 8 describes the extra-articular complications of RA. The guideline includes an appendix with instruments to facilitate the clinician's data collection for the initial classification and follow-up of patients with RA, and another appendix with the complete patient classification. To make it easier to follow the guideline recommendations, readers may wish to make use of a simplified algorithm or the other, complete algorithm. The key features of the guideline are contained in a summary version, the "rapid reference guide."

The bibliography has been divided into two sections, one listing all the references provided by the panelists or the investigators without a systematic search, and the other listing all the references used in the systematic review.

The Health Services Research Unit *(Unidad de Investigación en Servicios de Salud* - UISS) of the Carlos III Health Institute was commissioned by the SER to develop GUIPCAR. The project took 2 years to complete. During this time, the UISS became a private entity under the name of Advanced Research Techniques in the Health Services *(Técnicas Avanzadas de Investigación en Servicios de Salud* -TAISS). Novartis financed this project. The investigators established the necessary mechanisms to ensure that the guidelines would have no financing bias and that the persons involved in its development would have no conflicts of interest.

PREFACE

In 1998 the Spanish Society of Rheumatology (SER) undertook the development of a Clinical Practice Guideline (CPG) to help physicians make decisions about the diagnosis and treatment of patients with rheumatoid arthritis (RA). This initiative of the SER was in response to a phenomenon frequently seen in clinical practice: the large variability in the use of diagnostic, therapeutic, and rehabilitative procedures. RA is a disease with a relatively high prevalence, affecting from 0.2 to 0.8% of the population in Spain. The different specialties and levels of care involved in its treatment are not always well coordinated. Furthermore, recent years have seen rapid innovation in medical treatment, with the appearance of new drugs, new forms of combined treatment, and numerous studies on the effects of the drugs utilized. The large amount of information produced as a result of the ever-growing growing number of studies, their variable methodological quality, and the complexity of comparing the results of different studies constitutes a major obstacle for clinicians in keeping up to date on important knowledge in their field. Thus came about the project to produce a CPG for the management of RA (GUIPCAR), which was undertaken by the Health Services Research Unit (UISS) of the Carlos III Health Institute. This project took 2 years to complete. During this time, the UISS became a private company with the name of Advanced Research Techniques in the Health Services (TAISS).

CPGs should be based on scientific evidence, but when such evidence is absent or contradictory, they may be complemented by unbiased techniques of handling expert opinion. This guideline uses both methods, and is based on three central tasks: 1) a synthesis of the evidence on the efficacy of disease-modifying antirheumatic drugs (DMARDs); 2) specific recommendations on the diagnosis, evaluation, and treatment of patients with RA made by a panel of experts, generally rheumatologists with scientific prestige proposed by the SER, following a methodology designed to produce CPG recommendations; and 3) assignment of the level of scientific evidence that supports each recommendation for treatment with DMARDs.

The ultimate objective of this guideline is to aid clinical decision making by offering recommendations for the therapeutic management of RA that are based on the best available evidence. We have tried to present the recommendations in a clear and agreeable manner, so that it is easy to find the information sought. We hope it will prove useful to those who face the difficult task of making decisions about different courses of treatment and that, in the final analysis, it will result in better outcomes for patients with RA.

BACKGROUND

RA is a systemic disease of unknown etiology, which is characterized by chronic inflammation of the diarthrodial joints. It is frequently associated with severe morbidity, functional abnormalities involving work disability, reduced quality of life, and increased mortality. RA affects all populations, with an estimated prevalence of about 0.8% and an incidence of approximately 0.5/1,000 population per year [Silman, 1993]. In Spain, RA affects about 5 of every 1,000 adults [Villaverde, 2000] and causes 5% of all permanent work disability [Tornero, 1998].

The economic impact of this disease is reflected in direct costs (physician visits, diagnostic tests, drugs, hospitalization) and indirect costs (loss of income due to work disability). In one health district of Madrid it has been estimated that the mean annual cost of a patient with RA is 1.11 million pesetas (about US $5,700) Some 70% of these costs are direct costs — 32% for patient care and 38% not for patient care — and 30% are indirect costs, that is, lost hours of work. If these results are extrapolated to the whole Spanish population, based on the estimated prevalence of RA in this country, the annual social costs of this disease would reach more than 200 billion pesetas ($1.04 billion), of which 65 billion ($338.5 million) would be for health costs.

As with most diseases, there is enormous variability in the management of RA — among countries, among institutions, among physicians, and even within the same physician — and in the use of diagnostic procedures, follow-up methods, and therapeutic and rehabilitative measures. At times it may be thought that health resources are used inappropriately, or that a variety of different recommendations are followed due to the large amount of information about the disease that appears in different publications or other channels of communication. Sometimes modifications in disease management are introduced even though they do not have a clear advantage over existing strategies, while at other times effective strategies may be ignored. Health professionals caring for RA patients are faced not only with a disease whose etiology, management, and diagnosis are complicated, but also with an enormous amount of information that is not always easy to interpret.

CPGs are one of the most appropriate instruments to decrease unnecessary variability and improve clinical practice. A CPG is defined as a set of "systematically defined statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." A good CPG should have the attributes of validity, reliability, reproducibility, clinical applicability, flexibility, clarity, multidisciplinarity, and periodic review [IOM, 1990a; IOM, 1992]. CPGs are part of a cultural change which consists of moving from unsubstantiated confidence in the opinions of professionals to a more structured and well-founded support for clinical decisions.

The US Institute of Medicine (IOM) has suggested various criteria for selecting the contents of a CPG: first, the guideline should be applied to a clinical condition for which there is the potential to improve health for a significant number of persons; second, it should reduce clinically significant variations in services and procedures; third, it should reduce clinically significant variations in the outcomes of health care; and fourth, policies for guideline development should reflect the needs and priorities of the health system. Following these criteria, the SER considers that RA is a clinical condition that would benefit from the development of a CPG.

GUIDELINE OBJECTIVES

The objectives of this guideline are to improve the quality of care, to reduce variability in the management of RA, to move toward the integral management of RA, and to align clinical practice more closely with the best available scientific evidence.

Improving the Quality of Care

The quality of care can be seen, defined, and measured in many ways [Donabedian, 1980; OTA, 1988; Lohr, 1990; Rubenstein, 1990; Chassin, 1991; Brook, 1991; Keeler, 1992; Kassirer, 1993; Burstin, 1993; Gates, 1993; Miller, 1993; Hayward, 1993]. The IOM defines it as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" [IOM, 1990b]. According to the characteristics implicit in this definition, *quality* refers both to the physician-patient (individual) level and to the social (population) level; it can be measured in probabilistic terms (quantification of uncertainty); and it is based on scientific knowledge. Donabedian, who conceives quality of care as based on three dimensions (structure, process, and result), emphasizes the degree to which technology is used well in different centers or places [Donabedian, 1988].

Evaluating the quality of care is a critical component of the correct functioning of health systems. Quality of care can be evaluated and can dramatically improve medical practice [Brook, 1990]. It is rarely evaluated, however, even though sufficient methodological instruments are available.

Measuring outcomes is critically important in evaluating the quality of care. Two classic measures of the outcomes of clinical practice are efficacy and effectiveness. *Efficacy* refers to the patient outcome produced under ideal conditions (e.g., in a clinical trial), while *effectiveness* is the outcome produced under real conditions (e.g., in daily practice). The difference between efficacy and effectiveness can be produced by random error, by systematic error or bias (for example, the inventors of a drug or technology, consciously or subconsciously, may make it appear better than it really is), by variability in the quality of care, or by personal health characteristics that may or may not be controlled by the individual [Brook, 1990]. For this reason, the degree to which effectiveness (the effect achieved) approximates efficacy (the maximum achievable effect) can be considered as an indicator of the quality of care. This guideline will deal with both concepts.

Implementing quality measures involves constructive actions to establish a relation between the process of care and patient outcomes [Brook, 1990]. For example, statistically significant and clinically important differences have been shown in clinical outcomes depending on whether procedures are applied with a good or poor process of care [Kahn, 1990]. The evidence showing that improving the process of care leads to better outcomes and that CPGs are one of the instruments designed to improve the process of care is one of the reasons behind the development of this guideline.

Reducing Variability in the Management of Rheumatoid Arthritis

There is evidence that decisions made in identical clinical situations may differ depending on individual, institutional, or geographic factors that are unrelated with patient characteristics [IOM, 1990a; IOM, 1992]. This does not mean that variability in clinical practice is unacceptable. It may be acceptable when there is uncertainty about the advantages of one technique over another, when patient characteristics or preferences are different, when the characteristics of the center or its resources are different, or because of changing science or social and individual values. Such variability is not acceptable, however, when it is due to inadequate medical skill, poor institutional organization, ignorance, or the deliberate decision not to use procedures for which there is proven evidence of their superiority. Unacceptable clinical practice does not benefit patients; it may harm them, and it consumes resources unnecessarily.

In Spain there is large inter- and intra-hospital variability in the use of health resources, diagnostic procedures, and therapeutic procedures in patients with RA. For example, in one comparison among centers, the mean number of visits per person over a 2-year period ranged from a low of 5.1 (range 1-11) to a high of 10.2 (range 2-31). These differences remained after adjusting for disease severity and functional class, according to the preliminary results of the "Study of RA Management" (emAR). In the same study, the percentage of patients who underwent some orthopedic surgical procedure during the course of their disease ranged from 0 to 71%, depending on the center. Even though most patients were being treated with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and DMARDs, the use of specific drugs varied significantly, independently of the patient's clinical situation. That is, the variability observed cannot be explained solely by differences related with the disease itself, but is also associated with variables related with the hospital center, department, or physician responsible for the patient. This variability in RA management that cannot be explained by patient characteristics justifies the development of standards of quality for the treatment of RA.

Moving Toward Integral Management of Rheumatoid Arthritis

At any given time, a variety of specialists may collaborate in managing specific disease aspects, from diagnosis to treatment to follow-up. Primary care physicians, rheumatologists, radiologists,

ophthalmologists, orthopedic surgeons, rehabilitation specialists, orthopedists, psychologists or psychiatrists, and even other, non-medical health personnel, should be aware of the need to unify criteria and to integrate care in accordance with the best available scientific evidence. One way to avoid RA patients' receiving contradictory messages from different specialists is the development of CPGs that are easy to understand, and with a strong enough scientific basis to earn the support of all specialists who help manage patients with this disease.

Aligning Clinical Practice with the Best Available Scientific Evidence

Clinical practice in RA treatment has varied considerably in recent years, despite the fact that therapeutic resources have remained almost constant. There is growing use of early and aggressive treatment, which is supported by evidence that such measures may delay disease progression.

The controlled clinical trials showing the short-term efficacy of a treatment intervention in selected populations initially led to disparate treatment practices and options, which have not subsequently been supported by studies of effectiveness in persons with RA. For example, in clinical trials of short-term efficacy, the efficacy of all the available DMARDs is higher than that of placebo (PCB). In comparative studies of a similar duration, it is difficult to find evidence that one DMARD is better than others. In studies evaluating compliance with long-term treatment, the number of patients who continue taking a specific DMARD after 5 years is significantly higher for methotrexate. This type of evidence has led to the generalized use of methotrexate as the drug of choice in most centers that care for these patients.

There is insufficient scientific to support certain clinical decisions, however, and not all the scientific evidence is within easy reach of clinicians. Furthermore, the evidence available is of varying methodological quality, thus its scientific validity may be more or less solid. The use of more highly developed instruments to analyze information may facilitate changes in clinical practice as important as that of early intervention, based on the best available scientific evidence. Thus, this guideline is an attempt to base the process of care on the best available scientific evidence and, where this does not exist or is contradictory, applies the collective judgments of an expert panel selected according to specific criteria and using a scientific methodology developed to avoid biases.

METHODOLOGY

1. Synthesis of the Evidence

1.1 Objective

The synthesis of the evidence in the development of CPGs has three objectives: 1) to base the recommendations on the best available scientific evidence; 2) to allow users to obtain the information on which the recommendations are based; and 3) to make it possible to evaluate the quality of the guideline.

One problem in carrying out a synthesis of the evidence is that the amount of information may be so extensive as to be impossible to cover. There are more than 35,000 medical journals in the world, which publish over 3 million articles every year. In addition, these journals are published in many different languages, the designs of the studies may be very heterogeneous, the methodological quality is highly variable, the patients selected may be very different, the measure of results may refer to different outcomes, and different subjects may be treated for the same intervention (e.g., whereas one study focuses on clinical outcomes, others may focus on complications, utilization, physiopathological mechanisms, or costs). This makes it necessary to limit the search for scientific evidence. Limiting such searches is justified not only by real limitations on resources and time, but also because a search aimed specifically at key aspects of disease management may constitute one of the strengths of a CPG. This naturally depends on achieving an intelligent balance among the topics searched, the quality of the review process, and the available resources. Thus, once the large number of RA publications had been explored, it was agreed that, for this guideline, the synthesis of the evidence would focus on the efficacy of DMARDs.

1.2 Drugs included in the synthesis of the evidence

After making an initial estimate of the volume of literature to be reviewed, the project investigators and the members of the expert panel agreed to focus the synthesis of the evidence on studies evaluating the efficacy of treatment with DMARDs (clinical trials) by means of a systematic review. Table 1 shows the DMARDs included in the review.

Table 1. Disease modifying antirheumatic drugs included in the systematic literature review

- Antimalarials: Chloroquine (CLQ) and Hydroxychloroquine (HCQ)
- Azathioprine (AZA)
- Cyclophosphamide (CPA)
- Cyclosporin A (CSA)
- D-penicillamine (DP)
- Anti-tumor necrosis factor (anti-TNF) agents: infliximab (IFM) and etanercept (ETN)

- Leflunomide (LEF)
- Methotrexate (MTX)
- Gold salts: Oral gold (OG) and injectable gold (IG)
- Sulphasalazine (SSZ)

1.3 Search strategy for identifying the scientific evidence

The literature search for the synthesis of the evidence on the efficacy of DMARDs in RA was made in four databases, for the time periods noted below:

- MEDLINE: 1966-2000
- EMBASE (Drugs and Pharmacology section): 1984-2000
- Spanish Medical Index (*Indice Médico Español* - IME): 1971-2000
- Cochrane Library: year 2000 version.

The articles for the bibliographic search had to meet the following inclusion criteria: 1) controlled clinical trial, meta-analysis, or systematic review; 2) study referring to one or more of the selected DMARDs; 3a) comparison of the efficacy of a drug or combined therapy vs. another drug or combined therapy including at least one of the drugs listed in Table 1, or comparison of LEF or TNF with placebo; 3b) if a systematic review or meta-analysis, comparison of a drug or combined therapy vs. another drug or combined therapy including at least one of the drugs listed in table 1, or with placebo; 4) study carried out in patients with RA; 5) trial carried out in humans; and 6) published in English or Spanish.

The descriptors used were those specified in each database with regard to the research methodology (e.g., RANDOMIZED-CONTROLLED-TRIAL), rheumatoid arthritis (e.g., RHEUMATOID ARTHRITIS), and specific drugs (e.g., METHOTREXATE).

1.4 Selection of articles

We first identified all existing systematic reviews on DMARDs. Nine systematic reviews were located in the Cochrane Library that compared placebo with the following drugs: methotrexate, sulphasalazine, cyclosporin, oral gold salts, injectable gold salts, cyclophosphamide, d-penicillamine, azathioprine, and anti-malarials.

Using the search strategy described, we then located 982 bibliographic records in MEDLINE, 968 in EMBASE, 268 in the Cochrane Library, and 63 in IME, for a total of 2,281 records; of these, 666 were found in more than one database. Thus, the final number of records selected was 1,615.

All the bibliographic records selected were read independently by two reviewers (a rheumatologist and a physician with training in epidemiology), both of whom had received training in how to carry out a synthesis of the evidence. The objective of reading the title of the bibliographic record was to verify that the article met the inclusion criteria.

A 4-phase strategy was used to screen the records:

1. **Review of the title.** Resulting in the following two possibilities:
    a. The record was rejected because it did not meet the inclusion criteria.
    b. The record was accepted either because it met the criteria described or because it was not possible to decide whether or not it met the inclusion criteria based on the data provided.

Of the 1,615 records selected, 289 were rejected during the first phase; thus, 1,326 bibliographic records went on to the second phase.

2. **Review of the abstract.** In those cases in which the record passed the first phase and had an abstract, the abstract was read, which led to two options:
    a. It was rejected because it did not meet the inclusion criteria.
    b. It was accepted, either because it met the criteria described or because it was not possible to decide whether or not it met the inclusion criteria based on the data provided.

All the articles passing the first phase that did not have an abstract passed directly to the third stage.

Of the 1,326 articles that passed to the second phase, 1,225 had an abstract and 101 did not. After reading the abstract, 1,039 were eliminated and 186 were accepted and passed to the third phase, together with the 101 records with no abstract. That is, 287 articles passed to the "request for articles" stage.

In the first two stages of screening the records, each rheumatologist-methodologist team compared the records read and, in case of discrepancy, the two reviewers discussed the article. If no agreement was reached, the record was read by another pair of reviewers. Discrepancies between reviewers occurred in 4% of records, and agreement was reached in 100% of cases.

3. **Request for articles.** In this phase the articles that had not been rejected after phases 1 and 2 were requested. The requests were directed first to the National Library of the Health Sciences (*Biblioteca Nacional de Ciencias de la Salud* - BNCS) of the ISCIII, to which the UISS also belonged. If the article was not in the BNCS, it was requested from the library of a Madrid hospital, generally the *12 de Octubre* Hospital or the *Ramón y Cajal* Hospital. If the article could not be found in any Madrid library, the Loan Service of the BNCS requested it through a biomedical library within Spain, and if it could not be found in any Spanish library of the health sciences, it was requested from the British Library or from the Netherlands Institute for Scientific Information Services *(Nederlands Instituut voor Wetenschappelijke Informatiediensten* - NIWI).
4. **Data collection and evaluation of the quality of the evidence.** The relevant information for each article was collected using a form designed with four objectives in mind: 1) to identify the bibliographic information included in the review; 2) to verify that the article, in its complete text, met the inclusion criteria for the review; 3) to collect the relevant clinical information for each article accepted; and 4) to evaluate the methodological quality and the level of evidence of the trials.

Objective 1: To identify the bibliographic information for each article included in the review. General information was obtained on the relevant bibliographic data of the article (e.g., first author, year of publication, journal). Each article was coded to facilitate its location in the database.

Objective 2: To verify that the article, in its complete text, met the inclusion criteria for the review. This verification process resulted in four possibilities:

1. All inclusion criteria were met, in which case the article was *included.*
2. At least one of the inclusion criteria was not met, in which case it was *excluded.*
3. The inclusion criteria were met, but the article was *redundant.* Articles were considered to be redundant if they were published on successive occasions, generally in a different journal from the first publication, but referred to the same clinical trial and did not provide additional information in comparison to the first publication. In this case, one of the publications was selected to complete the form with the study data, and the redundant one was excluded.
4. The inclusion criteria were met but the article was a *complement* to a previous one. Articles were considered to be complementary if, in comparison with another previous publication of the same trial, they included different outcome measures or, if they included the same outcome measures, these were collected for a different period of time (e.g., clinical variables in one journal and radiographic variables in another; or radiographic variables up to 6 months in one journal and up to 3 years in another). In these cases, the results of both publications were combined; the complete information from one of the articles was used to fill out the form, adding the new and complementary information provided by the other article on the same form.

Redundant or complementary articles were identified *a posteriori* after reading the articles, by verifying that the study was written by the same authors, used the same guidelines for the treatments compared, and used the same study design.

Objective 3: To collect the relevant clinical information from each article accepted. If the article met the inclusion criteria, data were collected on the number and characteristics of the participants (gender, age, mean time of disease progression, previous use of NSAIDs and DMARDs), interventions, outcome measures evaluated, persons lost to follow-up and withdrawals from the study, reliability of the measurement instruments used, follow-up of the groups, and statistical analysis.

Objective 4: To assess the methodological quality and level of evidence of the trials. The methodological quality of the trials was assessed using the Jadad scale for rating the quality of clinical trials (Table 2) [Jadad, 1996a]. The level of evidence was assessed in accordance with the Hadorn scale designed to evaluate the quality of the evidence of publications used to develop CPGs (Table 3) [Hadorn, 1996].

Table 2. Jadad scale for rating the quality of evidence from clinical trials

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To rate the quality of a clinical trial, three questions are posed:

1. Was the study described as randomized?
2. Was the study described as double blind?
3. Was there a description of withdrawals and drop outs?

One point is given for each "yes" and 0 points for each "no". There are no intermediate scores.

An additional point is given in question 1 if the randomization method is described and is appropriate, and an additional point is given in question 2 if the method for making the study double blind is described and is appropriate.

One point is subtracted in question 1 if the randomization method is described but is inappropriate, and one point is subtracted in question 2 if the study is described as double blind, but the blinding method is inappropriate.

An article can receive a score of 0 to 5 points. An article is considered to be of good quality if the score is 3 or higher, and of poor quality if the score is less than 3.

Table 3. Hadorn scale for rating the quality of scientific evidence from articles for CPGs

	Level of evidence
1. Well-conducted multicenter randomized controlled trials including 100 or more patients	**A**
2. Well-conducted randomized controlled trials with fewer than 100 patients, in one or more institutions	
3. Well-conducted cohort studies	
4. Well-conducted case-control studies	**B**
5. Poorly controlled or uncontrolled studies	
6. Conflicting evidence in favor of the recommendation	
7. Expert opinion	**C**

Levels 1, 2, and 3 refer to a high level of evidence (A); levels 4, 5, and 6 refer to a level of evidence with potential biases that could invalidate the results (B); and level 7 is the evidence most vulnerable to potential biases (C).

Since only clinical trials were evaluated in the synthesis of the evidence for this guideline, the levels of evidence assigned are A1 (1 on the Hadorn scale), A2 (2 on the Hadorn scale), and B (5 on the Hadorn scale).

Data collection form. A form was designed to collect the bibliographic data for each article, information about the study methodology, clinical data, the quality of the methodology, and the level of evidence. The first version of the form was evaluated by three reviewers (two rheumatologists and one methodologist) who applied it to 10 articles. After introducing the appropriate modifications, the reviewers began to use the form. It was necessary to change the form for later articles, however, in order to adapt it to the peculiarities of each trial (for example, the number of interventions compared, outcomes measured, and so on) and to be able to create homogeneous and unbiased evidence tables. After 13 successive versions, the definitive form was obtained, which was sufficiently valid to permit inclusion and categorization of the relevant information from each article. This form is available to interested readers (milena@taiss.com).

Evaluation of the articles. Five reviewers read and evaluated the articles: two specialists in rheumatology and three in research methodology. All had been trained in techniques for the critical review of the scientific literature. Each article was read independently by two reviewers, one physician with training in epidemiology and one rheumatologist. Each reviewer completed one form for each article. Each epidemiologist-rheumatologist team then compared the individual forms and, if they agreed, completed the final form. The two reviewers discussed any discrepancies in an attempt to reach consensus. If they did not agree, the article was read and discussed by all the reviewers until agreement was reached, at which point the final form was completed.

Each form made up one record in the database designed for the synthesis of the evidence. The form describes a comparison between two different treatment interventions. This means that a trial assessing more than two treatment interventions, making different comparisons among them, would give rise to more than one form. Thus, the number of forms is larger than the number of clinical trials included in the synthesis of the evidence.

Of the 287 articles requested, 162 did not meet at least one of the inclusion criteria, 13 were redundant and 9 were articles comparing drugs with placebo that had already been included in the systematic reviews of the Cochrane Library. Consequently, a total of 103 articles was included in the review, 91 of which were different clinical trials (12 were complementary articles), allowing 140 comparisons between different treatment strategies (single drugs or combinations thereof). Thus, there are 140 records in the database for the efficacy of DMARDs (see Table 4).

(Table 4 of the GUIPCAR CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS guideline is available in the original guideline document.)

These 91 trials and the 140 resulting comparisons are grouped by the Jadad and Hadorn scales for classifying the quality of the evidence as shown in Tables 5 and 6, respectively.

Table 5. Clinical trials and comparisons by the Jadad scale for rating the quality of the evidence

LEVEL OF EVIDENCE (Jadad Scale)	CLINICAL TRIALS	COMPARISONS
1	7 (8%)	7 (5%)
2	19 (21%)	24 (17%)
3	18 (20%)	31 (22%)
4	32 (35%)	53 (38%)
5	15 (16%)	25 (18%)
TOTAL	91 (100%)	140 (100%)

Table 6. Clinical trials and comparisons by the Hadorn scale for rating the quality of the evidence

LEVEL OF EVIDENCE (Hadorn Scale)	CLINICAL TRIALS	COMPARISONS
A1	13 (14%)	25 (18%)
A2	13 (14%)	20 (14%)
B	65 (72%)	95 (68%)
TOTAL	91 (100%)	140 (100%)

Thirty-eight of the 140 comparisons assessed a DMARD vs. certain drugs not included in the systematic review (e.g., collagen II, tiopronin, or pyrithinol). These 38 comparisons were excluded because the expert panel believed they were not relevant. Thus, the final 102 comparisons refer only to the DMARDs listed in Table 1.

For the purposes of the synthesis of the evidence, the comparisons were grouped by drug to make it easier to find the clinical trials comparing a specific drug (alone or in combination) with any of the other drugs in table 1 (also alone or in combination).

For each possible comparison we identified the number of existing studies, their level of evidence, and the intervention favored by the outcome measures collected in each study. (The tables synthesizing the outcome measures collected in each study for the comparisons are available to interested readers by contacting milena@taiss.com).

The panel was consulted when a) different studies comparing the same drugs included different outcome measures, some (e.g., clinical effect) in favor of one treatment intervention and others (e.g., radiographic results) in favor of the other intervention; and b) to assess the clinical relevance of some outcome measures with statistically significant differences when the differences were not significant for many other outcomes. In these divergent cases, greater weight was given to outcome measures in agreement with the American College of Rheumatology (ACR) criteria, especially

the number of swollen joints and radiographic damage. For example, a study with A2 level evidence comparing chloroquine with oral gold salts shows significant differences in favor of chloroquine with regard to strength of grip and morning stiffness; however, functional status is significantly better in the group with oral salts, and no significant differences are found between the two groups with regard to the number of swollen joints, pain, or acute phase reactants. In this case it was concluded that there were no important clinical differences in the efficacy of chloroquine and oral gold salts.

Evidence tables

The results of the synthesis of the evidence are shown in Tables 7 and 8. Table 7 includes the comparisons of DMARDs used in monotherapy. Table 8 includes the comparisons of single or combined drugs vs. combinations of drugs.

For those comparisons for which evidence exists, there are three lines in the corresponding box with the following data:

Line 1. Number of studies and level of evidence of these studies (e.g., "3-A1; 2-B" means there are three studies with an A1 level of evidence and two with level B).

Line 2. The identification numbers for these articles (used as the bibliographic reference). Numbers separated by a dash (e.g., 7-9) mean that all articles in the interval are included (7, 8, and 9). Numbers separated by a comma (e.g., 7, 9) represent references only to those specific articles (7 and 9).

Line 3. One of the following possibilities is shown in bold print:
- The drug or combination of drugs (COMB) which the evidence favors (using the abbreviations shown in table 1.)
- NS: if the differences are not significant.

Table 7. Comparisons of DMARDs used only in monotherapy

	PCB	AUR	AZA	CPA	CLQ	CSA	DP	ETN	HCQ	IFM	LEF	MTX	IG
CPA			1-B 1 **CPA**										
CLQ		1-A2 2 **NS**	1-B 3 **NS**										
CSA			1-B 4 **NS**		1-A2 5 **NS**								
DP		1-B 6 **DP**	3-B 7-9 **NS**		1-B 10 **NS**	1-A2 11 **NS**							
ETN	2A1;1B 12-14 **ETN**							2-A1 15,72 **NS**					
HCQ		1-B 16 **NS**					2-B 17-18 **NS**						

IFM	2-A2 19,20 **IFM**									1-A2 21 **DOSE=10***			
LEF	2-A1;3-B 22-26 **LEF**												
MTX		1-A1;1-B 27, 28 **MTX**	2-A2;2-B 29-32 **MTX**			1-B 33 **NS**		2-A1 72 **NS**		3-B 34-36 **NS**	1-A1;2-B 37-39 **NS**		
IG		1-A1;1-A2; 8-B 40-49 **NS**	2-B 50,51 **AZA**	1-B 52 **CPA**	1-B 53 **NS**	1-A2 54 **NS**	3-B 55-57 **NS**					1-A2;4-B 58-62 **NS**	
SSZ		1-B 63 **NS**					2-B 64, 65 **NS**		2-A2 66, 67 **SSZ**		1-A1 68 **NS**	1-A1;1-A2 69, 70 **NS**	1-B 71 **NS**

* Compares doses of 1 mg/kg vs. 10 mg/kg

Table 8. Comparisons of single or combined DMARDs vs. drug combinations

	AUR+MTX	**AZA+MTX**	**CLQ+DP**	**MTX+CLQ**	**CSA+IG**	**CSA+MTX**	**HCQ+DP**	**MTX+ETN**	**HCQ+IG**	**SSZ+HCQ**	**HCQ+MTX**	**MTX+SSZ+HCQ**	**IFM+MTX**	**MTX+SSZ**
AUR	1-B 73 **NS**													
AZA		1-B 74 **COMB**												
CPA														
CLQ			1-B 75 **NS**											
CSA														
DP			1-B 76 **NS**				1-B 77 **NS**							
ETN														

HCQ							1-B 78 **NS**			1-A2 79 **COMB**	1-B 80 **COMB**			
IFM														
LEF														
MTX	1-B 81 **NS**	1-B 82 **COMB**		1-A2 83 **COMB**		1-A1 84 **COMB**		1-B 85 **COMB**				1-A2 86 **COMB**	7-B 87-93 **COMB**	1-A1:1-A2 94,95 **NS**
IG					1-B 96 **NS**				1-A1;1-B 97,98 **NS**					
SSZ										1-A2 99 **NS**				1-A1:1-A2 100, 101 **NS**
SSZ+HCQ												1-A2 102 **COMB. TRIP.**		

Tables 9a and 9b show the mean time of disease progression, previous use of DMARDs (if the box is blank, this data was not included in the article), duration of treatment in the trial (if the box is blank, this data was not included in the article), the level of evidence, the bibliographic reference for each comparison (cited in references 2.2, 2.3, and 2.4), and the identification number for each article (used to locate it in Tables 7 and 8).

Table 9a. Mean time of RA progression, previous DMARD use, duration of treatment in the trial, level of evidence, bibliographic reference, and ID number in the comparisons of DMARDs used in monotherapy included in the synthesis of the evidence

DMARDs compared (used in monotherapy)		Mean time of RA progression (in months)	Previous DMARD use	Duration of treatment (in weeks)	Level of evidence	Bibliographic reference	ID N°
Azathioprine	Cyclophosphamide	60		72	B	1, R1	1
Oral gold salts	Chloroquine	39.4		24	A2	2	2
Azathioprine	Chloroquine	23		24	B	3	3
Cyclosporin	Azathioprine	79.2	YES	26	B	4	4
Cyclosporin	Chloroquine	78	NO	24	A2	5	5
Oral gold salts	D-penicillamine	83	YES	52	B	6	6
		113.4		52	B	7, R2	7

Azathioprine	D-penicillamine	134	YES	24	B	8	8
		132	YES	96	B	9	9
D-penicillamine	Chloroquine	30	YES	48	B	10	10
Cyclosporin	D-penicillamine	86.4	YES	24	A2	11	11
Etanercept	Placebo	150	YES	26	A1	12	12
		138	YES	26	A1	12	13
			YES	12	B	13	14
Etanercept	Etanercept	144	YES	26	A1	12	15
Oral gold salts	Hydroxychloroquine	124.5		48	B	14	16
Hydroxychloroquine	D-penicillamine	71.4	YES	96	B	15	17
			NO	96	B	16	18
Infliximab	Placebo	99	YES	4	A2	17	19
		97.8	YES	4	A2	17	20
Infliximab	Infliximab	88.8	YES	4	A2	17	21
Leflunomide	Placebo	79.8	YES	24	A1	18	22
		83.4	YES	52	A1	19, R3	23
		96	YES	24	B	20	24
		100.8	YES	24	B	20	25
		102.6	YES	24	B	20	26
Methotrexate	Oral gold salts	70.3	YES	36	A1	21, C1	27
		59.5	NO	48	B	22, C2	28
Methotrexate	Azathioprine	104.4	YES	24	A2	23	29
		133.2	YES	24	A2	24, R4, R5	30
		96	YES	48	B	25, R6, R7	31
		156	YES	24	B	26	32
Cyclosporin	Methotrexate	25.8	NO	96	B	27	33
Infliximab	Methotrexate	91.2	YES	26	B	28	34
		92.4	YES	26	B	28	35
		103.8	YES	26	B	28	36
		81	YES	52	A1	19	37

Leflunomide	Methotrexate	45	YES	52	B	29	38
		43.8	YES	104	B	29	39
Oral gold salts	Injectable gold	76		21	A1	30, C3, R8, R9	40
		115.8	YES	96	B	31	41
		83.4		48	B	32	42
		61.8	YES	96	B	33, C4	43
		144	YES	48	A2	34	44
		63.6	NO	48	B	35	45
		109.2	NO	24	B	36	46
		45.6	YES	52	B	37, C5	47
		63		48	B	38	48
		24		48	B	39, C6, R10	49
Azathioprine	Injectable gold	60		72	B	1	50
		25		24	B	3	51
Cyclophosphamide	Injectable gold	48		72	B	1	52
Injectable gold	Chloroquine	20		24	B	3	53
Cyclosporin	Injectable gold	11.76	YES	72	B	40	54
Injectable gold	D-penicillamine	66		24	B	41, R11	55
		14.8		48	B	42	56
				21	B	43	57
Injectable gold	Methotrexate		NO	26	B	44	58
		14		48	B	45	59
		17.5	YES	24	B	46	60
		23.9	YES	144	B	47, C7, C8	61
		68.4	YES	26	A2	48	62
Sulphasalazine	Oral gold salts	114	YES	240	B	49, C9	63
Sulphasalazine	D-penicillamine	84		576	B	50, C10	64
		105		48	B	51	65
Hydroxychloroquine	Sulphasalazine	12.8	NO	48	A2	52, C11, C12, R12	66
		75.6	YES	24	A2	53	67

Leflunomide	Sulphasalazine	90	YES	24	A1	18	68
Sulphasalazine	Methotrexate	3.05	NO	52	A2	54	69
		14.6	NO	52	A1	55	70
Injectable gold	Sulphasalazine	68	NO	48	B	56	71
Etanercept	Methotrexate	11.5	YES	48	A1	57	72

Table 9b. Mean time of RA progression, previous DMARD use, duration of treatment in the trial, level of evidence, bibliographic referenc,e and ID number in the comparisons of DMARDs used in monotherapy or combined therapy vs. drug combinations included in the synthesis of the evidence

DMARDs compared (used in monotherapy or combined therapy vs. drug combinations)		Mean time of RA progression (in months)	Previous DMARD use	Duration of treatment (in weeks)	Level of evidence	Bibliographic reference	ID N°
Oral gold salts	Methotrexate Oral gold salts	64.5	NO	48	B	22	73
Azathioprine	Methotrexate Azathioprine	96	YES	48	B	25, R6, R7	74
Chloroquine	Chloroquine D-penicillamine	24	YES	48	B	10	75
D-penicillamine	Chloroquine D-penicillamine	18	YES	48	B	10	76
D-penicillamine	Hydroxychloroquine D-penicillamine	72.6	YES	96	B	15	77
Hydroxychloroquine	Hydroxychloroquine D-penicillamine	70.8	YES	96	B	15	78
Hydroxychloroquine	Sulphasalazine Hydroxychloroquine	75.6	YES	24	A2	53	79
Hydroxychloroquine	Hydroxychloroquine Methotrexate			24	B	58	80
Methotrexate	Methotrexate Oral gold salts	69	NO	48	B	22	81
Methotrexate	Methotrexate Azathioprine	96	YES	48	B	25	82
Methotrexate	Methotrexate Chloroquine	92.58		24	A2	59	83
Methotrexate	Methotrexate Cyclosporin	122.4	YES	24	A1	60	84

Methotrexate	Methotrexate Etanercept	156	YES	24	B	61	85
Methotrexate	Methotrexate Sulphasalazine Hydroxychloroquine	120	YES	96	A2	62	86
Methotrexate	Infliximab Methotrexate	103.8	YES	54	B	63, R13	87
		96.6	YES	54	B	63, R13	88
		107.4	YES	54	B	63, R13	89
		105.6	YES	54	B	63, R13	90
		131.4	YES	26	B	28	91
		118.2	YES	26	B	28	92
		112.2	YES	26	B	28	93
Methotrexate	Methotrexate Sulphasalazine	14.5	NO	52	A1	55	94
		2.8	NO	52	A2	54	95
Injectable gold	Injectable gold Cyclosporin	133.2	YES	24	A2	64	96
Injectable gold	Hydroxychloroquine Injectable gold	24	YES	48	A1	65	97
		78	YES	24	B	66	98
Sulphasalazine	Sulphasalazine Hydroxychloroquine	75.6	YES	24	A2	53	99
Sulphasalazine	Methotrexate Sulphasalazine	10.7	NO	52	A1	55	100
		2.9	NO	52	A2	54	101
Sulphasalazine Hydroxychloroquine	Methotrexate Sulphasalazine Hydroxychloroquine	96	YES	96	A2	62	102

Evaluation of the methodological quality of meta-analyses

The quality of the Cochrane Library meta-analyses was rated using the index of the quality of review articles, as revised by Oxman and Guyatt [Oxman, 1991a; Oxman, 1991b; Jadad, 1996b].

This index is based on answers to the following questions:

1. Were the search methods used to find evidence on the primary question stated?

☐ No ☐ Partially ☐ Yes

2. Was the search for evidence reasonably comprehensive?

☐ No ☐ Can't tell ☐ Yes

3. Were the criteria used for deciding which studies to include in the review reported?

☐ No ☐ Partially ☐ Yes

4. Was bias in the selection of studies avoided?

☐ No ☐ Can't tell ☐ Yes

5. Were the criteria used for assessing the validity of the included studies reported?

☐ No ☐ Partially ☐ Yes

6. Was the validity of all of the studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analyzing the studies that are cited)?

☐ No ☐ Can't tell ☐ Yes

7. Were the methods used to combine the findings of the studies reported?

☐ No ☐ Partially ☐ Yes

8. Were the findings of the relevant studies combined appropriately relative to the primary question the overview addresses?

☐ No ☐ Can't tell ☐ Yes

9. Were the conclusions made by the author(s) supported by the data and/or analysis reported in the overview?

☐ No ☐ Partially ☐ Yes

10. How would you rate the scientific quality of this overview?

Extensive flaws		Major flaws		Minor flaws		Minimal flaws
☐	☐	☐	☐	☐	☐	☐
- 1 -	- 2 -	- 3 -	- 4 -	- 5 -	- 6 -	- 7 -

The score for question 10 (overall scientific quality) is based on the replies to the previous 9 questions. If the answer to one or more questions is "Can't tell" the overview probably has, at the very least, minor flaws, and it is difficult to exclude major flaws (score of 4 or less). If the answer to questions 2, 4, 6, or 8 is "No," the overview probably has major flaws (score of 3 or less), depending on the number and severity of the flaws). The score for the quality of the overview can range from 1 to 7, as shown in the figure for question 10.

In accordance with the previously described methodology, the quality of the scientific evidence for the nine meta-analyses found is shown in Table 10.

Table 10. Evaluation of the quality of the meta-analyses of DMARDs

	Questions in meta-analysis ratings									
DMARD [Systematic review citation]*	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Auranofin [RS1]	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	4
Azathioprine [RS2]	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	4
Cyclophosphamide [RS3]	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	4
Cyclosporin [RS4]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	3
D-penicillamine [RS5]	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	4
Hydroxychloroquine [RS6]	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	4
Methotrexate [RS7]	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	4
Injectable gold [RS8]	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes	Yes	4
Sulphasalazine [RS9]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	3

* The citation for each systematic review is shown in reference list 2.1.

Table 11 shows the conclusions of the systematic reviews of the Cochrane Library and the quality of these reviews.

Table 11. Conclusions of the Cochrane Library meta-analyses and their level of evidence

DMARD [Systematic review citation]*	**Conclusions**	**Level of Evidence (1-7)**

Auranofin [RS1]	Auranofin appears to be efficacious in the short-term treatment of patients with RA. It has a small clinically and statistically significant benefit on disease activity. It may be more appropriate for patients with early and mild disease, who probably respond to less aggressive treatments.	4
Azathioprine [RS2]	Appears to be beneficial in the short term in the treatment of patients with RA. It cannot be considered more efficacious than other DMARDs, however, and its toxicity is greater. This suggests that other DMARDs should be used before considering azathioprine.	4
Cyclophosphamide [RS3]	Cyclophosphamide appears to be an effective drug in treating patients with RA, but its use is limited due to its toxicity. Since its efficacy appears to be similar to that of other, less toxic antirheumatic drugs, its use should be limited to patients who do not respond to other treatments.	4
Cyclosporin [RS4]	Cyclosporin has an important clinical benefit in the short-term treatment of patients with progressive RA.	3
D-penicillamine [RS5]	D-penicillamine appears to be efficacious for the short term treatment of patients with RA. It has a clinically and statistically significant benefit on disease activity. Its effects on long-term functional status and radiographic progression are not clear at this time. There does not appear to be any clear advantage to using doses higher than 500 mg/day.	4
Hydroxychloroquine [RS6]	Hydroxychloroquine appears to be efficacious in the treatment of RA. Its total effect appears to be moderate, but its low toxicity profile should be considered in treating RA patients.	4
Methotrexate [RS7]	Methotrexate has a clinical and statistically significant benefit in the short-term treatment of patients with RA.	4
Injectable gold [RS8]	Although its use may be limited due to the incidence of serious toxicity, injectable gold has a clinical and statistically significant benefit in the short-term treatment of patients with RA.	4
Sulphasalazine [RS9]	Sulphasalazine appears to be efficacious in the short-term treatment of patients with RA. It has a clinically and statistically significant benefit on disease activity. Its effects on functional status and radiographic progression are not clear at this time, but they appear to be modest.	3

* The citation for each systematic review is shown in reference list 2.1.

2. Development of the Recommendations

Several of the tasks involved in making this guideline, including the development of the recommendations, were carried out by the expert panel.

2.1 Selection of the expert panel

Panel nominations were provided by the SER, by independent rheumatologists, and by investigators familiar with the methodology for producing CPG recommendations.

To help make the guideline more valid, the principal investigator proposed to those responsible for nominations that the panel should meet the following criteria: 1) **multidisciplinarity,** that is, the panel should include not only rheumatologists, but also other specialists whose opinions would help improve RA management or improve the methodology for developing the recommendations (e.g., rehabilitation specialists, orthopaedists, or epidemiologists); 2) **professional prestige,** that is, that by virtue of their professional trajectory the opinions of the expert panel would be respected by the scientific community; 3) **geographic diversity,** that is, if the guideline is to be applied at the national level, an attempt should be made to have a reasonable representation of Spain's different autonomous communities; 4) **diversity in levels of care,** so that the recommendations would make sense in both hospital and outpatient settings; 5) **diversity of academic level,** so as to represent the viewpoints of teaching centers and highly developed academic and research centers, as well as the perspectives of professionals who manage patients in less academic centers; and 6) **representation of both men and women** on the panel.

Although it was not easy to incorporate all these criteria, a list of nominees was produced. Panelists were contacted to request their participation, and a panel of 15 members was formed: 12 rheumatologists, one rehabilitation specialist, one orthopaedist, and two epidemiologists (one of the rheumatologists is also an epidemiologist). The autonomous communities from which there was at least one panel member were: Andalucía, Canary Islands, Cantabria, Cataluña, Extremadura, Galicia, Madrid, La Rioja, and Comunidad Valenciana. Finally, there were 4 women and 11 men on the panel.

The most important individual criterion for selection was the explicit absence of conflicts of interest. Each panelist signed a document assuring that he or she was not affected by any of the conflicts described in a comprehensive list of possible conflicts of interest. Nominees with conflicts of interest were excluded. Another individual criterion for acceptance was availability during the time needed to carry out the tasks. Panelists received no remuneration for their work.

2.2 Panel tasks

The panel's tasks were: 1) to define the contents of the guideline; 2) to develop the recommendations; 3) to write the definitions; 4) to review and contribute to the synthesis of the evidence; 5) to write parts of the guideline that had not originally been foreseen (for example, the most frequent extra-articular complications); and 6) to review the text written by the investigators.

The panelists were asked to write recommendations that would provide practical and specific advice on the subjects covered. They were explicitly told that their recommendations should be based on the risk-benefit balance for the patient and that costs were not to be taken into account. That is, the recommendation should be made considering what would be best for the patient, consistent with the objective of improving the quality of care.

2.3 Formulation of the recommendations

The 15 panelists formed 10 working groups of 3 persons each; thus, each panelists could serve on more than one group The working groups were responsible for writing different chapters of the guideline. The draft recommendations made by each group were sent to the investigators, who edited and circulated them to the rest of the panelists for suggestions, and in subsequent interactions the pre-definitive version of the recommendation was written. A joint document was written based on all this information, which was submitted to all the panel members for discussion and correction. Panelists interacted by telephone, email, regular mail, and small group meetings; the project investigators held four joint meetings with the whole panel. Thus, although each group wrote the initial version of a specific part of the guideline, all the panelists had the opportunity to contribute their knowledge and opinions in the rest of the guideline recommendations.

There was large inter-panelist variability with relation to patient classification and the treatment approach in managing RA. Part of this variability may have been due to the fact that one panelist was thinking of a patient with certain characteristics while another was thinking of a patient with different characteristics. To classify patients by disease characteristics and to group them in a clinically meaningful way, various clinical variables were used. The variables considered for patient classification were: a) receipt of NSAIDs and/or corticosteroids in the previous 3 months (2 categories); b) number of swollen joints (<6, 6-10 or >10) (3 categories); c) presence of erosions (0, 1-3 or >3 erosions) (3 categories); d) presence of elevated acute-phase reactants (2 categories); Health Assessment Questionnaire (HAQ) score (<1 or ≥1) (2 categories); and f) rheumatoid factor (<40, 40-100 or >100 UI/mL) (3 categories). Combining the categories of these clinical variables yielded 144 different patient scenarios that might call for different treatment. The panelists provided anonymous and independent recommendations about the initial treatment for each of these 144 clinical scenarios.

If the recommendations differed, panelists were free to express their arguments and the evidence supporting their opinion to try to convince the rest of the panel, but they were not obliged to reach consensus. That is, this guideline is based not on consensus, but rather on the best available scientific evidence and, when this was absent or contradictory, on the judgment of an expert panel that

was not forced to reach a consensus. In other words, since part of the variability in clinical practice may be due to the fact that there is insufficient scientific evidence on the efficacy of the different DMARDs, this guideline recognizes that fact and considers that it is admissible for different professionals to have different opinions.

The panel members chose the best treatment for each of the 144 different patient scenarios. Their recommendations were analyzed mathematically, especially the proportion of panelists who suggested each treatment recommendation. Since the recommended treatment was similar for many of the 144 different patient scenarios, these were grouped into 52 scenarios in which the treatment decisions were the same. Reducing the number of options seems more reasonable for guideline users, and these are the classification options reflected in the decision algorithm for the initial treatment of RA that is included at the end of this guideline. (Both the panel votes and the mathematical analysis are available to interested readers by contacting TAISS at milena@taiss.com.)

The treatment decisions are further simplified in the text of the recommendations, where the use of corticosteroids and/or NSAIDs is treated separately from DMARD treatment, since the former are used only in particular, very specific situations. Thus, it is necessary to consider only the two objective parameters (number of swollen joints and presence of erosions) that have been shown to be the most important in disease classification due to their treatment implications.

The reduced scenario classification was used to establish the alternative treatment in case of toxicity or unsatisfactory response to initial treatment. The panelists again voted individually, and the alternative treatment options with the most votes were chosen, ordered by preference of use.

The systematic scientific review of the literature on DMARDs made it possible to identify the level of evidence supporting the panel recommendations for medical treatment. In the other chapters, each panelist or group provided the evidence on which they had based their recommendations. In other words, support for the recommendations based on a systematic review and evaluation of the scientific evidence in this guideline is limited to management with DMARDs. The rest of the recommendations are based on a non-systematic review of the scientific evidence, which is cited as the bibliographic reference, or on expert opinion.

HOW TO USE THIS GUIDELINE

This guideline is organized by chapters. Each chapter shows the recommendations in bold print, followed by a more detailed justification or explanation of the recommendations.

We have tried to make the recommendations clear and practical, without losing flexibility. Thus, at times the choice between various possibilities considered equally valid by the panel is left to the judgment of the rheumatologist (e.g., various methods to evaluate RA severity). One of the attributes of this guideline is its flexibility, allowing it to be applied to the real world where situations may vary, for example with regard to local characteristics of the center (availability of certain technologies, training, etc.), personal preferences of the patient, or other situations that may affect clinical decision making in patients with RA.

Rheumatologists using this guideline for the first time may find it useful to read the chapters in order, since this is the natural order of a medical evaluation: diagnosis, initial evaluation, classification, treatment, criteria for response to treatment, adverse effects of drug treatment, and possible extra-articular complications.

Several documents are included with this guideline that may be of use to readers in evaluating and monitoring patients: data collection forms for initial patient evaluation and follow-up (Appendix 1) and an algorithm to aid treatment choices (Appendix 2). This algorithm allows the user to follow a logical decision-making process in patient management.

The user of this guideline can consult the quality of the scientific evidence supporting the use of DMARDs and identify the articles from which the evidence was obtained.

Also included is a "Rapid Reference Guide," which is a brief version of the guideline recommendations and includes the simplified algorithm.

CONTENTS AND LIMITATIONS OF THE GUIDELINE

RA is a disease that can affect different patient subgroups, can be managed in different settings, can be treated with a variety of therapeutic approaches, and can affect various organs or systems. To cover all these aspects in a guideline, besides being an endless task, would be impractical. Thus, the SER, together with the expert panel and the investigators, agreed to limit its contents as follows:

- It is intended for rheumatologists.
- It focuses on RA in adults (juvenile RA is excluded).
- It includes diagnosis, evaluation, prognosis, treatments (drugs, rehabilitation, etc.), and extra-articular complications (amyloidosis, anemia, Sjögren's syndrome, etc.).

- The synthesis of the scientific evidence based on a systematic review of the literature focuses on the efficacy of DMARDs.
- The remaining recommendations or considerations are based on scientific evidence obtained without systematic review or on expert opinion.

CHAPTER 1. DIAGNOSING RHEUMATOID ARTHRITIS

The diagnosis of RA is essentially a clinical task. RA should be suspected in patients over 16 years of age who have joint inflammation or effusion of more than 6 weeks duration in three or more joints, preferably of the hands and feet. To date, the only universally accepted and used diagnostic criteria for RA are those proposed for classification of the disease by the American College of Rheumatology (ACR) in 1987 [Arnett, 1988].

According to the ACR, the diagnosis of RA requires confirmation of at least four of the following criteria:

1. Morning stiffness lasting at least one hour before maximal improvement, for at least 6 consecutive weeks.
2. Soft tissue swelling or fluid, observed by a physician, in at least three of the following joint areas (right or left): proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, or metatarsophalangeal (MTP) joints, for at least 6 consecutive weeks.
3. Swelling or fluid, observed by a physician, in the proximal interphalangeal, metacarpophalangeal, or wrist joints, for at least 6 consecutive weeks.
4. Symmetrical (right and left sides) swelling or fluid in the joints mentioned in point 2, observed by a physician, for at least 6 consecutive weeks.
5. Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Demonstration of serum rheumatoid factor (RF) detected by any method that has been positive in less than 5% of control subjects.
7. Radiographic evidence in the hands or wrists of articular erosions or osteopenia in or around the affected joints.

These criteria have a sensitivity of 91% and a specificity of 89%. However, their predictive value varies depending on the prevalence of RA in the clinical or population setting, as can be seen in Table 12 [Balsa, 1996; Villaverde, 2000].

Table 12. Predictive values (%) for RA diagnostic criteria in different settings

Population	RA prevalence	Positive predictive value	Negative predictive value
General	0.5	4.7	99.9
Primary care medical consultation for osteomuscular pain	19	69.9	97.2
Specialized consultation for polyarthritis	67	95.3	80.3

Thus, if a patient in the general population does not meet the RA criteria, for all practical purposes the disease can be ruled out (probability of error 1/1000). If the criteria are positive, however, the patient is unlikely to have the disease, which makes it necessary to confirm or rule out the diagnosis using additional techniques. In a consultation for polyarthritis, on the other hand, patients meeting the criteria are highly likely to have RA (95%), and if they do not meet the criteria, the probability of having RA is 20%.

CHAPTER 2. INITIAL EVALUATION

2.1 Patients with RA should be evaluated and treated by physicians who are familiar with the clinical management and treatment of the disease.

RA is a chronic disease, with an estimated prevalence of 0.5% (0.2-0.8%) in the Spanish adult population [Villaverde, 2000]. Its evaluation and treatment are somewhat complex, especially when the disease is clinically active. For this reason it is recommended that the diagnosis, monitoring, and treatment of RA be carried out by physicians who can identify patients in the early stages of the disease, evaluate the disease stage correctly, plan appropriate treatment for each stage of disease evolution, and measure the response to treatment.

The recommendations in the following sections should always be followed in the initial evaluation and monitoring of patients. This systematic evaluation of patients is needed to plan appropriate treatment in accordance with disease characteristics and to measure the response to the treatment undertaken.

2.2 The initial evaluation of a patient with RA should include a clinical history and physical examination.

The same as in any other clinical process, the first evaluation should include a **clinical history** and **physical examination.** The history should include a personal and family history (of diseases, surgical interventions, allergies), with special emphasis on processes that were life threatening or required medical treatment or hospitalization. The history should review life styles with regard to exercise, nutrition, smoking, and alcohol use. Gynecological history and date of first menstruation should also be recorded.

The **sociodemographic data** to be collected include age, gender, educational level, main occupation, and work setting, because of their importance as prognostic factors in RA.

In the initial evaluation of a patient with RA, the rheumatologist should keep in mind the **previous history of the disease.** Some patients will have RA of short evolution, for which hardly any medical treatment has been received, while others may visit the physician following a more or less prolonged period of arthritis, with a clinical and therapeutic history that must be considered. In these cases, the clinical characteristics of the disease should be obtained by interviewing the patient and reviewing reports and other documents provided by the patient, such as radiographs and certain laboratory tests.

To understand the evolution of RA, it is critically important to identify any previous or concurrent treatment, especially with analgesics, NSAIDs, corticosteroids, and DMARDs. A detailed history should be taken of DMARDs received to date, the dosage, duration, and reasons for discontinuing the medication. The same information should be obtained for corticosteroid use. With regard to NSAIDs, the physician should ask about their observed tolerance and side effects, with special regard to digestive problems.

In the **physical examination,** in addition to the signs that would be observed for any patient, careful note should be taken of the presence of pain, joint inflammation, deformities, and subcutaneous nodules.

2.3 The evaluation and monitoring of RA should be based on a systematic evaluation of a minimum set of parameters including joint pain and inflammation (2.3.1), the patient's global assessment of pain (2.3.2), global assessment of disease (2.3.3), functional disability (2.3.4), acute phase reactants (2.3.5), and radiologic evidence of damage (2.3.6).

The clinical evaluation of RA has been the subject of interesting debate. At the first conference of OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials), held in Maastricht in 1992, North Americans [Felson, 1993a; Felson 1993b] and Europeans [Scott, 1992] reached a historic consensus, with experts from different countries agreeing on a minimum set of parameters to be used in evaluating RA patients included in clinical trials [OMERACT, 1993]. These recommendations were subsequently ratified by the ACR [Felson, 1993a], the World Health Organization (WHO), the European Leagues Against Rheumatism (EULAR), and the International Leagues Against Rheumatism (ILAR) [Boers, 1994]. The parameters were chosen by consensus after examining the reliability, validity, and sensitivity of those most frequently used in the clinical evaluation of RA, with the aim of obtaining a set of parameters that would allow evaluation of all relevant aspects of the disease, without redundancy. This core set of parameters, which was originally selected for use in clinical trials, has been shown to be useful in daily clinical practice.

The core set of parameters recommended by the OMERACT conference includes: 1) number of painful joints, 2) number of swollen joints, 3) pain, 4) the patient's overall assessment of disease, 5) the physician's overall assessment of disease, 6) physical functional capacity, and 7) acute phase reactants. Another parameter recommended in this conference for studies lasting at least 1 year was radiologic evaluation of damage, although more recent investigations have shown that radiographs of the hands and feet can detect changes in periods of 6 months [Sharp, 2000]. In any case, radiologic evidence of damage is not a parameter that can be clinically evaluated very often, therefore it should not be systematically assessed at all visits, but only once a year (see section 2.3.6.).

There are clear advantages to using these parameters to monitor patients [Pincus, 1996; Wolfe, 1999a]. Nevertheless, rheumatologists do not systematically monitor patients with RA, and their use of different parameters for disease evaluation varies greatly [Bellamy, 1998; Bellamy, 1999]. According to the emAR study [Hernández-García, 2001], the use of quantitative measures of disease activity or functional damage is very limited in Spain. For example, joint counts were made at all or most visits in only 23% of 1,379 patients over a 2-year period; the figures for pain assessment or global assessment of disease status by visual analogue scale or the use of functional capacity questionnaires were still lower. The infrequent use of the OMERACT parameters and part of this variability could be explained by the fact that the application of standardized clinical instruments in daily practice involves additional time and effort in a high pressure setting. However, variability in the results of different treatments and the emergence of new, more costly and efficacious therapies with uncertain adverse events in the medium term will require closer patient monitoring if we aim to make more effective decisions at a socially acceptable cost.

2.3.1 Validated methods should be used to assess the number of painful joints and the number of swollen joints. For individual assessment of disease activity the use of a complete index is recommended, based on the examination of 68 joints for pain and 66 for swelling (excluding the hip).

Articular indices assess the degree of pain and swelling by counting the number of painful joints and the number of swollen joints. Three different methods have been described, varying in the

number of joints evaluated, although only four are in widespread use:

- **ACR Count.** The ACR (previously the ARA - American Rheumatism Association) count can be defined as the most complete index [Deandrade, 1965; Williams, 1983; Ward, 1983; Paulus, 1984]. It is the US standard. It includes evaluation of tenderness in 68 joints and swelling in 66 joints (excluding both hips). The following joints are assessed: distal interphalangeal, proximal interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, acromioclavicular, sternoclavicular, temporomandibular, hip (only for pain), knee, ankle, subtalar-midtarsal, metatarsophalangeal, and proximal interphalangeal joints.
- **Ritchie Index.** This is the European index most commonly used. It includes assessment of pain alone in 53 joints and is calculated based on 26 joints, since some joints are considered together [Ritchie, 1968]. The following joints or groups of joints are evaluated: right and left proximal interphalangeal,(2), right and left metacarpophalangeal (2), wrist (2), elbow (2), shoulder (2), cervical spine (1), acromioclavicular (1), sternoclavicular (1), temporomandibular (1), hip (2), knee (2), ankle (2), subtalar (2), midtarsal (2), and right and left metatarsophalangeal (2) joints. This method quantifies joint tenderness or pain on motion only in the case of the cervical spine, hip, subtalar and midtarsal joints. Pain is scored on a 4-level scale: 0 = no pain; 1 = pain; 2 = pain and wincing; 3 = pain, wincing, and withdrawal (maximum score: 78). In the case of joint groups, the highest score assigned to any of the joints in the group is assigned to the whole group.
- **44-Joint Index.** Swelling is evaluated in the following 44 joints: proximal interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, acromioclavicular, sternoclavicular, knee, ankle, and metatarsophalangeal joints. The fact that swollen joints are included in this index makes it a complement to the Ritchie index.
- **28-Joint Index.** Fuchs et al. [Fuchs, 1989] observed that a simple evaluation of tenderness and swelling in 28 joints provided the same sensitivity to change in clinical trials as more complex indices [Fuchs, 1994]. The index includes the following joints: proximal interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, and knee joints.

When counting joints, one can either make a simple count of the number of painful and swollen joints (present/absent) or semi-quantify the degree of pain and swelling in each joint using a 4-level ordinal scale (0-3). This guideline recommends counting painful and swollen joints without adding any type of quantification. The advantages obtained by quantifying are lost in the increased variability of the measurements.

The ACR recommends the use of complete counts of 68 joints, although it later accepted the use of counts based on 28 joints in clinical trials. The same committee emphasized, however, that indices based on 28 joints exclude those in the foot and ankle, which are affected in over 50% of patients, therefore they provide less information at the individual level in daily clinical practice [OMERACT, 1994]. The use of a reduced index does not mean that these joints should not be examined. Thus, this guideline recommends the use of the ACR index with 68 joints.

2.3.2 Pain should be assessed by the patient him or herself. It is recommended that pain be measured using a horizontal visual analog scale, 10 cm in length, divided by vertical marks into ten equal 1-cm segments. The measurements should be accompanied by numeric descriptors from 0 to 10, with indicators at each end showing no pain (0) and worst pain (10).

Pain is a subjective experience, therefore it should be quantified by the individual patient. Among the different methods used to measure pain, those that stand out due to their simplicity and ease of use are visual scales, or Likert-type scales, which usually have five or seven levels. The visual analog scale (VAS), with a horizontal 10 cm line and descriptors at each end, is the most widespread method. The ACR/OMERACT recommendations advise the use of either of the two methods, although there is a clear preference in studies for the VAS. Most patients are able to complete this scale. It is first necessary to devote some time to explaining the scale and giving a specific example; patients then answer quickly and with confidence. Some modifications, such as the use of numeric descriptors, may improve reliability in persons with a low educational level [Ferraz, 1990]. The VAS for pain shows a good correlation with the Likert scale, and both are sensitive to clinically important changes, with the VAS showing certain advantages [Langley, 1984; Anderson, 1993; Buchbinder, 1995].

2.3.3 A global assessment of disease should be made from the medical point of view and another one from the patient's point of view. For this measurement, the use of a 10 cm horizontal visual analog scale is recommended, with vertical marks dividing it into 10 equal 1-cm segments. The measurements should be accompanied by numeric descriptors from 0 to 10, indicating at each end "very good" (0) and "very poor" (10).

Global disease assessments by both the physician and the patient are useful because their evaluations may be quite different. The global assessment is very sensitive to clinical changes [Anderson 1989; Buchbinder, 1995].

2.3.4 Self-perceived functional disability attributed to the disease should be evaluated using specific, previously validated questionnaires such as the Health Assessment Questionnaire (HAQ) (see Appendix 1).

There are various ways to estimate functional capacity based on joint mobility or the ability to perform certain tasks as evaluated by an observer. The most widespread methods currently used consist of specific questionnaires for rheumatic disease such as the HAQ, the Modified Health Assessment Questionnaire (MHAQ) (shortened version of the HAQ), or the Arthritis Impact Measurement Scales (AIMS). They are based on the patient's own opinion about his or her disease. These questionnaires are standardized instruments, which have been shown to be valid and reliable. They evaluate those health dimensions that are most affected by RA, particularly disability, especially in relation to physical function, and pain.

The HAQ is a 20-item, self-administered questionnaire that evaluates self-perceived physical disability to perform certain basic activities of daily living, grouped into eight areas: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities [Fries, 1980]. A Spanish version of the questionnaire has been validated [Esteve-Vives, 1993]. The MHAQ is a shortened version of the HAQ, with only eight items. Its main advantage is its simplicity, which makes it possible to use it in routine patient monitoring [Pincus, 1983]. The Spanish version of the MHAQ can be self administered by most patients with RA [Esteve-Vives, 1994].

This guideline recommends the use of the HAQ as a standardized instrument to evaluate disability because of its widespread dissemination, acceptance, and proven metric characteristics.

Persons interested in evaluating broader aspects of health-related quality of life can also use the so-called generic questionnaires, such as the Short-Form 36 (SF-36), the Nottingham Health Profile (NHP), the Sickness Impact Profile (SIP), or the EuroQoL-5D. These questionnaires provide an estimate of self-perceived physical, psychological, and social health status based on questions about activities, feelings, and emotions covering a large number of daily life situations. The generic questionnaires provide complementary information and make it possible to compare the level of health with other diseases.

2.3.5 Laboratory tests should include two acute phase reactants (APRs): erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). The behavior of these two APRs is closely related with the inflammatory activity of the disease.

Laboratory tests should consist of a complete blood count, acute phase reactants (ESR, CRP), rheumatoid factor (RF), liver function (GOT, GPT, GGT, alkaline phosphate, albumin), kidney function (creatinine), calcium, and urinalysis. The presence of hepatitis B and C virus should be evaluated (in relation to the hepatotoxicity of some of the drugs used in treatment).

These basic tests will facilitate RA monitoring and early detection of disease complications and side effects of treatment (see chapter 6).

Measurement of APRs is very helpful in monitoring inflammatory processes in general, and of articular inflammation in particular. Their levels are associated with the intensity of underlying inflammation. There are several acute phase reactants but, in practice, the ESR and CRP are the most widely used. Both were included in the ACR recommendations and have been shown to be about equally useful in the evaluation of inflammatory activity [Paulus, 1999]. The advantage of the ESR is that it is inexpensive and available in any laboratory, and its disadvantage is its low specificity, since its levels can be modified by factors that are independent of articular inflammation. The advantage of the CRP is that its levels are virtually non-existent in the absence of inflammation, and its synthesis is closely related with inflammatory activity, with a very short half life. The techniques for measuring CRP are currently available in most laboratories. Persistent elevation of acute phase reactants with respect to normal reference values, especially for CRP, has been associated with poorer disease outcome [Dawes, 1986; van Leeuwen 1993; van Leeuwen, 1997].

Whether to include other complementary tests is left to the judgment of the individual physician, who should evaluate each case in terms of history, age, associated treatments, the possibility of using preventive interventions (e.g., cholesterol, glucose control), and associated co-morbidity.

2.3.6 Radiographs of the hands, feet, and chest are recommended at the initial evaluation. Radiographs of the feet and hands should be repeated annually for the first 3 years of disease evolution, and thereafter as deemed appropriate.

One of the findings to be looked for in the radiographs are bony erosions, which are more frequent at the onset of disease. About 70% of patients have erosions in the hands or feet by the end of the first 2 or 3 years [Van der Heijde, 1995b; Hulsmans, 2000]. Their presence and the speed of onset are associated with poorer outcome. Radiographic changes are moderately associated with physical disability [Drossaers-Bakker, 1999; Scott, 2000].

Numerous methods have been described to quantify radiographic changes in the joints. Almost all of them are based on radiograph readings of the hands, although some authors have pointed out the importance of including a systematic evaluation of the feet [Van der Heijde, 1992b]. Most of these methods are based on the Larsen method [Larsen, 1977; Larsen, 1995; Edmonds, 1999] or on the Sharp method [Sharp, 1971; Sharp, 1985; Kaye, 1987; van der Heijde, 1992b; Sharp, 1995]. There is no clear preference for either one [Pincus, 1995], although the van der Heijde method [Van der Heijde, 1992b], which includes hands and feet, appears to have some advantage. The disadvantage of all these methods is that they are very time-consuming to apply, therefore they are generally reserved for use in research.

This guideline recommends a simple **qualitative evaluation** to identify the presence of new erosions or their progression. Radiographs of both hands and feet are justified by the fact that asymmetrical erosions (right or left) may appear, and by the observation that in the first 2-3 years of the disease, erosions appear only on the feet, without clinical symptoms, in up to 23-36% of patients [Brook, 1977; Paimela, 1992; van der Heijde, 1999].

Other imaging techniques, such as magnetic resonance and sonography, have shown promising results in the early detection of inflammatory changes and structural damage like bony erosions [Wakefield, 2000]. These techniques involve the use of advanced technology that is not available in the vast majority of clinical centers. In addition, there is not enough evidence to date to make recommendations in this respect, thus their use remains reserved, for the moment, to the field of experimentation [Grassi, 2001].

With regard to the chest X-ray, a baseline radiograph is recommended, both to have knowledge of the baseline situation and to identify possible problems as the disease evolves and is treated.

Table 13. Summary of instruments for the measurement of parameters in RA evaluation

PARAMETER	VALID OPTIONS	RECOMMENDATION
Joint inflammation and pain	ACR count Ritchie index 44-joint index 28-joint index	ACR count
Global assessment of pain	VAS for pain rated by the patient Likert scale	VAS for pain rated by the patient
Global assessment of disease by the patient	VAS Likert scales for severity and/or activity	VAS for disease rated by the patient
Global assessment of disease by the physician	VAS Likert scales for severity and/or activity	VAS for disease rated by the physician
Functional capacity	HAQ MHAQ AIMS	HAQ
Laboratory tests	ESR CRP	ESR and CRP
Radiographic damage	Presence of absence of erosions Sharp index Larsen index	Presence or absence of erosions evaluated qualitatively by radiography

2.4 An alternative procedure that is useful and valid in assessing disease activity is the use of composite indices summarizing the information for various parameters in a single indicator. If this method is preferred, this guideline recommends the use of the Disease Activity Score (DAS).

Different composite indices have been published, and their validity has been reviewed in the framework of the OMERACT conference [OMERACT, 1993]. Some good examples are the Pooled index, the Mallya and Mace index, the Stoke index, the Scott index, and the DAS. These indices differ in the number of parameters included as well as the methods used for their calculation. Their advantages in comparison to conventional evaluation using single parameters are that they avoid duplicate measurements and are more sensitive to change. Their disadvantages are a certain degree of complexity in the calculations, difficulty of interpretation, and some problems related with how they are constructed.

The DAS deserves particular mention [Van der Heijde, 1990; van der Heijde, 1992a]. It includes the Ritchie index (RI), number of swollen joints out of 44 joints (NSJ44), erythrocyte sedimentation rate (ESR), and the patient's global assessment of health (PGA) on a visual analog scale (0 cm "very good" - 10 cm "very poor"). The patient's global assessment of disease can be substituted for the global assessment of health, using the same scale. The DAS is calculated using the following formula:

$$DAS=0.54\ (\sqrt{RI}) + 0.065\ (NSJ44) + 0.33\ (\ln ESR) + 0.0072\ (PGA)$$

There is a modified DAS based on the number of painful joints (NPJ28) and swollen joints (NSJ28) out of 28 joints [Prevoo, 1995]:

$$DAS28=0.56(\sqrt{NPJ28})+0.28(\sqrt{NSJ28})+0.70(\ln ESR)+0.014(PGA)$$

The score for the complete DAS and the DAS28 can range from 0 to 10. The DAS is of particular interest because it is the basis for the EULAR improvement criteria [Van Gestel, 1996].

2.5 The initial and subsequent evaluation of patients with RA should include a continual estimate of disease prognosis.

The outcome of RA varies considerably among patients. Some treatment strategies, more aggressive and therefore more toxic, improve RA outcome when used early in patients with a high risk of serious disease, understood as functional disability, structural damage, and/or mortality. The decision of whether or not to use these aggressive strategies should be based on the prognosis in each individual patient. Since most radiographic changes and, to a lesser extent, loss of functional capacity, occur in the first 2 or 3 years of evolution, the earlier a disease prognosis is formulated, the sooner an informed decision can be made on the most appropriate treatment strategy.

The factors that predict serious disease can be classified into three types: sociodemographic, disease-dependent and treatment-dependent. No single parameter, by itself, will permit estimation of RA outcome, therefore a combination of several parameters should be used. Furthermore, it is difficult to separate the individual effect of a particular risk factor from its interrelation with other factors associated with poor outcome.

The following factors are considered to be predictive of functional disability, radiographic erosions, and/or mortality, and therefore of poor outcome:

Sociodemographic factors:
Female gender. Being a woman is associated with presentation of functional disability 4 years after disease onset (Odds Ratio=3.01) [Pease, 1999]. Not all cohort studies have reproduced this finding. Female gender is probably related with other prognostic factors.
Age at disease onset. This is a controversial prognostic factor. Different groups have shown poorer, better, or equal outcome in elderly patients.
Low educational level. This is associated with increased mortality. Less than secondary level education is associated with over 50% decrease in functional status or with mortality at 9 years (OR=7.5) [Pincus, 1985]. In Mexican patients with RA, fewer than 6 years of formal education is associated with severe forms of RA (OR=3.52) [Glave Testino, 1994].
Genetic markers. These have not been confirmed in all populations. They are limited to experimental use.

Disease-dependent factors:
Positive RF. Positive RF from 1/80 or = 60 IU by nephelometry is associated with the development of erosions (OR: 4.2 - 12) [Van der Heijde, 1995a]. The persistence of elevated RF is associated with erosions at 6 years follow-up. At 3 years from symptom onset, the presence of positive RF IgA is associated with more erosions, worse HAQ score, and more painful and swollen joints.
Large number of swollen joints. A large number of swollen joints (>20 at disease onset) is predictive of future activity, including mortality [Van Zeben, 1992]. Cumulative joint inflammation is associated with progression to radiographic damage in 1 year (OR=2) [Pincus, 1985].
Elevated acute phase reactants. A CRP of twice the normal value at the patient's initial evaluation is associated with the development of erosions in 4 years (OR=1.81) [Glave Testino, 1994]. A continuous ESR higher than 60 mm in the first hour is associated with the presence of disability at 18 years (OR=4.88) [Furst, 1994a].
Elevated HAQ at initial visit (≥1 out of 3). This is associated with disability at 4 years (OR=3.02) [Pincus, 1985]. For each HAQ unit over 0 at the baseline visit, the OR for disability increases by 1.60 to 2.94 [Wolfe, 1998]. In patients with a baseline HAQ of at least 2.5, the relative risk for developing disability is 2.15 [Wolfe, 1991].
Early involvement of large joints (≥2) is associated with the presence of erosions at 1 year (OR=2.03) [Brennan, 1996].
Rapid appearance of erosions (≥2/year). The speed with which erosions appear is associated with poorer outcome.
Presence of extra-articular manifestations (rheumatoid nodules, vasculitis, scleritis, or others). In general, these manifestations are associated with seropositive RF, therefore their prognostic value by themselves is unclear. The presence of extra-articular manifestations is associated above all with increased mortality [Gordon, 1973].

Treatment-dependent factors:
Length of treatment. Longer treatment time with DMARDs is associated with better long-term functional outcome. For example, the difference between patients treated with DMARDs throughout the course of their disease and those who never received treatment is 0.53 HAQ units. [Fries, 1996].
Early treatment with DMARDs. Patients who delay beginning DMARD treatment have poorer functional outcome than those who begin treatment early. The longer the delay in beginning treatment, the smaller the probability of reaching a satisfactory response (OR=5.57), and this in turn implies poorer functional outcome (with a mean increase of 0.12 HAQ units for each visit in which a 50% improvement is not reached) [Tsakonas, 2000].

2.6 Consideration should be given to the psychological and social effects on the patient, since these factors are involved in pain assessment and the development of disability.

In addition to the evaluation of structural damage, disability, and health-related quality of life, certain important psychological and social factors should be evaluated.

Psychological disturbances (depression and anxiety) are very frequent in RA from the time of disease onset [Van der Heijde, 1994], due to the impact of confronting its diagnosis and evolution. There is a close relation between depression, anxiety, and chronic pain. This can make the assessment (VAS rating by the patient and physician) more difficult and should be taken into account when planning treatment. In addition, anxiety and depression appear to play an important role in the development of disability [Escalante, 1999].

It is currently thought that some psychological characteristics of the patient (level of perceived helplessness, coping ability, level of self-management) play an important role as factors predictive of disability and health status. A high level of helplessness makes for a poorer outcome, whereas a greater coping ability and level of self-management improves it [Scharloo, 1999].

With regard to social factors, one third of patients lose their job during the first year of the disease [Jantti, 1999], in close association with their inflammatory activity [Wolfe, 1998; Reisine, 1998]. The reduced income associated with job loss affects all members of the family unit [Wolfe, 1998]. Patients who receive substantial social support from family and friends, especially from their spouses, have better outcomes and less disability [Fitzpatrick, 1991, Kraaimaat, 1995]. Some clinical manifestations, such as pain or fatigue, are more frequent in persons who lack social support [Riemsma, 1998].

2.7 A detailed evaluation should be made to rule out latent tuberculosis infection before beginning treatment with immunosuppresants, anti-TNF agents, or corticosteroids in doses higher than 15 mg/day. If latent tuberculosis infection is present, prophylactic treatment with isoniazide is recommended.

Treatment with anti-TNF agents or corticosteroids is a risk factor for tuberculosis (TB) in persons who have a primary infection with the Koch bacillus. A chest X-ray and tuberculin test should be included in the initial evaluation, with a repeat test (booster) in a week if the result is negative. A positive result is considered to be an induration larger than 10 mm, or larger than 5mm if the patient has a history of TB, or radiographic signs on a simple chest X-ray. If the tuberculin test is negative, the patient should be monitored for TB. If it is positive, the eradication treatment to use is isoniazide for a minimum of 4 months, and preferably 6. Prophylaxis can be given concomitantly with RA treatment if there is no evidence of liver toxicity.

CHAPTER 3. CLASSIFYING RHEUMATOID ARTHRITIS

3.1 General classification

The two characteristics that have the most influence on the initial classification between serious and mild disease, and therefore on the treatment decision, are the presence or absence of erosions and the number of swollen joints. The classification may be made more precise if other factors, such as APR, HAQ, and RF, are taken into account. The subsequent classification will depend on the response to treatment.

Two types of RA with special characteristics are not included in this classification: "burnt-out" RA and pseudopolymyalgic RA (sections 3.2 and 3.3).

RA cannot be neatly classified into different categories. In this guideline, the classification of patients is based on two principles: first, classifying RA is useful for making treatment decisions and estimating patient outcome; second, the classification should help the physician in actual practice. In accordance with these two principles, RA is classified based on the two parameters that, in the panel's opinion, have the most influence on the treatment decision and on outcome: the presence of erosions and the number of swollen joints. The use of two categories for the presence of erosions (yes/no) and two categories for the number of swollen joints (<6/≥6), gives four types of RA which, on a scale of increasing severity, would go from non-erosive disease with few swollen joints to erosive disease with swelling of multiple joints at clinical presentation. This simple alternative makes it possible to classify patients rapidly and is proposed in the recommendation for initial treatment in this guideline.

While this guideline was being developed, we found that panelist disagreement about the initial treatment proposed was often due, not to a true difference of opinion, but to the fact that there are many different forms of RA. The differences arose because panelists were thinking about different types of patients within the same category. Thus, it was decided to include more variables in the categorization to be able to discriminate more precisely among different types of patients. Other factors were taken into account, such as APRs, HAQ, RF, and previous treatment with corticosteroids and/or NSAIDs. The combination of these factors resulted in 144 different scenarios describing different types of patients, from the mildest clinical presentation (no erosions, <6 swollen joints, normal APRs, HAQ<1 and negative RF) to the most severe form of disease (erosions present, >10 swollen joints, elevated APRs, HAQ≥1 and high titers of positive RF). Each patient, according to the initial disease characteristics, should begin a specific treatment option (see chapter 4). If the response to initial treatment is unsatisfactory, the disease is considered to have a poor prognosis and thus should be considered as severe.

The parameters that the physician should consider when classifying a patient within the continuous spectrum of disease severity are probably more extensive than those proposed in this guideline. The inclusion of characteristics such as age and time of evolution, among others, or the inclusion of additional categories for the parameters used would be feasible, however it would lead to an exponential increase in the number of types of RA.

It is also debatable which parameters are most useful in classifying RA and which cut-off points best discriminate the milder forms of disease from those that are more severe. Since the evaluation and follow-up of RA patients should be based on longitudinal monitoring of measures of disease activity, joint damage, and health status, any classification should be made as a function of these parameters. Based on these parameters, we propose the two classifications of RA (simpler and more complex) included in this guideline. Nevertheless, new research may lead to a more precise classification of RA with implications for the clinical management of these patients.

3.2 "Burnt-out" or end-stage rheumatoid arthritis

In "burnt-out" or end-stage RA there is no inflammatory activity and there is complete or practically complete destruction of the patient's joints. It is characterized clinically by joint pain at rest or with minimal exertion, joint deformities, significant muscular atrophy, extreme functional disability, and radiographic evidence of major joint destruction (erosions, subluxations, and ankylosis) [Schur, 1999].

The evaluation should rule out the possible presence of the extra-articular complications or manifestations of RA that most frequently appear at this stage of the disease, for example, skin ulcers, vasculitis, and amyloidosis [Gordon, 1973; Thurtle, 1983; Vollertsen, 1986; Breedveld, 1989].

Their management will be based on symptomatic treatment and repair of function. Special considerations should be taken into account for elderly patients (section 4.7).

3.3 Pseudopolymyalgic rheumatoid arthritis

Pseudopolymyalgic rheumatoid arthritis is a disease that affects patients over 60 years of age and is characterized by the sudden onset of symptoms, mainly affecting the proximal joints (shoulders and hips) as well as the knees and carpal joints. It is accompanied by considerable morning stiffness, negative RF, and a marked increase in acute phase reactants. Erosions do not usually develop, and the prognosis is generally good. The disease may remit spontaneously in 6-24 months [Healey, 1986].

The main problem with pseudopolymyalgic RA is the difficulty of making a differential diagnosis since it is very similar to polymyalgia rheumatica.

Cases diagnosed as pseudopolymyalgia may include cases of polymyalgia rheumatica and RS3PE (remitting seronegative symmetrical synovitis with pitting edema), and perhaps some atypical forms of other arthropathies that are clinically indistinguishable from RA, a fact that may partially explain the good evolution in this subgroup.

It is usually managed effectively only with corticosteroids (section 4.5). If a satisfactory response is not obtained, it should be treated the same as RA in general, taking special considerations into account for elderly patients (section 4.7).

CHAPTER 4. MEDICAL TREATMENT OF RHEUMATOID ARTHRITIS

4.1 Initial treatment of rheumatoid arthritis

4.1.1 In general, all patients with RA should be treated with a DMARD as soon as the disease is diagnosed.

The aim of RA treatment is to induce complete disease remission or, alternatively, to achieve the best possible response. Treatment with DMARDs is the only way to ensure the most favorable evolution for the patient and to improve the quality of life.

The function of each drug prescribed should be explained to patients so that they know to discontinue or reduce symptom-modifying drugs (NSAIDs or analgesics) if pain and inflammation subside, but that a DMARD should never be discontinued without medical consultation, and that instructions for the use of corticosteroids should be followed closely.

All patients with RA should initiate DMARD treatment as soon as possible during the course of the disease. An attempt may be made to treat only with NSAIDs and/or corticosteroids for a maximum of 3 months, and only in patients who have not used these drugs during the 3 months before the disease was diagnosed, who have fewer than 6 swollen joints, no erosions, negative RF, and normal APRs.

Many patients in Spain experience an unacceptably long delay before the first DMARD treatment. According to the emAR study, the time from first symptoms to first treatment with any DMARD is high, ranging from 7 to 48 months, with a median of 16 months [Hernández-García, 2001]. Furthermore, this interval increases with increasing time between first symptoms and the patient's first visit for specialized care. [Hernández-García, 2000].

The time between first symptoms and initiation of DMARD treatment is one of the few variables that the physician can modify. Early commencement of treatment is associated with a higher probability of favorable response [Anderson, 2000; Villaverde, 2000] and a lower probability of functional and radiologic deterioration [Fries, 1996; Abu-Shakra, 1998]. Thus, it is essential not only

that all patients with RA be treated with DMARDs, but that this treatment should be initiated as early as possible in the course of the disease.

All the DMARDs in Table 1 have been shown to be more efficacious than placebo (Table 11). However, not all possible drug combinations in monotherapy or combined therapy have been compared in clinical trials (Tables 7 and 8).

For years DMARDs were used as monotherapy. If the response to one DMARD was not complete, it was discontinued and a second DMARD was initiated. This strategy often caused a reactivation of disease between the time one drug was withdrawn and the other begun. The fact that many RA patients are refractory to treatment led to the first use of combinations of two or more DMARDs [Ehrlich, 1982; Bitter, 1984; Gibson, 1987; Taggart, 1987; Scott, 1989; Williams, 1992; McCarty, 1995; Willkens, 1995]. The use of combined treatments slowed down, however, partly due to the results of a meta-analysis of five initial studies which concluded that combined therapy was no more efficacious and furthermore was more toxic than monotherapy [Felson, 1994]. The publication in the last decade of various clinical trials with sound methodology and a sufficient number of patients has encouraged renewed use of combined therapies in RA treatment [Tugwell, 1995; O'Dell, 1996; Stein, 1997; Boers, 1997; Haagsma, 1997].

The good results obtained using combined treatment in patients refractory to monotherapy have led some authors to propose they be used as sustained initial treatment or by sequentially discontinuing some of the drugs [Wilske, 1989; Boers, 1997]. The corticosteroids have also gained renewed acceptance as part of this "aggressive" strategy, especially while waiting for the DMARDs to take effect [Kirwan, 1995]. The introduction of new DMARDs opens the range of possibilities in RA treatment even wider. Some of these strategies are moving into daily practice. For example, in Spain almost 28% of patients included in the emAR study [Hernández-García, 2001] used some combination of two or more DMARDs throughout the study period. Another 72% followed some kind of treatment with corticosteroids. The impact of new treatments on the treatment strategy for RA is unknown. Whatever the case may be, with the limitations derived from our imperfect knowledge, RA patients have recourse to a wide range of strategies aimed at controlling their disease, which can be used pending the results of new comparative studies.

4.1.2 In addition to DMARD treatment, all RA patients should be treated with optimum doses of steroidal or nonsteroidal anti-inflammatory agents and/or analgesics if symptoms (pain and swelling) persist (sections 4.4, 4.5 and 4.6).

Regardless of DMARD treatment, all patients also require treatment with symptom-modifying drugs (NSAIDs and/or corticosteroids and/or analgesics) so long as there are persistent symptoms of joint pain and/or swelling.

4.1.3 Because of its efficacy and toxicity profile, methotrexate is the recommended initial treatment in all patients who have not previously received DMARD treatment. Nevertheless, initial treatment with other drugs is considered acceptable, depending on the clinical classification of disease (Table 14 or Appendix 2).

The advantages of methotrexate over other DMARDs with similar short-term efficacy are a well-known toxicity profile, easy management, and a lower rate of withdrawal from treatment in the medium and long term. For all these reasons, it is recommended as the drug of choice in this guideline.

The administration of 5 to 10 mg/wk of folic acid is recommended for RA patients treated with MTX [American College of Rheumatology, 1996]. Despite this recommendation, only slightly more than half of RA patients who receive MTX in Spain are treated with folic acid or folinic acid [Hernández-García, 2001].

Due to the clinical complexity of RA, the panel considers that the use of other DMARDs or DMARD combinations of proven efficacy is valid as initial treatment in some clinical situations, in accordance with the treatment scheme in Appendix 2 or Table 14.

Although the vast majority (93%) of RA patients who receive specialized care are treated with DMARDs, there is wide variability in their use in Spain. According to data from the emAR study, during a 2-year period and considering both monotherapy and combined therapy, 46% of patients had taken MTX, 21% anti-malarials, 14% IG, 8% SSZ, and 6% CSA. Among the factors associated with the use of each DMARD are patient age; some disease characteristics, such as functional class, rheumatoid factor, or disease activity; and the existence of associated disease. However, there is also significant variability that is associated, not with patient characteristics, but with physician specialty or characteristics, or with geographic region. Thus, for the same patient, the probability of receiving a particular DMARD depends on whether or not the prescribing physician is a specialist in rheumatology, his or her age, or the autonomous community of residence. About one-forth of patients treated with DMARDs use a combination of two or more drugs, although this percentage varies considerably between and among autonomous communities. The most frequent combinations include MTX and anti-malarials, followed by MTX with SSZ, MTX with CSA, and MTX with IG [Hernández-García, 2001].

Table 14. Initial treatment by simplified clinical classification of RA

SIMPLIFIED CLINICAL CLASSIFICATION OF RA		Recommended initial treatment, by order of preference (supporting evidence)
No erosions	<6 swollen joints	Methotrexate (1) Sulphasalazine (2) Chloroquine (3)
	≥6 swollen joints	Methotrexate (1) Injectable gold (4)
Erosions present	<6 swollen joints	Methotrexate (1)
	≥6 swollen joints	Methotrexate (1) Leflunomide (5) Methotrexate + injectable gold (6)

1. **Methotrexate** is more efficacious than oral gold (A1 evidence) or azathioprine (A2 evidence). No significant differences have been found in the efficacy of methotrexate compared with etanercept, leflunomide, sulphasalazine (A1 evidence), injectable gold (A2 evidence), cyclosporin, or infliximab (B evidence).
2. **Sulphasalazine** is more efficacious than hydroxychloroquine (A2 evidence), and no significant differences have been found in the efficacy of sulphasalazine compared with leflunomide, methotrexate (A1 evidence), oral or injectable gold, and D-penicillamine (B evidence).
3. **Chloroquine** is not significantly different in efficacy from cyclosporin, oral gold (A2 evidence), azathioprine, injectable gold and D-penicillamine (B evidence).
4. **Injectable gold** is not significantly different in efficacy from oral gold (A1evidence), cyclosporin and methotrexate (A2 evidence), or chloroquine, D-penicillamine and sulphasalazine (B evidence). It is less efficacious than azathioprine and cyclophosphamide (B evidence).
5. **Leflunomide** (A1 evidence) shows no differences in efficacy as compared to methotrexate and sulphasalazine (A1 evidence).
6. No clinical trials have evaluated the efficacy of treatment with **methotrexate+injectable gold** (C evidence).

4.2 Changes in treatment

After initiating any treatment, it is necessary to evaluate the response (chapter 5) and to monitor its toxicity (chapter 6). Treatment failure or toxicity should be evaluated within a maximum of 3 months, and a consequent change in treatment should be considered.

Whatever initial treatment is chosen, the patient should be monitored closely. If a satisfactory response is not obtained within 3 months, or if there is evidence of DMARD-related toxicity, consideration should be given to the possibility of a change in treatment by adding a new drug or modifying the dosage. It is critically important that a patient with RA who has not responded to a particular treatment with single or combined DMARDs have the option to try other treatments of proven efficacy in the shortest possible period of time.

4.2.1 If serious adverse effects appear, an alternative treatment should be substituted for the treatment of first choice, in accordance with Table 15.

Table 15. Alternative treatment in case of severe toxicity to initial treatment

SIMPLIFIED CLINICAL CLASSIFICATION OF RA		First-choice treatment used	Alternative treatment in case of toxicity, in order of preference (supporting evidence)
	<6 swollen joints	Methotrexate	Leflunomide (1) Injectable gold (2) Sulphasalazine (4)
		Sulphasalazine	Methotrexate (3) Injectable gold (2)

No erosions		Chloroquine	Methotrexate (3) Injectable gold (2)
	≥6 swollen joints	Methotrexate	Leflunomide (1) Injectable gold (2)
		Injectable gold	Methotrexate (3) Leflunomide (1)
Erosions present	<6 swollen joints	Methotrexate	Leflunomide (1) Injectable gold (2) Sulphasalazine (4)
	≥6 swollen joints	Methotrexate	Leflunomide (1) Injectable gold (2) Sulphasalazine (4)
		Leflunomide	Methotrexate (3) Anti-TNF (5)
		Methotrexate+injectable gold	Leflunomide (1) Anti-TNF (5)

The evidence supporting the alternative treatments proposed in case of toxicity or unsatisfactory response is as follows:

1. **Leflunomide** (A1 evidence) shows no differences in efficacy as compared to methotrexate and sulphasalazine (A1 evidence).
2. **Injectable gold** has not been shown to have significant differences in efficacy as compared to oral gold (A1 evidence), cyclosporin and methotrexate (A2 evidence), or chloroquine, D-penicillamine and sulphasalazine (B evidence). It is less efficacious than azathioprine and cyclophosphamide (B evidence).
3. **Methotrexate** is more efficacious than oral gold (A1 evidence) or azathioprine (A2 evidence). No significant differences in the efficacy of methotrexate have been found in comparison with etanercept, leflunomide, sulphasalazine (A1 evidence), injectable gold (A2 evidence), cyclosporin, or infliximab (B evidence).
4. **Sulphasalazine** is more efficacious than hydroxychloroquine (A2 evidence) and no significant differences have been found in the efficacy of sulphasalazine compared with leflunomide, methotrexate (A1 evidence), oral or injectable gold, and D-penicillamine (B evidence).
5. **Anti-TNF agents** (infliximab and etanercept) have been shown to be efficacious in the treatment of RA (A1 evidence), and they show no significant differences in efficacy with respect to methotrexate (B evidence for infliximab and A1 for etanercept).

4.2.2 If the treatment shows no toxicity but the response is unsatisfactory, even after using the maximum dosage (see 4.3), an alternative treatment should be substituted for the treatment of first choice, in accordance with Table 16.

Table 16. Alternative treatment in case of unsatisfactory response to initial treatment

SIMPLIFIED CLINICAL CLASSIFICATION OF RA		**First-choice treatment used**	**Alternative treatment in unsatisfactory response, in order of preference (supporting evidence)**
No erosions	<6 swollen joints	Methotrexate	Leflunomide (1)
		Sulphasalazine	Methotrexate (2) Leflunomide (1)
		Chloroquine	Methotrexate (2) Leflunomide (1)
		Methotrexate	Leflunomide (1)

	≥6 swollen joints	Injectable gold	Methotrexate (2) Leflunomide (1)
Erosions present	<6 swollen joints	Methotrexate	Leflunomide (1)
	≥6 swollen joints	Methotrexate	Leflunomide (1) Anti-TNF (3) Methotrexate+ anti-TNF (4) Methotrexate+chloroquine+sulphasalazine (5)
		Leflunomide	Methotrexate (2) Anti-TNF (3) Methotrexate+ anti-TNF (4)
		Methotrexate+injectable gold	Leflunomide (1) Anti-TNF (3)

1. **Leflunomide** (A1 evidence) has not shown differences in efficacy compared with methotrexate and sulphasalazine (A1 evidence).
2. **Methotrexate** is more efficacious than oral gold (A1 evidence) or azathioprine (A2 evidence). No significant differences in efficacy have been found in methotrexate as compared to etanercept, leflunomide, sulphasalazine (A1 evidence), injectable gold (A2 evidence), cyclosporin, or infliximab (B evidence).
3. **Anti-TNF agents** (infliximab and etanercept) have been shown to be efficacious in the treatment of RA (A1 evidence) in comparison with placebo, and they show no significant differences in efficacy as compared to methotrexate (B evidence for infliximab and A1 for etanercept).
4. The combination of **methotrexate+anti-TNF agents** (infliximab or etanercept) has been shown to be more efficacious than methotrexate alone (B evidence).
5. The combination of **methotrexate+chloroquine+sulphasalazine** has been shown to be more efficacious than methotrexate alone or chloroquine+sulphasalazine (A2 evidence).

In addition to the panel's recommendations, there is scientific evidence regarding the efficacy of several drug combinations in case of failure of treatment with methotrexate or the antimalarials.

In case of failure with methotrexate, the following combinations have been shown to be more efficacious:

- **Methotrexate+cyclosporin (A1 evidence)**
- **Methotrexate+chloroquine (A2 evidence)**
- **Methotrexate+azathioprine (B evidence)**

In case of failure with the antimalarials, the following combinations have been shown to be more efficacious:

- **Sulphasalazine+hydroxychloroquine (A2 evidence)**
- **Methotrexate+hydroxychloroquine (B evidence)**

4.2.3 In patients for whom the preceding guidelines are not useful, due to lack of efficacy, toxicity, or other causes, this guideline recommends the use of any DMARD or DMARD combination of proven efficacy; if these fail, experimental treatments are recommended.

The natural history of RA is long and no treatment has been shown to cure all patients. Thus, regardless of the recommendations in the preceding sections, it is admissible to introduce alternative treatments whose efficacy has been shown in clinical trials (Tables 7 and 8).

If disease control is not achieved with any of the proposed treatments, experimental treatments may be explored (new drugs or new combinations of existing drugs) so that the patient is never without some type of disease-modifying treatment.

4.3 Dosage for disease-modifying antirheumatic drugs

Table 17. Recommended doses and commercial names of DMARDs

DRUG	DOSE	COMMERCIAL NAMES
AZATHIOPRINE	**1.5 - 2.5 mg/kg/day, by mouth** Begin with low dose of around 1 mg/kg/day and increase in 4-6 weeks to maintenance dose of 100-150 mg/day.	IMURAN® Tab. 50 mg IMURAN®, Freeze-dried vial, 50
CYCLOPHOSPHAMIDE	**1.5 - 2.5 mg/kg/day, by mouth** Begin with 50 mg/day and increase dose every 4-6 weeks until a response is obtained, without exceeding 2.5 mg/kg/day.	GENOXAL® Amp. IV 1000 mg GENOXAL® Amp. IV 200 mg GENOXAL® Tab. 50 mg
CHLOROQUINE	**250 mg/day, by mouth** Do not exceed 4 mg/kg/day.	RESOCHIN® Tab. 250 mg
CYCLOSPORIN	**2.5 - 5.0 mg/kg/day, by mouth** The initial dose can be increased by 0.5mg/kg/day every 2 weeks up to 5 mg/kg/day.	SANDIMMUNE NEORAL® 100 mg SANDIMMUNE NEORAL® 50 mg SANDIMMUNE NEORAL® 25 mg SANDIMMUNE NEORAL® Oral sol. 100mg/ml
D-PENICILLAMINE	**125 - 500 mg/day, by mouth** Begin treatment with 125-250 mg/day and if there is no improvement, increase dose at 8 weeks by 125 mg/day. Dose can be increased gradually every 8 weeks up to 500-750 mg/day. Should be administered 2 hrs before the main meal.	CUPRIMENE® Caps .250 mg CUPRIMENE® Caps .125 mg CUPRIMENE® Tab.50 mg SUFORTANON® Tab. 250 mg
ETANERCEPT	**25 mg, reconstituted in 1 ml water, in subcutaneous injection, twice a week at intervals of 72-96 hours** One dose of 25 mg administered once a week offers a slower response and may be less effective.	ENBREL® Vial 25 mg
HYDROXYCHLOROQUINE	**400 mg/day, by mouth** Do not exceed 6.5 mg/kg/day	PLAQUENIL® Tab. 200 mg
INFLIXIMAB	**3 mg/kg intravenous perfusion for 2 hours** Then administer additional doses of 3 mg/kg in perfusion at weeks 2 and 6 following the first week, and one dose every 8 weeks thereafter. Dose may be increased to 5 mg/kg if ineffective or in case of relapse. Some patients require a shorter interval of infusion every 4-6 weeks, instead of the recommended 8 weeks for maintenance. Infliximab should be administered together with methotrexate.	REMICADE® Freeze-dried vial 100 mg

LEFLUNOMIDE	**20 mg/day, by mouth** Begin with 100 mg/day for 3 days and then 20 mg/day continuously.	ARAVA® Tab.100 mg ARAVA® Tab.20 mg ARAVA® Tab.10 mg
METHOTREXATE	**7.5-10 mg/week, by mouth** for 4 weeks, 15 mg/week for the next 4 weeks, and then increase up to 20 mg/week. In case of inefficacy or gastrointestinal toxicity, consider parenteral administration. Administer folic acid (5-10 mg/week) 24 hours after methotrexate.	METHOTREXATE ALMIRALL® Inj. sol. Vial 50 mg , A.D.1000 mg, 5000 mg, and 500 mg METHOTREXATE LEDERLE® Tab. 2,5 mg; Inj. sol. 25 mg/ml (2, 20, 40 and 200 ml); Freeze-dried vial 50 and 500 mg METHOTREXATE WASSERMANN® Inj. sol. 25 mg/ml (2 and 20 ml) EMTHEXATE® Vial 50 and 500mg/2ml
ORAL GOLD	**6 mg/day by mouth** 2 tablets per day.	RIDAURA® Tab. 3 mg CRISINOR® Tab. 3 mg
INJECTABLE GOLD	**50 mg/week in intramuscular injections** Increasing doses of 10, 25 and 50 mg/week, maintaining the dose (from 6 to 24 months) or adjusting it depending on clinical response or adverse effects.	MIOCRIN® Inj. sol. IM 10 mg MIOCRIN® Inj. sol. IM 25 mg MIOCRIN® Inj. sol. IM 50 mg
SULPHASALAZINE	**2-3 g/day, by mouth**	SALAZOPYRIN® Tab. 500 mg

4.4 Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs)

4.4.1 The NSAIDs are used to modify the symptoms of RA. The use of NSAIDs is recommended at disease onset, when a new DMARD is introduced, and when uncontrolled isolated symptoms persist despite good response to a DMARD.

The NSAIDs are used to modify the symptoms of RA. They have not been shown to have any additional effect on disease outcome.

The use of NSAIDs is recommended:

- **At disease onset.** If the disease is low risk (<6 swollen joints, no erosions, negative RF, and normal APRs), they can be used alone or in combination with corticosteroids for a maximum of 3 months.
- **When a new DMARD is introduced.** NSAIDs should be used until the disease and its symptoms can be controlled by the DMARD alone. NSAIDs should be used for 2-12 weeks, depending on the time needed for the DMARD to reach effective therapeutic levels. The period of combined use may sometimes be prolonged until the DMARD dose is adjusted.
- **When uncontrolled symptoms persist.** NSAIDs should be used when, despite treatment with a DMARD, some isolated symptom (painful inflammation or swelling or morning stiffness) is not sufficiently controlled, and there is no evidence of inflammatory activity that justifies increasing the DMARD dose or changing to a new treatment.

NSAIDs should not be used without first trying other analgesics such as acetaminophen for mechanical pain (pain that worsens with exercise and improves with rest, becomes worse during the day, with no joint stiffness after rest).

It is important to weigh the benefit-risk relation for the patient whenever an NSAID is used. The side effects and interactions of the NSAIDs used should be known.

4.4.2 All NSAIDs should be used at the full dose for at least 1 week before considering the treatment to have failed. Once symptoms have been controlled, the minimum effective dose should be used.

When the NSAIDs are withdrawn after prolonged use (over 3 months), they should be discontinued gradually to avoid the effects of rebound pain. No guidelines for withdrawal have been shown to be more effective than others.

Length of treatment with NSAIDs is a risk factor for gastric erosion.

Table 18. Usual dosage and frequency of administration of NSAIDs

DRUG	TOTAL DOSE (mg/24 h)	FREQUENCY OF ADMINISTRATION
AAS	3,000 - 6,000	6-8 h.
Ibuprofen	1,200 - 2,400	8 h.
Flurbiprofen Flurbiprofen Retard	200 - 300 200	12 h. 24 h.
Mefenamic acid	750 - 1,500	8 h.
Meclofenamic acid	200 - 400	8 h.
Diflunisal	500 - 1,000	12 h.
Sodium Tolmetin	800 - 1,200	6-8 h.
Naproxen	500 - 1,000	12 h.
Ketoprofen Ketoprofen Retard	200 200	8-12 h. 24 h.
Aceclofenac	200	12 h.
Diclofenac Diclofenac Retard	150 - 200 100	8-12 h. 24 h.
Phenylbutazone	200 - 400	12-24 h.
Indomethacin	75 - 150	8 h.
Sulindac	200 - 400	12 h.
Piroxicam	20	24 h.
Tenoxicam	20	24 h.
Droxicam	20	24 h.
Meloxicam	7.5 - 15	24 h.
Nimesulide	200	12 h.
Nabumetone	1,000-2,000	12-24 h.
Rofecoxib	12.5 - 25	24 h

Celecoxib	200 - 400	12-24 h.

4.4.3 There is no evidence that some NSAIDs are better than others, therefore the one that best fits the patient characteristics should be used.

There is no evidence that the efficacy of combined NSAIDs is greater than each NSAID alone. In a recent review of different meta-analyses and trials comparing the efficacy of the NSAIDs, it was not possible to show that some NSAIDs are more efficacious than others, although it was shown that they have different safety profiles, in favor of ibuprofen [Gotzsche, 2000a]. No controlled clinical trial of sufficient size has compared the efficacy of the NSAIDs to acetaminophen.

There are no convincing studies showing that specific patients benefit more from some NSAIDs than from others. Generally, different NSAIDs are tried until symptom control is reached. A large number of different NSAIDs is available in Spain, thus it is important to know them all, especially their different pharmacokinetic profiles, in order to adapt them to the patient's needs. Some NSAIDs, such as naproxen or acetylsalicylic acid (ASA) have more rapid uptake (about 20 minutes), and thus would be indicated for acute pain. Others with delayed uptake and prolonged action (retard forms) can be administered at night so they will act when the patient wakes up.

Selective cyclooxigenase inhibitors of the COX-2 isoenzyme, or coxibs (refecoxib, celecoxib, and others under investigation), have not been shown to have a safety profile significantly better than other NSAIDs, except in the gastrointestinal system [Schnitzer, 1999; Simon, 1999; Emery, 1999; Langman, 1999]. They should be used in patients at risk for gastroduodenal ulcers. Patients with cardiovascular disease can benefit from the platelet-inhibitory action of the NSAIDs, which is not shared by the coxibs. The SER (Spanish Society of Rheumatology) guidelines for the rational use of coxibs are recommended [SER, 2000a].

4.4.4 The need for co-treatment with gastric protectors should be evaluated on an individual basis.

Since the NSAIDs are associated with a high frequency of gastrointestinal adverse effects and are often used for prolonged periods, the need for a gastric protector should be evaluated in accordance with other existing risk factors for gastroduodenal ulcers.

4.5 Treatment with corticosteroids

4.5.1 The use of oral corticosteroids at low doses is recommended in patients in whom NSAIDs are not effective or are contraindicated for any reason. They can be used instead of NSAIDs or in association with them.

The corticosteroids should never replace treatment with DMARDs, unless their possible role as a disease modifying agent should be shown. They are indicated as the treatment of choice only in the case of pseudopolymyalgic RA (section 3.3).

Corticosteroids should be used:

- When NSAIDs are contraindicated or have a high risk of adverse effects (the elderly, associated morbidity).
- As bridge therapy until the onset of DMARD action.
- When NSAIDs do not effectively control inflammation (generally, by adding corticosteroids to the NSAID treatment).
- In the treatment of pseudopolymyalgic RA.

It is not clear what role the corticosteroids should play in RA treatment. More studies are needed to analyze their efficacy in comparison with the NSAIDs. However, it is doubtful that corticosteroids alone should constitute an alternative to NSAIDs if the latter treatment fails and cannot be considered as first-line treatment when rapid control of inflammation is needed. Some studies that have used a high initial dose, especially in very aggressive RA [Boers, 1997], indicate that treatment with methylprednisolone pulses may constitute an alternative for the initial control of disease activity (always in association with a DMARD and pending the onset of its effect).

4.5.2 Low-doses of oral corticosteroids (<15 mg/day of prednisone or the equivalent) are an effective anti-inflammatory treatment in RA. Doses not exceeding 15 mg/day of prednisone should be used during the shortest possible period of time, and maintenance doses should not exceed 10 mg/day of prednisone or the equivalent.

The use of corticosteroids in RA treatment is controversial, but they are used frequently, especially in the long term. The corticosteroids are better than placebo and similar to or better than NSAIDs or chloroquine in controlling RA activity [Saag, 1997; Criswell, 2000; Gotzsche, 2000b]. Several authors have studied the role of the corticosteroids in RA management from different perspectives: as disease modifiers [Kirwan, 1995; Hickling, 1998; Weiss, 1989] and as "bridge" therapy while waiting for the DMARDs to take effect [Harris, 1983; Caldwell, 1991; Van Gestel, 1995].

The use of corticosteroids has been associated with increased mortality, and their chronic use, at low doses, is related with increased morbidity. It is difficult, however, to separate the effect of corticosteroid use from the fact that patients who usually take them have more severe disease that cannot be controlled with NSAIDs alone.

4.5.3 No corticosteroid preparation has been shown to be superior to any other, thus any of them can be used at equivalent doses.

There is currently no evidence that the most commonly used preparations (prednisone, prednisolone, methylprednisolone, and deflazacort) are significantly different in efficacy or adverse effects when used at equivalent doses.

The dosage of corticosteroids always depends on the underlying disease for which they are prescribed, and on its clinical and biological activity. Whenever possible, a single daily dose should be recommended at the beginning of the day. The dose should be progressively reduced (changing fractionated doses to a single dose before decreasing the dose).

Table 19. Classification of the corticosteroids by duration of action

Short-acting corticosteroids	Hydrocortisone, prednisone, and prednisolone
Intermediate-acting corticosteroids	Methylprednisolone, paramethasone, triamcinolone, and deflazacort
Long-acting corticosteroids	Betamethasone and dexamethasone

4.5.4 Given the association between corticosteroid use and rapid loss of bone mass, the use of vitamin D plus calcium is recommended as a minimum measure; if treatment is expected to exceed 3 months, other preventive osteoporosis treatments (section 8.4) should be evaluated.

4.6 Treatment for pain

4.6.1 Analgesics are indicated to control pain. If there is no response, surgical treatment can be considered, especially to restore function and mobility.

Pain control treatment should be instituted if pain persists despite the adoption of previous disease-control measures. Simple analgesics (e.g., acetaminophen, ASA) should be used first, increasing to the maximum dose of 3-4 g/day in the case of acetaminophen and up to 4gr/day for ASA. If pain persists, dipyridamole, NSAIDs, or codeine may be used.

If pain is due to neuropathy, tricyclic antidepressants (amitryptiline) and some anticonvulsants (gabapentine or carbamazepine) may be used.

When pain is very localized, local analgesics such as capsaicin cream may be used. The ideal dose is 0.75 mg of cream (not available in Spain).

Surgical treatment should be considered when pain does not respond to pharmacological treatments and is due to joint destruction, producing changes in the patient's functional capacity [Dunbar, 1998].

If pain is intense, there is no response to previous analgesic treatments, and surgery is not an option, opiate analgesics may be administered. [Hazes, 1994; Schur, 1999].

4.7 Special considerations in the treatment of elderly patients

4.7.1 Kidney and liver function should be monitored in elderly patients, and the dosage intervals of the drugs eliminated by these routes should be adapted accordingly.

Aging may be accompanied by changes in various organs, especially those responsible for metabolizing and excreting different drugs. This means that the pharmacokinetic and pharmacodynamic properties of a large number of drugs used in elderly patients may be different than in younger individuals [Morgan, 1986; Bird, 1990]. Optimal pharmacological treatment in a particular patient depends on a variety of factors, which are frequently not well known or are difficult to determine; this fact may contribute to the large variability among different individuals in the response to the same drug, a phenomenon that is especially notable in the elderly [Bird, 1990].

The dosage of drugs eliminated by the renal route should be adjusted so that it is similar to what is used in patients with renal failure (decreasing the dose and/or lengthening the intervals between doses). Even in the absence of kidney disease, renal clearance in elderly individuals is decreased by 35-50%. The elderly, and especially those who suffer RA, have reduced muscular mass, which produces a decline in the production of creatinine. Thus, an elderly individual may have a normal creatinine value even though creatinine clearance is altered. [Oates, 1998].

Aging may also produce alternations in hepatic function, thus the metabolization of drugs that are broken down in the liver may also be reduced [Morgan, 1986].

4.7.2 The possible appearance of adverse effects and drug interactions should be monitored in elderly patients.

Adverse drug effects have traditionally been considered more frequent in elderly individuals [Hurwitz, 1969; Dahl, 1990], although little information is available about most drugs in this age group, including those used in RA patients. The lack of data is due to the frequent exclusion of extreme age groups in clinical trials. For this reason, unexpected side effects are not uncommon in individuals with late onset RA, once the drugs have come into generalized use [Morgan, 1986; Dahl, 1990].

In general, elderly patients have more than one disease and need treatment with multiple drugs. This means there is an increased probability of drug interactions and contributes to a larger number of side effects [Buchan, 1991]. The use of multiple drugs in elderly patients is often accompanied by a lack of treatment compliance, which has been estimated at 10% [Bird, 1990].

The DMARDs and the immunosuppressors have a similar efficacy and safety profile in young and old individuals, although for the reasons mentioned above, toxicity should be monitored more closely in the elderly [O´Callaghan, 1986].

4.8 Special considerations in the treatment of rheumatoid arthritis during pregnancy

4.8.1 Women of childbearing age should be informed of the possible effects of RA on pregnancy, in particular, because of the implications for treatment.

There is no evidence that RA has a negative effect on pregnancy outcome. However, treatment with DMARDs can have negative consequences on pregnancy, the fetus, and breastfeeding. Thus, women of childbearing age should know the risk so they can act accordingly.

The symptoms of RA disappear during pregnancy in 70% of cases, to reappear early in the postpartum period [Nicholas, 1988]. When there is improvement, this usually occurs in the first trimester. Nevertheless, the disease commonly fluctuates and, at the very least, cycles of analgesics will be required. The disease almost always recurs early in the postpartum period, and this does not seem to depend either on breastfeeding or on the return of menstruation. Most patients need full doses of NSAIDs in the postpartum period.

Children of mothers with Sjögren's syndrome with Ro antibodies have an increased risk of neonatal lupus.

4.8.2 The use of NSAIDs during pregnancy and breastfeeding should be avoided insofar as possible. Corticosteroids can be used under controlled conditions. DMARDs should be managed on an individual basis, and should preferably be continued during pregnancy.

Teratogenic effects in the early weeks of pregnancy have been observed in animals receiving larger than pharmacological doses of NSAIDs. In both humans and animals, premature closure of the ductus arteriosus has also been observed in the last trimester. NSAIDs are not recommended near the time of delivery due to their inhibitor effects on platelets and the uterine musculature. All NSAIDs are transmitted, in greater or lesser measure, to the mother's milk. For these reasons, the NSAIDs should be avoided in the first and last trimester and during breastfeeding. If necessary, NSAIDs with a short half-life (ibuprofen or ketoprofen) should be used. During breastfeeding, NSAIDs should be taken while the baby is feeding to avoid elevated concentrations in the milk.

There is no evidence that the corticosteroids produce serious adverse effects at average doses during pregnancy, except for promoting glucose intolerance, fluid retention, and hypertension. Consequently, they should be administered under controlled conditions.

Table 20 shows the considerations to be taken into account with regard to DMARD use during pregnancy and breastfeeding. The decision to withdraw continuous treatment during pregnancy should be made on an individual basis. If the disease is aggressive, it is preferable not to withdraw the DMARD (unless it has been shown to affect the embryo, fetus, or infant) and to leave it at the minimum effective dose. Total withdrawal of the drug could provoke a recurrence of disease during pregnancy and a poorer outcome. Thus, for women of childbearing age, treatment involving the least risk for the fetus should be proposed to avoid drastic, last-moment decisions.

Table 20. Use of DMARDs during pregnancy and breast-feeding

Drug	FDA classification*	Transmitted through the placenta	Effects on the mother	Effects on the fetus	Breastfeeding
Auranofin	C	Yes	Not studied	Insufficient data	Compatible**
Aurothiomalate	C	Yes	Not studied	Complex malformation of the central nervous system has been described in animals.	Compatible**
Azathioprine	D	Yes	Contraindicated during pregnancy	Intrauterine growth retardation, premature birth. Transitory immunosuppression in the neonate. Potential alternation of the germ cells.	Contraindicated due to potential immunosuppression
Cyclophosphamide	D	Not studied	Not studied	Severe malformations	Contraindicated due to bone marrow depression
Cyclosporin A	C	Yes	Not studied	Intrauterine growth retardation, premature birth	Contraindicated due to potential immunosuppression
Antimalarials: Chloroquine, Hydroxychloroquine	C	Yes	Rare	Rare	Compatible, with precautions***
D-penicillamine	D	Yes	Not studied	Connective tissue abnormalities, cutis laxa.	Not studied
Etanercept	B	Not studied	Not studied	Unknown	Not studied
Infliximab	C	Not studied	Not studied	Unknown	Not studied
Leflunomide	X	Yes	Contraindicated in pregnancy	Unknown	Not studied
Methotrexate	X	Yes	Spontaneous abortion	Fetal abnormalities (including cleft palate and hydrocephaly)	Contraindicated. Potential accumulation in the infant's tissues
Sulphasalazine	B and D near time of delivery	Yes	Not studied	Kernicterus if administered near delivery	Compatible, with precautions***

*** FDA classification of drug teratogenicity:**
Category A: Appropriate and well controlled trials have not shown risk for the fetus in the first trimester of pregnancy, and there is no evidence of risk in subsequent trimesters.
Category B: Indicates one of the following:
a) No evidence of teratogenic effects in animal studies, but this has not been confirmed in humans.
b) Some evidence of teratogenic effects in animal studies, but this has not been confirmed in humans.
Category C: Indicates one of the following:
a) Teratogenic effects have been detected in animal studies, but no studies in humans have been carried out.
b) No studies have been carried out (either in animals or in humans).
Category D: Studies have shown teratogenic effects on the human fetus, but at times the benefit obtained with the use of these drugs may exceed the expected risk (use in extreme situations of possible maternal death).
Category X: Drugs that have unquestionably been shown to have clear teratogenic effects and whose risks greatly exceed the possible benefit obtained.
** 20 % of the dose administered is excreted in the milk. Rashes, hepatitis, and blood disorders have been described in infants.
*** 7% of the dose is secreted in the milk. There is evidence of accumulation in the infant if renal excretion is reduced.
**** Between 40% and 60% of the dose administered is secreted in the milk. Bloody diarrhea in the infant has been described.

CHAPTER 5. CRITERIA FOR REPONSE TO TREATMENT

5.1 The objective of RA treatment is to induce complete disease remission or, alternatively, to achieve the best possible response.

RA patients who have spontaneous or drug-induced remissions in the course of their disease have a better medium-term outcome than those who have persistent clinical activity [Eberhardt, 1998]. However, the rates of complete remission with DMARDs and/or corticosteroids are low (18-25%) [Wolfe, 1985; Prevoo, 1996; Harrison, 1996; Eberhardt, 1998] and are rarely prolonged. Consequently, criteria to evaluate the patient's clinical improvement are needed to aid the clinician in making treatment decisions. Complete disease remission, or at least attainment of the lowest possible level of inflammatory activity, is the only way to improve disease outcome and to assure the most favorable evolution for the patient.

Two basic approaches to defining clinical remission in RA have been described: the ACR criteria and the EULAR criteria.

5.1.1 ACR criteria for clinical remission

- Morning stiffness absent or not exceeding 15 minutes
- No fatigue
- No joint pain (by clinical history)
- No joint tenderness
- No soft tissue swelling in joints or tendon sheaths
- Normal erythrocyte sedimentation rate

The presence of five or more of these criteria for at least 2 months is sufficient to classify a patient as in complete remission, with a sensitivity of 72-80% and a specificity of 96-100% [Pinals, 1981; Wolfe, 1985]. The predictive values of these criteria may vary in different populations [Alarcón, 1987]. Their main disadvantages are the lack of guidelines on how to measure them, the fact that they are dichotomous (meaning that small changes in disease activity may change the classification), and that two of the criteria (fatigue and morning stiffness) are not included in the parameters recommended for the evaluation of RA patients [van Riel, 1992; Tugwell, 1993; Felson, 1993b; Boers, 1994; Wolfe, 1999b].

5.1.2 EULAR criteria for clinical remission

The EULAR criteria use the DAS as a continuous variable of disease activity [Van der Heijde, 1990]. A cut-off point below 1.6 on the DAS is consistent with the ACR definition of remission [Prevoo, 1996]. Since the measurement scale is continuous, the cut-off point recommended by the EULAR may vary depending on future investigations.

5.2 Patients with RA should be clinically monitored for an indefinite period of time. Patients in complete disease remission should be seen every 6 months or 1 year, and patients with recent disease onset, frequent flare-ups, or persistent activity should be seen "on demand" (in general, every 1 or 2 months), depending on the treatment used and disease activity, until control is achieved.

No treatment has been shown to cure RA, thus all patients who suffer this disease should be monitored clinically for an indefinite period.

Patients in complete disease remission should be seen every 6 or 12 months. To avoid an overload of patients, they can be seen in primary care during the periods between rheumatologist appointments so as to assure clinical and laboratory monitoring and permit rapid referral to the specialist in case of disease reactivation and/or adverse effects.

Patients with recent disease onset, frequent flare-ups, or persistent activity should be seen "on demand," depending on treatment used and disease activity, until the best possible control is achieved. These patients should be monitored every 1 or 2 months, at the same time as laboratory tests are done.

5.3 Follow-up of patients with RA should be based on longitudinal monitoring of the parameters described in the initial evaluation: joint pain and inflammation, global pain assessment by the patient, global disease assessment, functional disability, acute phase reactants, and radiologic damage.

No studies have established the core set of parameters to be used in the routine clinical monitoring of patients with RA.

The quantitative measurement of disease characteristics (e.g., the Ritchie index) offers several advantages: it provides information about disease severity that is valid, reliable, and of proven sensitivity; it can be used to classify the patient within the continuous spectrum of disease; and it can be used to guide the decisions that must be made by the physician, patient, and/or third parties.

One way to improve the quality of care for patients is to apply the treatment response criteria designed for use in clinical trials to daily clinical practice. Thus, it is proposed that the same parameters assessed at the initial evaluation be used to monitor patients and evaluate their response to treatment: pain and joint inflammation, global pain assessed by the patient, global disease activity assessed by the patient and by the physician, functional disability, and acute phase reactants. The same instruments used in the initial evaluation should be used in follow-up.

5.4 The criteria for treatment response applied to individual patients should take into account: a) changes in disease activity and b) current level of activity. The clinician should evaluate the response to treatment, classifying it as satisfactory (complete remission of disease or sufficient even if not complete remission) or unsatisfactory (complete or almost complete lack of improvement). The evaluation can be made in accordance with any of the response criteria proposed in sections 5.4.1, 5.4.2, 5.4.3, and 5.4.4.

Many approaches to defining clinical improvement in RA have been described, most of them focusing on the application to clinical trials. There is no published clinical experience in daily practice with any of the response indices developed for clinical trials. Although there is no scientific evidence to support a uniform recommendation, in the near future it is likely that these types of studies will be carried out, new indices will appear, or existing ones will be modified for application in daily practice.

The treatment response criteria used throughout this guideline are based on two categories: **satisfactory response,** meaning complete remission of disease or a "sufficient" response, even though complete remission is not achieved, and **unsatisfactory response,** meaning complete or almost complete lack of improvement. The clinician can apply different response criteria to classify a patient in one of these categories. The following sections describe four approaches that have been explored in the literature on rheumatology: the ACR criteria for improvement [Felson, 1995], the EULAR definition of response [Boers, 1994], the simplified Scott index [Scott, 1993], and the modified Paulus criteria [Paulus, 1990].

5.4.1 ACR response criteria [Felson, 1995]

The ACR response criteria define a dichotomous result (response/no response) according to the following criteria:

- At least 20% improvement in the painful joint count and in the swollen joint count; and
- At least 20% improvement in at least three of the following parameters: ESR or CRP, physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, and physical disability.

These criteria are known as the ACR20, reflecting the need for a 20% improvement in each parameter, which is considered the clinically relevant cut-off point. Some authors have proposed that this requirement be raised to 50% (ACR50) or 70% (ACR70). The ACR improvement criteria use the core variables proposed by the ACR itself, which can be applied without major problems in daily practice [Felson, 1993b]. The fact that the criteria do not consider the current activity level, however, limits their application in daily clinical practice unless they are adapted to take this factor into account. The ACR improvement criteria are likely to be modified in the near future; in the meantime, it is proposed that they be adapted as follows [SER, 2000b]:

- **Satisfactory response:** Meeting the ACR20 criteria, fewer than 6 swollen joints, and no impairment of any joint that, for the particular patient, produces intolerable loss of functional capacity in the opinion of the patient or physician.
- **Unsatisfactory response:** Not meeting the criteria for satisfactory response.

5.4.2 EULAR response criteria

The EULAR response criteria use the Disease Activity Scale (DAS), which combines different clinical information into a single index that can be used to classify patients in different categories. Although the proliferation of modified DAS scales [Van der Heijde, 1998] has caused some confusion, two basic formulas have been validated [Van Gestel, 1998] and can be applied to the EULAR improvement criteria: the original DAS [Van der Heijde, 1990; van der Heijde, 1992a], which uses the Ritchie articular index [Ritchie, 1968] and a count of the number of swollen joints out of 44 joints, and the DAS28, which uses a non-graduated count of 28 joints (Appendix 1).

Unlike the ACR criteria, the EULAR definition takes into account both the patient's current status and the amount of improvement. It has been shown to have comparable validity to the ACR response criteria in clinical trials of RA patients [Van Gestel, 1999]. The definitions of satisfactory and unsatisfactory response as a function of the original DAS and the DAS28 are shown in Table 21.

Table 21. EULAR definition of response

EULAR DEFINITION OF RESPONSE (DAS)			
	DAS decrease		
Current DAS	**>1.2**	**0.6 - 1.2**	**<0.6**
<2.4	Satisfactory	Unsatisfactory	Unsatisfactory
2.4 - 3.7	Unsatisfactory	Unsatisfactory	Unsatisfactory
>3.7	Unsatisfactory	Unsatisfactory	Unsatisfactory

EULAR DEFINITION OF RESPONSE (DAS28)			
	DAS28 decrease		
Current DAS28	**>1.2**	**0.6 - 1.2**	**<0.6**
<3.2	Satisfactory	Unsatisfactory	Unsatisfactory
3.2 - 5.1	Unsatisfactory	Unsatisfactory	Unsatisfactory
>5.1	Unsatisfactory	Unsatisfactory	Unsatisfactory

5.4.3 Simplified Scott index [Scott, 1993]

The simplified Scott index takes into account the change in disease activity and the current activity level, which makes it possible to apply it to individual patients. It is easy to apply, which facilitates its use during physician visits, but it requires further validation before it can be recommended for routine use. Its scoring system from 0 to 6 (a total of 7 categories) may be too wide for classification of treatment response.

It is based on the following criteria:

- Morning stiffness absent or lasting no more than 15 minutes
- At least 50% reduction in pain
- No more than 3 painful joints
- No more than 3 swollen joints
- ESR less than or equal to 30
- Functional improvement greater than or equal to 40%.

For each category, the patient receives 1 point if the response criterion is met after 6 months of treatment; this gives a range of possibilities from 0 (no improvement) to 6 (complete improvement).

5.4.4 Modified Paulus criteria [Paulus, 1990]

These criteria have been used in recent clinical trials [O´Dell, 1996]. They define a dichotomous result (response/no response) in accordance with the following criteria:

- Morning stiffness absent or reduced by 50%
- 50% decrease in the number of tender joints
- 50% decrease in the number of swollen joints

- ESR less than 30 mm/hr for women and less than 20 mm/hr for men.

These criteria combine reduction in disease activity with the patient's current status.

5.4.5 Physician's subjective assessment of disease activity

This is the most commonly used clinical criterion in daily practice. It is not recommended for use as the only criterion of response. If the physician's assessment of disease activity is the only criterion used to judge response to treatment, this assessment needs to be adapted to the treatment objectives (complete remission of disease or achieving the best possible response). It should be a combination of objective and quantifiable parameters evaluating disease activity, joint pain, and health status, with the final results classified into the categories of satisfactory or unsatisfactory response.

CHAPTER 6. ADVERSE EFFECTS OF DRUGS USED IN THE TREATMENT OF RHEUMATOID ARTHRITIS

6.1 Antimalarials

6.1.1 The antimalarials are relatively safe drugs if they are used at the recommended doses. The most frequent side effects are gastrointestinal toxicity, skin rashes, and constitutional symptoms. Most of these side effects are reversible and do not require discontinuation of treatment [Maksymowych, 1987).

6.1.2 *Monitoring:* A baseline opthalmological examination should be made in patients over 40 years of age and/or with a family history of ocular disease [ACR Committee, 1996]. All patients should receive an opthalmological examination including funduscopic and visual field evaluation every 6-12 months. Patients with kidney failure or those who take the drug for more than 10 years should be monitored more frequently.

6.1.3 *Contraindications:* Allergy to 4-aminoquinoline derivatives. Retinopathy or visual field deterioration.

Hydroxychloroquine is generally better tolerated and less toxic than chloroquine [Finbloom, 1985]. Toxicity is more closely related with daily dose than with cumulative dose or duration of treatment [Rynes, 1983].

The most frequent contraindication is **gastrointestinal toxicity** with nausea, vomiting, pain, and bloated abdomen. In these cases, if the patient was taking chloroquine, the dosage can be reduced by half or the patient can be switched to hydroxychloroquine. Since its bioavailability is not reduced by taking it with food, it can be administered with meals, which improves tolerance.

Skin toxicity rarely leads to withdrawal of the medication. Side effects include maculopapular, scaly, or morbilliform rashes, urticaria and pruritus; loss and graying of hair; lichenoid reaction; and exfoliative dermatitis. In cases of yellowish hyperpigmentation of the skin and mucosa, which generally appears after periods of prolonged treatment, especially in patients treated with quinacrine, it may be useful to reduce the dose by half.

Ocular toxicity is very infrequent if the recommended doses are not exceeded. It can be detected early if periodic ophathalmological (funduscopic and visual field) examinations are performed.

There are two types of ocular toxicity:

- Deposits on the corneas or the ciliary bodies, accompanied by blurry vision, photophobia, visual halos, or difficulty in focusing, which generally disappear when treatment is discontinued.
- Retinopathy, which may lead to lasting loss of vision and may progress despite withdrawal of treatment.

Other rare side effects, such as neuromyopathy (< 1%), usually with symptoms of myopathy predominating, resolve by discontinuing treatment. In patients with a deficiency of glucose 6-phosphase dehydrogenase (G6PD), antimalarials, and especially chloroquine, can lead to hemolytic anemia. Cases of aplastic anemia in patients treated with quinacrine have also been reported.

6.2 Anti-TNF agents

6.2.1 The safety profiles of the two commercial preparations (etanercept and infliximab) are not sufficiently well known. Their potential adverse effects, however, may be related with increased risk of infection, tumors, hematologic changes, and multiple sclerosis.

6.2.2 *Monitoring:* Rule out acute or chronic infection before initiating treatment. Rule out the presence of active or latent tuberculosis. Do not use live vaccines. Monitor the appearance of neoplasms.

6.2.3 *Contraindications:* Sepsis or clinically manifest infections and/or abscesses. Past medical history of hypersensitivity to infliximab or other murine proteins.

Infections are infrequent [CCOHTA, 1999]. Although the use of anti-TNF agents exacerbates the outcome of sepsis [Fisher, 1996], there is no evidence to confirm a higher incidence of serious infections in patients treated with these drugs [Moreland, 1997; Maini, 1998; Maini, 1999; Moreland, 1999; Weinblatt, 1999a].

To date, 28 cases of tuberculosis infection have been reported, both miliary and extrapulmonary (9 in the United States and 19 in Europe), one of which had a fatal outcome. In most cases, the infection presents shortly after the second or third infusion. Given the severity of these complications, the Spanish Medicines Agency, in agreement with the European Agency for the Evaluation of Medicinal Products, recommends evaluation for active or latent (inactive) tuberculosis before beginning treatment with infliximab. The evaluation should include previous history of and/or contact with the disease, chest X-ray, and tuberculin test. Tuberculin tests in severely ill or immunodepressed patients may have a false negative result. If latent (inactive) tuberculosis is diagnosed, preventive measures should be taken to avoid activating the tuberculosis and to evaluate the benefit-risk relation before beginning treatment with infliximab. The patient should be instructed to inform the physician of the appearance of signs and/or symptoms that suggest tuberculosis, for example, persistent cough, weakness/weight loss, and low-grade fever. If active tuberculosis is suspected, infliximab treatment should be discontinued until the diagnosis is ruled out or the infection has been treated according to accepted guidelines.

For both preparations (infliximab and etanercept), upper respiratory infection is the most frequently reported side effect; this is usually mild and does not require discontinuation of treatment.

Since the potential immunosuppressive effect of anti-TNF agents may favor infection, vaccination with live vaccines while they are being used is not recommended. (Although this guideline focuses on RA in adults, children should be up-to-date on all their vaccinations before beginning treatment with etanercept [CCOHTA, 1999].)

Some authors have mentioned the development of neoplasia as an adverse effect [Koopman, 1998; Camussi, 1998], although there is no evidence of a higher incidence of tumors in patients treated with anti-TNF agents. Pending the results of long-term studies on the use of anti-TNF agents and their association with tumors, it is essential to monitor the patient clinically for possible neoplasms.

In pharmacological surveillance studies following the commercialization of etanercept, 10 cases of **blood disorders** have been reported in patients treated with this drug (of an estimated total of 5,500 patients, 3 aplastic anemias and 7 pancytopenias), with 5 deaths attributed to this cause (Pharmacological surveillance report from Wyeth).

Nine cases treated with etanercept have presented with abnormalities, detected by magnetic resonance imaging, compatible with **demyelinating disease of the central nervous system.** Five of these patients were diagnosed with multiple sclerosis and one with possible multiple sclerosis. It is difficult at present to establish a causal relation between the drug and multiple sclerosis, although anti-TNF agents are known to exacerbate the clinical course of this disease [LMSSG, 1999].

Local reactions at the injection site (erythema, localized pain, edema) occurred in 49% of patients treated with 25 mg of etanercept [Moreland, 1999] and in 42% of those who received etanercept plus methotrexate [Weinblatt, 1999a]. These complications are generally self-limiting, lasting 3-5 days; they tend to appear in the first month of treatment and do not require its interruption. Five percent of patients treated with infliximab have had non-specific symptoms during intravenous administration such as fever, chills, chest pain, hypertension or hypotension, pruritus/urticaria, headache, sinusitis, rhinitis, and non-specific cardiorespiratory symptoms. In 16% of this 5% of patients, the infusion had to be discontinued [Remicade, 1999].

The appearance of antinuclear and anti-DNA antibodies has been described for both preparations more frequently than in control groups; in the case of etanercept, this was not associated with autoimmune disease.

6.3 Azathioprine

6.3.1 The most frequent side effects of azathioprine are gastrointestinal intolerance, blood disorders, and infections.

6.3.2 *Monitoring:* Baseline laboratory tests should be performed, including a complete blood count (leukocytes, hemoglobin, and platelets), creatinine, and liver function tests. Thereafter, a blood count should be made every 1-2 weeks while the dosage is being adjusted, and every 1-3 months upon reaching a stable dose [ACR Committee, 1996]. Liver function tests are recommended every 6-8 weeks. The dose should be reduced in patients with renal failure. Extreme precaution should be taken if it is used concurrently with allopurinol or with the angiotensin-converting enzyme inhibitors.

6.3.3 *Contraindications:* Known neoplastic disease.

The most frequent **gastrointestinal symptoms** (20%) are anorexia, nausea, and vomiting. Less frequent are diarrhea (<1%) or elevated liver enzymes (5%). Although these side effects may make it necessary to discontinue the drug (10%), they usually improve or resolve by reducing the dose.

Blood disorders are dose-dependent; the most frequent are leukopenia (25%) and thrombocytopenia (5%), although cases of pure red-cell aplasia have been described. Mild blood disorders may resolve by reducing the dose. A xanthine oxidase deficiency increases side effects in general and hematologic ones in particular [Black, 1998]. The use of allopurinol (a xanthine oxidase inhibitor) should be avoided; if it must be used, the AZA dose should be reduced (50-75%), and the leukocyte count should be monitored more frequently.

Infections appear in about 10% of patients treated with AZA. Viral infections are the most frequent, especially herpes zoster. Bacterial infections usually develop in patients with neutropenia [Singh, 1989].

A hypersensitive reaction has been described in the first weeks of treatment, which includes fever, general malaise, arthralgias/myalgias, skin lesions, leukocytosis, elevated liver enzymes, and even hypotension and shock [Blanco, 1996].

The risk of neoplasia appears to be increased in RA patients (relative risk 2.2-8.7), mainly skin cancers and hematologic neoplasias [Silman, 1988].

6.4 Cyclophosphamide

6.4.1 Cyclophosphamide has frequent adverse effects, which vary in relation with dose and route of administration [Decker, 1973;Williams, 1980]. Intravenous administration is recommended. Most side effects are reversible by discontinuing the drug. The most frequent side effects are gonadal, urologic, and bone marrow toxicity, neoplasms, and infections. Other frequent but less important effects are alopecia, nausea, and vomiting.

6.4.2 *Monitoring:* Complete blood count every 1-2 weeks during the first 2-3 months of treatment, then every 2-4 weeks once the dosage has been stabilized [Clements, 1986]. In patients with pulses of intravenous therapy, a blood count should be obtained before each infusion of cyclophosphamide. Monthly tests should be obtained for liver enzymes, urinalysis, and urinary sediment. If microscopic hematuria is detected, other, more specific studies are indicated, such as cystoscopy and urinary cytology.

6.4.3 *Contraindications:* Pregnancy, chronic or active infection, liver disease, or history of neoplasia. Renal failure is a relative contraindication that requires adjustment of the dosage.

CPA is a useful drug in the treatment of serious RA complications. Administration by intravenous pulses is recommended, since they are as effective as oral administration and have less serious side effects.

Gonadal toxicity from CPA is produced in women at the level of the primordial and antral follicles, giving rise to oligomenorrhea and amenorrhea [Warne, 1973]. In men it is produced in the epithelial germ layer of the seminal vesicles, causing azoospermia or oligospermia, and testicular atrophy or reduction in size [Fairley, 1972; Schilsky, 1980]. Libido and sexual function are normally not affected [Sherins, 1973; Schilsky, 1980]. Accepted risk factors for infertility are age over 25 years, concomitant radiation therapy, and prolonged treatment [Roubenoff, 1988].

Table 22. CPA dosage producing toxicity

Gender	Age (years)	CPA dosage producing toxicity
Men [Kovarsky,1983]		≥18 g
Women [Damewood, 1986]	20-29	20.4 g
	30-39	9.3 g
	≥40	5.2 g

Intravenous treatment with CPA entails a risk of sustained amenorrhea (understood as lasting over 1 year), which is associated with patient age, dose administered, and duration of treatment [Schilsky, 1980; Damewood, 1986; Boumpas, 1993; Ramsey-Goldman, 1997]. Women who do not develop amenorrhea may experience early menopause [Fosdick, 1968; Miller, 1971; Roubenoff, 1988].

Oral CPA administration may provoke amenorrhea in up to 36% of cases, and is irreversible in 27% [Wang, 1995].

Table 23. Percentage of women treated with CPA who develop amenorrhea

		% of women with amenorrhea
Age	≤ 25 years	12
	26-30 years	27
	≥31 years	62
Duration of treatment	Short cycles (<7 bolus injections)	12
	Long cycles (>15 bolus injections)	39

Although recovery of spermatogenesis has been described after suspending treatment in young patients treated with CPA for short periods [Fairley, 1972; Trompeter, 1981], recovery of ovarian function or spermatogenesis is uncertain, and irreversible sterility may result [Fosdick, 1968; Miller, 1971; Fairley, 1972] Thus, freezing of ova or sperm is recommended before beginning treatment with CPA.

The risk of infertility in women may be reduced by treatment with gonadotropin inhibitors [Langevitz, 1992; Ataya, 1993] or by using oral contraceptives [Chapman, 1981], and in men by the use of testosterone [Masala, 1997].

The **urologic toxicity** of CPA consists basically of the development of hemorrhagic cystitis [Hutter, 1969; Decker, 1973; Aptekar, 1973; Townes, 1976; Plotz, 1979; Fauci, 1983; Ansher, 1983; Hansen, 1983], vesicle fibrosis [Johnson, 1971], and squamous cell and transitional cell bladder cancer [Worth, 1971; Wall, 1975; Ansell, 1975; Plotz, 1979; Baker, 1987; Pedersen-Bjergaard, 1988; Thrasher; 1990].

Hemorrhagic cystitis is present in 15-30% of patients treated with CPA [Fauci, 1983], and its appearance, the same as with vesicle fibrosis, is directly related with oral administration. Patients treated intravenously do not develop hemorrhagic cystitis or neoplasms [Plotz, 1979; Austin, 1986; Balow, 1987; Klippel, 1987a].

There is a high risk of developing malignant vesicle neoplasm with total doses exceeding 80 g. Tumors may appear early or several years after initiation of treatment. The risk remains even years after discontinuing treatment [Baker, 1987; Hoffman, 1992; Radis, 1995]. The development of carcinoma of the bladder does not appear to be related to pre-existing hemorrhagic cystitis [Pedersen-Bjergaard, 1988].

Abundant oral (2-3 liters in 24 hours) or intravenous hydration and frequent urination are recommended to decrease vesicle toxicity [Ahmed, 1984; Balow, 1987; Klippel, 1987b]. The use of acetyl cysteine [Steinberg, 1981] or 2-mercaptoethane sodium sulfonate together with intravenous CPA also reduces vesicle toxicity [Bryant, 1980; Brock; 1982; Hows, 1984; Ehrlich, 1984; Nashel, 1985].

If the patient shows signs of reduced vesicular volume (e.g., polakiuria), CPA should be discontinued and cystometry performed. If there is hematuria suggesting the presence of incipient hemorrhagic cystitis or other urological complications, treatment should be discontinued and cystoscopy and urinary cytology should be performed.

The inhibition of DNA replication produces **bone marrow toxicity,** which is cumulative.

Its hematologic effects are:

- Neutropenia. 32% of patients treated with high doses (150 mg) and 6% of those treated with low doses (75 mg).
- Leukopenia [Weinstein, 1985]. Dose-dependent. Maximum suppression occurs 8-12 days after intravenous administration [Klippel, 1998]. Avoid leukocyte count dropping below 3,000/mm^3

and neutrophils below 1,000/mm^3, adjusting the dosage until the desired levels are regained. Avoid concomitant treatment with allopurinol due to the increased risk of leukopenia [Clements, 1986].
- Anemia and thrombopenia are less frequent, and aplasia, if it occurs, is transitory.

Several authors have studied **tumor development** in association with the use of CPA. Whereas some have found a high incidence of neoplasms [Baltus, 1983], others have not found significant increases [Kirsner, 1982]. There have been reports in the literature of leukemias and malignant lymphomas [Love, 1975; Grunwald, 1979; Penn, 1981; Wheeler, 1981; Baltus, 1983; Baker, 1987], sarcomas [Steinberg, 1981], and skin cancer [Baltus, 1983; Baker, 1987; Radis, 1995]. The factors that appear to be related with the development of carcinomas are total CPA dose [Greene, 1986; Baker, 1987] and duration of treatment [Pedersen-Bjergaard, 1985; Baker, 1987].

Upper respiratory tract infections are related with the use of CPA, as are **bacterial, fungal, and viral infections** [Bradley, 1989; Kattwinkel, 1991], especially with herpes zoster (incidence from 21 to 33%) [Moutsopoulos, 1978; Balow, 1987; Klippel, 1987a; Klippel, 1998]. Risk factors are considered to be the involvement of multiple organs, concomitant treatment with high-dose steroids, and leukocyte counts under 3,000 cells/mm^3 [Pryor, 1996]. Patients being treated with CPA and high-dose steroids should receive prophylaxis for *Pneumocystis carinii* with trimethoprim-sulphamethoxazol [Ognibene, 1995].

Other adverse effects that have been observed are gastrointestinal toxicity (mainly nausea and vomiting) [Belmonte, 1988; Fox, 1994; Klippel, 1998], pulmonary toxicity [Patel, 1976; Medrano, 1986; Klippel, 1998], cardiac toxicity [Appelbaum, 1976; Klippel, 1998], hepatic toxicity [Bacon, 1982; Goldberg, 1985; Fox, 1994 Klippel, 1998], ophthalmological toxicity [Jack, 1981], hypersensitive reactions [Klippel, 1988; Knisack, 1994], hypogammaglobulinemia [Fauci, 1989], alopecia [Kovarsky, 1983; Belmonte, 1988; Fauci, 1989], nail abnormalities [Klippel, 1998], and inadequate secretion of the antidiuretic hormone [De Fronzo, 1973; Steinberg, 1981; Bressler, 1985; Klippel, 1998]. These effects are dose-dependent, occurring more frequently at high drug doses.

6.5 Cyclosporin A

6.5.1 The most serious and relatively frequent adverse effects are nephrotoxicity and hypertension. Both are dose-dependent and constitute the most important limitation to their use.

6.5.2 *Monitoring:* Before beginning treatment, the following tests should be obtained: blood pressure (two measurements), complete blood count, liver and kidney biochemistry (with special attention to serum urea and creatinine), and urinalysis with sediment.

Blood pressure, renal function, and K^+ and Mg^{++} electrolytes should be monitored every 2 weeks during the first trimester and monthly thereafter.

If the dose is changed or if there is an increase in creatinine levels or blood pressure, the patient should be monitored weekly until stabilization. If the levels of serum creatinine increase by more than 30% with respect to baseline, the dose should be reduced by 25-50%.

If renal function does not improve in 1 month, cyclosporin should be discontinued; it may be resumed if creatinine returns to levels within 10% of the pre-treatment value.

If hypertension is detected, treatment with angiotensin converting enzyme inhibitors or beta-blockers may be initiated. The drug of choice is nifedipine (which does not increase the levels of cyclosporinemia).

6.5.3 *Contraindications:* co-existing cancer (except non-melanoma skin cancer), uncontrolled hypertension, renal dysfunction, uncontrolled infections, and primary or secondary immunodeficiency [Cush, 1999].

The **nephrotoxicity** produced by CSA may provoke:

- Reversible functional changes: tubular dysfunction (reduced reabsorption of Mg^+, reduced secretion of K^+, and reduced excretion of uric acid with resulting hypomagnesemia, hypercalcemia, and hyperuricemia) and vascular dysfunction (vasoconstriction, reduced renal perfusion and filtration with elevated serum urea and creatinine).
- Structural changes: reversible proximal tubular disease and vessel disease (affecting the afferent arterioles that condition glomerulosclerosis; ischemia, tubular atrophy, and interstitial fibrosis.

Reversible changes are frequent, while persistent structural changes are rare and usually present with elevated serum levels of CSA and associated risk factors such as concurrent treatment with

nephrotoxic drugs, pre-existing nephropathy, and hypertension [Grant, 1987; Land, 1988; Morris, 1988; Mihatsch, 1989; Landewé, 1996; Rodríguez, 1996]. At the usual doses (2.5 to 5 mg/kg/day), renal dysfunction is not severe and is rapidly reversible [Dougados, 1989; Tugwell, 1990; Boers, 1990; Van Rijthoven, 1991; Landewé, 1994]. High doses (from 10 mg/kg/day at initiation of treatment) produce more severe and less reversible changes in renal function (Boers, 1988; Berg, 1989].

To prevent structural nephropathy the following recommendations are made:

- Exclusion of patients with potential risk factors such as renal dysfunction
- Limitation of the maximum dose to 5 mg/kg/day
- Use of the smallest possible maintenance dose, depending on the level of serum creatinine
- Frequent and careful monitoring of renal function
- Routine clinical examination and laboratory tests [Panayi, 1993; Panayi, 1994; Tugwell, 1995a].

The frequency of **hypertension** is 10-20% [Cohen, 1992]. The patient should have normal blood pressure before beginning therapy. If diastolic BP is higher than 95 mmHg or systolic BP higher than 160, the dose should not be increased. If hypertension is present (diastolic BP >105 mmHg or sustained at more than 95 mmHg) at two consecutive measurements, antihypertensive treatment should be initiated or the CSA dose reduced [Panayi, 1993; Panayi, 1994].

Other **non-renal adverse effects** related with the use of CSA are gastrointestinal effects (dyspepsia, nausea, vomiting, abdominal pain, and diarrhea), hypertrichosis, gingival hypertrophy, and paresthesias. These are usually dose-dependent and are reversible by reducing the dose of the drug. Less frequent manifestations are fatigue, leukopenia, sinusitis, arthralgias/myalgias, flushing, ocular pain, gynecological symptoms (menorrhagia, breast hypertrophy or pain), hyperlipidemia, hepatic abnormalities (hyperbilirubinemia and hypertransaminemia), and neurological effects (headache, tremor). Other rare adverse reactions, present in 2% or less of patients are: conjunctivitis, fever, allergic reactions (exanthema, angioedema with reduced C1-esterase inhibitor), anemia, thrombocytopenia, anorexia, confusion, convulsions, weak and broken nails, and peptic ulcer [Klintmalm, 1981; Maddux 1986; Grant, 1987; Tindall, 1987; Lin, 1989; Cairns, 1992; Arellano, 1993; Fauci, 1993; Forre, 1994; Furst, 1994b; Tugwell, 1995b; Klippel, 1998; Rodríguez, 1998].

6.6 D-penicillamine

6.6.1 The most frequent side effects of D-penicillamine are skin lesions, gastrointestinal symptoms, and renal involvement.

6.6.2 *Monitoring:* Baseline tests should be performed, including a complete blood count, creatinine, and urinalysis (including sediment). These tests should be repeated every 2 weeks until a stable dose is reached and every 1-3 months thereafter (ACR Committee, 1996].

6.6.3 *Contraindications:* Kidney disease, blood disorders (leukopenia, thrombocytopenia).

All types of **skin lesions** may appear (25-50%), from morbilliform and pruritic rashes to pemphigus-like lesions [Willemsen, 1990]. These generally disappear when medication is withdrawn [Munro, 1997]. Muscosal lesions, especially mouth ulcers, are less frequent.

About 30% of patients have **gastrointestinal symptoms** (nausea, anorexia, abdominal pain, and diarrhea) during the first months of treatment. These symptoms usually disappear even though DP is continued, although it is sometimes necessary to suspend it [Munro, 1997].

About one fourth of patients report dysgeusia (altered sense of taste) during the first months of treatment. This symptom usually disappears spontaneously despite continued treatment, or it may improve following the administration of zinc [Jaffe, 1977].

Some 30% of RA patients treated with DP have some type of **renal involvement.** This most frequently takes the form of proteinuria accompanied by microscopic hematuria [Stein, 1980]. About 7% of patients develop a nephrotic syndrome secondary to membranous glomerulonephritis which disappears completely in a variable period of time after discontinuing treatment [Hall, 1988a]. Much less frequent is the development of acute renal failure secondary to a rapidly progressive "half-moon" glomerulonephritis [Ntoso, 1986].

Other side effects are **blood disorders** (thrombocytopenia 8-10% and leukopenia), pulmonary toxicity (bronchiolitis obliterans <1%), breast hyperplasia [Taylor, 1981], development of autoimmune processes, systemic lupus erythematosus [Chalmers, 1982], inflammatory myopathies [Lund, 1983], myasthenia gravis [Andonopoulos, 1994], and Goodpasture syndrome [Munro, 1997].

6.7 Leflunomide

6.7.1 The most frequent adverse effects in published clinical trials are gastrointestinal and respiratory. These effects are generally mild, are not dose-dependent, and do not require discontinuation of treatment.

6.7.2 *Monitoring:* Liver enzymes should be monitored, initially every 4 weeks until a stable treatment dose is reached. If they are elevated to over twice the maximum reference value, the dose should be reduced to 10 mg/day. If a reduction to 1.2 times the maximum reference value is not obtained, leflunomide should be discontinued and cholysteramine or charcoal administered. If the transaminases remain elevated, a liver biopsy should be performed [Weinblatt, 1999b; Arava, 1999]. Periodic monitoring for possible anemia and leukopenia is recommended.

6.7.3 *Contraindications:* Serious immunodeficiency, dysplasias, uncontrolled infection (due to the theoretical possibility of immunosuppression), moderate or severe renal failure (there is no experience in this group of patients), liver function disorder, significant bone marrow disorder, severe hypoproteinemia.

The most frequent adverse effects in published clinical trials are **gastrointestinal** (diarrhea 17%, nausea 9%, and abdominal pain 6%) and **respiratory** (upper tract infections 15% and bronchitis 7%). These effects are generally mild, are not dose-dependent, and do not require that treatment be discontinued. [Mladenovic, 1995; Weinblatt, 1999b; Arava, 1999; Smolen, 1999; Strand, 1999;].

Elevated transaminases have been described in about 6% of RA patients treated with 25 mg/day, and are reversible on discontinuing treatment. Generally these elevations do not exceed twice the normal maximum value and they tend to remit over time [Mladenovic, 1995; Smolen, 1999; Weinblatt, 1999b; Strand, 1999]. Cases of severe liver disease have been reported, some resulting in death, most of which occurred during the first 6 months of treatment.

Other less frequent effects are hypertension (10%), headache (7%), vertigo (4%), weight loss (4%), and reversible alopecia (1% with a dose of 10 mg/day and 7% with 25 mg/day) [Mladenovic, 1995; Furst, 1995; Strand, 1999]. One case of anaphylaxis has been reported.

In experimental models, treatment with leflunomide has been associated with **anemia and leukopenia** [Yuh, 1995]. This toxic effect has not been produced in clinical trials in humans, but until long-term pharmacological surveillance data are available, the patient should be monitored periodically for the possible appearance of anemia and leukopenia.

In animal models, leflunomide has severe teratogenic effects and increases the risk of fetal death [Arava, 1999]. As its safety in humans is unknown, contraceptive measures are recommended before beginning treatment, not only in women of childbearing age but also in men, due to the possibility of teratogenic effects caused by the paternal route. If pregnancy occurs or if a man wishes to have children, it is recommended that the drug be immediately discontinued, and the patient should be treated with 8 g of cholestyramine, three times a day, for 11 days.

Because it is potentially immunosuppressive, it is assumed to promote or exacerbate infection, but so far no serious infections during clinical use have been reported. Due to its potential immunosuppressive effect, and in the absence of safety and efficacy studies on the concomitant use of leflunomide and live vaccines, vaccination is not recommended during treatment with this drug.

6.8 Methotrexate

6.8.1 The most important side effects of MTX are pulmonary, hepatic, and hematologic toxicity. Other adverse effects are carcinogenesis, infections, nodules, gastrointestinal toxicity, and neurological toxicity.

6.8.2 *Monitoring:* Before beginning treatment a complete blood count, liver and kidney biochemistry, and serum albumin should be obtained, together with hepatitis A, B, and C serology. If pre-existing liver disease or exposure to liver toxins is suspected, a liver biopsy should be performed before beginning treatment. If the patient has a history of pleuropulmonary disease, a chest X-ray, as well as folic acid and vitamin B12 levels should be obtained. Follow-up tests should be obtained every 4 to 8 weeks to monitor blood count and liver and kidney biochemistry. A follow-up liver biopsy should be performed if there are persistent abnormalities in liver biochemistry that can not be attributed to concomitant treatment with nonsteroidal anti-inflammatories. Other non-routine studies are indicated if symptoms suggestive of specific complications appear (e.g., blood gas analysis and chest X-ray if pneumonia is suspected).

6.8.3 *Contraindications:* Pregnancy, alcohol abuse, hepatitis B or C, and cirrhosis of any origin are considered to be absolute contraindications. Relative contraindications are renal failure, chronic pulmonary disease, and active infection not associated with Felty's syndrome.

Six MTX-induced clinical syndromes of pulmonary toxicity are known: acute interstitial pneumonitis, interstitial fibrosis, pulmonary nodules, non-cardiogenic pulmonary edema, pleuritis, and pleural effusion [Cannon, 1997]. The first three have been described in RA patients and the latter three in patients with neoplasms. The most frequent type of pulmonary toxicity (from 2 to 6%) is acute

interstitial pneumonitis or hypersensitivity pneumonitis [Furst, 1994b]. This is a potentially lethal complication [Furst, 1990] by itself or as a result of pulmonary superinfection [Searles, 1987]. It is not associated with either duration of treatment, weekly dose, or cumulative dose received [White, 1989; Hargreaves, 1992; Alarcón, 1995; Kremer, 1995; Cannon, 1997]. Pre-existing pulmonary disease is a risk factor [Golden, 1995]. Treatment consists basically of withdrawing MTX, administering corticosteroids, and managing the respiratory insufficiency.

The **hepatic toxicity** of MTX manifests as fibrosis and cirrhosis, especially in patients who consume excessive amounts of alcohol (more than 100 g/week) or have pre-existing liver disease [Farell, 1998]. Nonetheless, although transaminases are frequently elevated [Songsiridej, 1990], fibrosis rarely progresses to cirrhosis [Furst, 1990], even after cumulative MTX doses exceeding 5 g [West, 1997]. The main risk factors are diabetes mellitus [Erickson, 1995; Bass, 1996; Farrell, 1998], alcohol abuse, obesity, fatty liver, underlying liver disease (chronic liver disease due to hepatitis B, C, or other viruses), age over 60 years, renal failure, cumulative doses of MTX exceeding 1.5-2 g, concomitant treatment with NSAIDs, and related systemic disease [Walker, 1993; O´Dell, 1997; Farrell, 1998]. It has been suggested that patients with a deficiency of alpha-1 antitrypsin are more susceptible to MTX hepatotoxicity [Hilsden, 1995; O´Dell, 1997]. Hepatotoxicity is reduced by using low doses and following recommended guidelines for weekly administration of the drug [Sznol, 1987]. Pre-treatment biopsy is indicated only in patients with a history of excessive alcohol consumption, persistent transaminase elevation, or pre-existing liver disease [Kremer, 1992; Kremer, 1994]. If liver biopsy shows acute fibrosis or cirrhosis (Roegnick stages class III-b or IV), the treatment is contraindicated [Kremer, 1994]. It should also be discontinued in patients who refuse biopsy if they have persistent liver test abnormalities (5 of 9 GOT measurements above the normal range in a 12-month period, or 6 of 12 if tested monthly) or hypoalbuminemia [Kremer, 1994].

Hemotologic toxicity (5-25%), consists of leukopenia, thrombocytopenia, megaloblastic anemia, and pancytopenia (1-2%) [Gutiérrez Ureña, 1996]. It is usually mild or moderate and remits when the dosage is reduced. Pancytopenia responds to folic acid and supportive treatment (steroids, transfusions, antibiotics, and hematopoietic stimulating factors) [McKendrey, 1997]. Probable risk factors are considered to be folate deficiency and macrocytosis [Al-Awadhi, 1993], concomitant treatment with other antifolate drugs such as sulphasalazine [Morgan, 1993] or trimethoprim-sulphanotoxazol, concurrent viral infections [Naides, 1995], advanced age, and renal failure [Al-Awadhi, 1993, RACTAG, 1995].

Increased risk of **cancer** has not been shown in numerous studies of patients with diseases other than RA who were treated with MTX. Tumors of the liver [Ruymann, 1977] and lymphomas [Ellman, 1991; Shiroky, 1991; Kingsmore, 1992; Kamel, 1993; Bachman, 1996], however, have been observed in RA patients. Studies of lung cancer incidence in RA patients treated with MTX have yielded contradictory results, with increases shown in some cases [McKendry, 1993] and normal incidence in others [Alarcón, 1994]. It does not appear to increase the risk of hematologic malignancies [Moder, 1995].

MTX treatment may increase the risk of bacterial, viral, herpes zoster, or opportunistic **infections** in patients with RA. The risk is higher with combined steroid treatment [Kanik, 1997].

Some 60% of patients treated with MTX have **gastrointestinal toxicity** (stomatitis, nausea, vomiting, dyspepsia, abdominal pain, indigestion, diarrhea, anorexia, or weight loss) [McKendry, 1997]. These effects are generally reversible by reducing the drug dosage or changing from the oral to the parenteral route of administration [O´Dell, 1997]. They can be prevented and treated with folic acid supplements. Exceptionally, hemorrhagic enteritis may occur.

Neurotoxicity occurs at high doses (more than 1 g/m^2) in 15% of patients. It may manifest as depression, confusion, memory loss, drowsiness, headache, fatigue, or discomfort; it most frequently occurs within 24 hours of drug administration [McKendry, 1997]. Exceptionally, hallucinations or leukoencephalopathy may appear [Worthley, 1995].

Nodules are histologically indistinguishable from rheumatoid nodules; they regress when treatment is discontinued and reappear when it is renewed [Kerstens, 1992]. They may be associated with vasculitis [Segal, 1988], pleural effusion, and pericardial tamponade [Abu-Shakra, 1994].

Other toxic manifestations are rashes [Neiman, 1985; Bannwarth, 1994], alopecia, osteopathy [McKendry, 1997], arthralgias/myalgias, general malaise on the first or second day of treatment, or even fever unrelated with infection. These "post-dose" effects are the second most common cause of MTX withdrawal [Halla, 1994].

6.9 Gold salts

6.9.1 The most important clinical side effects are hematologic and renal toxicity. Both are more frequent with intramuscular treatment. They require careful clinical monitoring and the immediate discontinuation of treatment to prevent irreversible sequelae.

6.9.2 *Monitoring:* Periodic testing for proteinuria by routine urinalysis (qualitative or semiquantitative) every 4 weeks during the first 6 months and every 3 months thereafter. If proteinuria is detected, a 24-hour urine quantification should be obtained. If the proteinuria exceeds 500 mg/24 h, treatment should be discontinued until it disappears or drops below 200 mg/24 h, after which it may be renewed. If the proteinuria is severe (above 1 g/24 h), treatment should be discontinued permanently.

6.9.3 *Contraindications:* Severe liver or kidney disease and blood or bone marrow disorders.

The most frequent **hematologic effects** are related with the hematopoietic system: eosinophilia and thrombocytopenia (1-3%), followed by neutropenia [Lockie, 1985; Ridaura, 1995; Myochrysine, 1997]. Aplastic anemia and pure red-cell aplasia have also been reported. Of all these effects, the only one that does not require discontinuation of treatment is eosinophilia, which some authors consider a warning sign for the presentation of other toxic effects [Davis, 1974; Bretza, 1983]. Thrombocytopenia may appear suddenly or progressively; treatment should be discontinued if platelet counts drop below 100,000 platelets/mm^3 [Ridaura, 1995].

The most frequent **renal toxicity** is membranous glomerulonephritis, usually preceded by proteinuria and/or hematuria, followed in frequency by nephrotic syndrome and acute renal failure, which may be secondary to acute tubular necrosis [Robbins, 1980; Hall, 1988b].

Other adverse effects are skin toxicity (dermatitis, pruritus) [Ridaura, 1995]; ulcers of the mouth, gums, or tongue, including the upper palate and pharynx; abnormal taste sensations (dysgeusia, metallic taste); hepatic toxicity (jaundice with or without intrahepatic cholestasis); pulmonary toxicity (hypersensitivity pneumonitis, bronchiolitis obliterans); gastrointestinal toxicity (diarrhea, especially with auranofin - 47%, toxic enterocolitis); neurologic toxicity (peripheral neuropathy, cranial neuropathy, Guillan-Barré syndrome, encephalopathy); vaso-vagal hypotension; conjunctivitis (auranofin); and corneal ulcers and gold deposits (sodium aurothiomalate).

6.10 Sulphasalazine

6.10.1 The most frequent sites of adverse reactions (33%) to sulphasalazine are the central nervous system and gastrointestinal tract. These are usually mild and do not require discontinuation of treatment. Other less frequent adverse effects are hematologic and hepatic toxicity.

6.10.2 *Monitoring:* Blood cell count every 4 weeks during the first 3 months and every 3 months thereafter.

6.10.3 *Contraindications:* Allergy to salicylates or sulfonamides.

The adverse effects on the **central nervous system** (headache, vertigo) and **gastrointestinal tract** (anorexia, nausea, vomiting, abdominal pain) are generally mild and do not require discontinuation of treatment [Amos, 1986; Farr, 1986; Williams, 1988].

Hematologic toxicity occurs particularly in the hematopoietic system: macrocytosis (9%), leukopenia (3.7%), neutropenia (2%) and megaloblastic anemia (<1%). Isolated episodes of aplastic anemia, agranulocytosis, thrombocytopenia, and leukocytosis have been reported. Hematologic toxicity may present at any time during treatment, although it usually appears early (between the 5th and 12th week), except for macrocytosis and megaloblastic anemia, which may present after prolonged periods of treatment [Drugex, 1999].

These effects are reversible if the drug is discontinued and treatment is initiated [Guillemin, 1989; Canvin, 1993]. Folic acid treatment (5-10 mg/day) should be used in the case of megaloblastic anemia. A deficiency of glucose 6-phosphase dehydrogenase (G6PD) may produce hemolytic anemia [ACR Committee, 1996].

Hepatic toxicity manifests as acute, febrile episodes, with pruritic skin lesions, lymphadenopathy, hepatomegaly, lymphocytosis, eosinophilia, and elevated transaminases [Williams, 1979; Losek, 1981; Boyer, 1989; Marinos, 1992; Vyse, 1992]. This situation is serious and can lead to death [Pears, 1989; Marinos, 1992]. Discontinuing medication is not sufficient to prevent the patient's deterioration, and corticosteroids are needed.

Continued treatment with sulphasalazine has been associated with male infertility (spermiogram abnormalities in 86% and oligospermia in 72%) [Birnie, 1981]. These abnormalities are reversible after discontinuing treatment for 3 months [Toovey, 1981].

There have been isolated reports of cases of altered taste (ageusia and metallic taste), skin abnormalities (drug-induced exanthema, pruritic maculopapular rashes, Stevens-Johnson syndrome, toxic epidermic necrolysis), pulmonary disorders (eosinophilic pneumonia, fibrosing alveolitis, subacute hypersensitivity pneumonitis), neurologic disorders (motor and sensory neuropathy, aseptic meningitis), muscular disorders (myopathy), and renal disorders (hemolytic-uremic syndrome, nephrotic syndrome, bilateral kidney stones).

Table 24. Adverse effects of DMARDs

Drug	Toxicity	Initial evaluation	Clinical effects	Tests	Most common reasons for suspending treatment

Antimalarials	Gastrointestinal, retina, skin	Funduscopic examination in persons over 40 years of age, visual field.	Visual disturbances, skin lesions.	Funduscopic examination every 6-12 months.	Corneal deposits, retinopathy.
Anti-TNF agents	Hematologic, central nervous system, immune system (toxicity assumed).	Rule out acute or chronic infection (particularly TB). Rule out multiple sclerosis.	Local or anaphylactic reactions. Signs or symptoms of infection or neoplasm, myelosuppression or demyelinating disease.	CBC on administration of infliximab, and every 4-6 weeks with etanercept treatment.	Systemic infection.
Azathioprine	Hematologic, gastrointestinal.	Baseline CBC, creatinine, liver function.	Signs or symptoms of infection or neoplasm.	CBC every 1-2 weeks until dosage stable, then every 1-3 months. Liver function tests every 6-8 weeks.	Leukopenia (<3,000 leukocytes and/or <1,000 neutrophils). Thrombocytopenia (<150,000 /mm^3). Systemic infection.
Cyclophosphamide	Gonadal, urological, bone marrow.	Rule out pregnancy, infections, neoplasms, or re-existing liver disease.	Signs or symptoms of infection or neoplasm, alopecia, nausea, vomiting.	CBC every 1-2 weeks until dosage stable, then every 2-4 weeks. Liver enzymes, urinalysis, urinary sediment, monthly.	Leukopenia (<3,000 leukocytes and/or <1,000 neutrophils). Thrombocytopenia (<150,000 /mm^3). Systemic infection, hemorrhagic cystitis.
Cyclosporin A	Kidney, hypertension.	Rule out neoplasms or premalignant lesions. Two BP tests for hypertension. CBC, hepato-renal biochemistry, routine urinalysis with sediment.	Signs or symptoms of infection or neoplasm.	Monitor for hypertension, renal and electrolyte function every 2 weeks the first 3 months, and then monthly.	≥ 30% increase in creatinine not reversed after halving dose. Development of uncontrolled hypertension.
D-penicillamine	Skin, gastrointestinal, kidney.	CBC, creatinine, urinalysis.	Skin lesions, anaphylactic reactions.	CBC, creatinine, urinalysis every 2 weeks until dosage stable, and then every 1-3 months.	Proteinuria >500 g/24 h. Leukopenia (<3,000 leukocytes and/or <1,000 neutrophils). Thrombocytopenia (<150,000 /mm^3).
Leflunomide	Pulmonary, gastrointestinal, hepatic.	Begin contraceptive use. Rule out active infection, liver disease, and renal failure.	Skin lesions, hair loss, weight loss, hypertension.	CBC and GOT, GPT every 4 weeks until dosage stable.*	Liver enzymes persistently elevated to more than twice the reference values.

Methotrexate	Pulmonary, hepatic, hematologic, gastrointestinal, and neurological.	CBC, liver and kidney biochemistry, serum albumin, hepatitis A, B, C serology. If there is history of pleuropulmonary disease: chest X-ray, folic acid and vitamin B12 levels. If excessive alcohol consumption or previous liver disease, liver biopsy.	Dry cough, shortness of breath, fever, hemorrhage, nausea, vomiting, diarrhea, nodules, adenopathy.	CBC and kidney and liver biochemistry every 4-8 weeks. If liver function abnormalities persist: follow-up liver biopsy.	Pregnancy, pulmonary toxicity, liver enzymes persistently elevated to more than twice the reference values. Leukopenia (<3,000 leukocytes and/or <1,000 neutrophils). Thrombocytopenia (<150,000 mm^3).
Gold salts	Hematologic and renal.	Baseline	Skin lesions, mouth ulcers, edema, diarrhea, signs or symptoms of myelosuppression.	CBC and proteinuria every 4 weeks for the first 6 months, and then every 3 months.	Proteinuria >500mg/24 h. Leukopenia (<3,000 leukocytes and/or <1,000 neutrophils). Thrombocytopenia (<150,000 /mm^3).
Sulphasalazine	Central nervous system, gastrointestinal, hematologic.	Hypersensitivy to sulfonamides. History compatible with G6PD deficiency.	Skin lesions, signs or symptoms of myelosuppression.	CBC every 4 weeks for 3 months, and then every 3 months.	Hypersensitivity syndrome. Leukopenia (<3,000 leukocytes and/or <1,000 neutrophils). Thrombocytopenia (<150,000 /mm^3).

- Because there has been little experience with its use, it is not possible to recommend a specific period of time for monitoring adverse effects once a stable dose has been reached (3 months would seem to be prudent).

CHAPTER 7. OTHER TREATMENTS

7.1 Surgical treatment

7.1.1 The rheumatologist should consider surgical treatment when articular function does not improve or is notably worse, when incapacitating pain persists, or when there are potentially serious or limiting neurological complications [Dreyer, 1999; Grob, 1999].

Appropriate medical treatment will reduce the indications for surgery and will improve the likelihood of surgical success. Consultation with an orthopedic surgeon should not always be an indication for surgery, but the exchange of opinions and clinical evaluation will help improve the patient's clinical and functional status.

A number of factors should be considered before surgical treatment: bone quality, the patient's level of motivation and preferences, the probability that surgery will modify the course of the disease, and an estimate of the extent to which surgical treatment can reconstruct articular function and make the patient more independent [Bogoch, 1999].

In deciding on surgical intervention, clinical and functional evaluation should predominate over simple radiographic change in the disease.

RA patients who consult the orthopedic surgeon often have various joints needing surgical evaluation, therefore priorities need to be established. The joint that the patient finds most incapacitating will usually be treated first.

Patients who cannot walk due to lower limb pain or deformity need to have functional upper limbs to facilitate the post-surgical period. When the upper limbs are affected (pain, deformity, or stiffness) to the point that they would impede the use of walking aids, the upper limbs should be reconstructed first. If the joints are affected with different degrees of severity, the one with the best

prognosis should be reconstructed first.

7.1.2 The joint prosthesis is the most efficient surgical means to arrest progressive loss of functional capacity. Prosthetic implant in any joint should be performed before irreparable deformities occur (e.g., flexus or axial deviations and instabilities) because these will limit the success of arthroplasty [Waldman, 1998; Creighton, 1998; Hargreaves, 1999].

Synovectomy may produce slight improvement in the synovectomized joints, but this effect is not maintained at 3 years.

Arthrodesis is a good control measure but is more limited from the functional point of view. It remains a commonly used technique in RA to palliate damage from joint destruction, especially in the interphalangeal joints of the hand, the metacarpophalangeal joint of the thumb, the wrist, ankle, and hindfoot [Bogoch, 1999]. Arthrodesis of other joints is less acceptable.

Surgical success or complications in RA are associated with the surgeon's experience, the patient's previous status, and post-operative care, especially rehabilitation and occupational therapy. The latter two factors are an important aid in establishing optimal joint function, especially after arthroplasy of the knee or shoulder and hand surgery.

The incidence of infection in orthopedic surgery may increase during the perioperative period, although this has not been conclusively established. A reasonable course of action is to omit the weekly dose of MTX in the week before and after surgery, which reduces the small possibility of perisurgical complications, at the expense of the also small risk of reactivating the disease [Bridges, 1991; Carpenter, 1996].

7.2 Rehabilitative therapy

7.2.1 The objective of a rehabilitation program in RA patients is to improve pain relief, joint mobility, and the performance of the activities of daily living. This is intended to prevent disability and maintain maximum personal independence [Sutej, 1991]. Rehabilitative techniques that may be used in treating RA patients are thermotherapy, physical exercise, prescription of splints, and occupational therapy.

Although rehabilitation is prescribed relatively frequently in RA patients, few studies with sound methodology have demonstrated its benefits with respect to control groups.

Several studies show that patients who undergo a rehabilitation program have a 25 to 40% improvement in function. Other benefits that have also been attributed to rehabilitation are improvement in "disease perception" as well as in indicators of disease "activity" [Conaty, 1971; Spiegel, 1986].

Rehabilitation techniques that may be used in treating RA patients are thermotherapy, physical exercise, prescription of splints, and occupational therapy.

7.2.2 Thermotherapy (the use of heat or cold as an analgesic method in joints with symptoms of inflammation) is useful in the treatment of RA. Superficial heat is indicated in RA, whereas deep heat is formally contraindicated. The local application of cold increases the pain threshold in the inflamed joints.

Heat can be applied superficially (hot compresses, paraffin, infrared rays) or deeply (microwaves, ultrasound). Deep heat raises the temperature of the inflamed joints, while superficial heat, paradoxically, decreases it and thus reduces pain. Consequently, superficial heat is indicated in RA, while deep heat is formally contraindicated.

Superficial heat increases the blood flow to the inflamed joints, producing a cooling effect, whereas deep heat does not increase blood flow [Lehmann, 1966; Harris, 1974; Feibel, 1976].

Cold should only be applied superficially in the form of cold compresses, ice massage, or cold spray. The local application of cold increases the pain threshold in inflamed joints [Benson, 1974].

The application of cold is contraindicated in the case of Raynaud's phenomenon, hypersensitivity to cold, cryoglobulinemia, or paroxysmal nocturnal hemoglobinuria [Olson, 1972].

7.2.3 The ideal type of physical exercise in patients with RA is static or isometric active exercise, which involves minimal increase in intra-articular pressure or bone destruction. Resistance active exercises (lifting weights) are formally contraindicated because they increase joint inflammation, pain, muscular fatigue, temperature, and intra-articular pressure.

In passive exercise there is no voluntary muscular contraction on the part of the patient. The physiotherapist moves the joints. Its main objective is to maintain articular balance in joints at risk of

developing ankylosis or contractures. Its efficacy in RA patients, however, is uncertain. If used, it should never cause pain [Merritt, 1983].

In active exercise there is voluntary muscular contraction by the patient. There are three types:

- Static or isometric active exercise: limited muscular contraction without joint motion but with maximal muscular tension.
- Dynamic or isotonic active exercise: muscular contraction associated with joint motion that may act with or against the force of gravity.
- Resistance active exercise: exercise performed against the force of gravity and with added weight.

The ideal type of physical exercise for RA patients is static or isometric active exercise, which involves a minimal increase in intra-articular pressure or bone destruction [Castillo, 1965; Jaison, 1970]. Isometric exercise of the quadriceps has been shown to be beneficial for the knee joint [Ekblom, 1975a].

Resistance active exercises (lifting of weights) are formally contraindicated in RA patients because they increase joint inflammation, pain, muscular fatigue, temperature, and intra-articular pressure.

Patients without active disease who have developed sufficient muscular strength through isometric exercise may benefit from repetitive isotonic active exercises with minimal resistance, so long as they are performed with a reduced range of joint motion. Some ways of practicing these exercises would be swimming, stationary bicycling, or gardening, with the stipulation that fatigue should be avoided [Ekblom, 1975b; Minor, 1989].

7.3 Local therapy

7.3.1 Local therapy in RA is indicated in joints with persistent disease activity despite adequate systemic control of the disease. The smaller the radiographic damage in a joint and the less systemic inflammatory activity of RA, the higher the probability that local treatment will have good results.

Local treatment in RA is understood as therapy applied to an individual joint. During the course of RA it is frequently found that, although the disease's systemic inflammatory activity is controlled with the use of DMARDs and anti-inflammatories (steroidal or nonsteroidal), some joints still have active inflammation characterized by the presence of pain at rest, tenderness, pain on motion, swelling, and localized warmth. In these situations the systemic medication that is controlling the disease should be maintained, adding a local treatment to reduce inflammation in the joint where it is not controlled.

7.3.2 Intra-articular steroid injection is the procedure of choice. The most effective corticosteroid preparation is triamcinolone hexacetonide due to its prolonged intra-articular duration. If corticosteroid infiltration fails, radioisotopic synoviolisis and chemical synoviolisis with osmic acid may be useful procedures before referring the patient for arthroscopic or surgical synovectomy.

The first step is to obtain synovial liquid for testing. The presence of infection should be ruled out by Gram stain and appropriate cultures.

The administration of intra-articular corticosteroids is the local therapy of choice for an out-of-phase joint when infection has been ruled out. A number of drugs exist, including methylprednisolone acetate, paramethasone acetonide, triamcinolone acetonide, and triamcinolone hexacetonide. This guideline recommends the use of triamcinolone hexacetonide because of its prolonged action, lasting several months [Bain, 1972; Bird, 1979; Blyth, 1994]. After administering the corticosteroid, it is a good idea to prescribe joint rest for at least 24 hours [Chakravarty, 1994].

Radioisotopic synovectomy consists of the intra-articular administration of a radioactive drug that emits high energy beta particles. The synovial membrane receives local radiation, destroying the synovial membrane cells and reducing their thickness, which improves the symptoms of inflammation in the medium- and long term. The most commonly used drugs in large joints such as the knee are dysprosium-165, 90-yttrium, and samarium-153. For medium-sized joints such as the elbows, carpals, or ankles, rhenium-186 has been used. For small joints such as the metacarpophalangeal or proximal interphalangeal joints, erbium-169 has been used [Muller, 1975; Gumpel, 1979; Sledge, 1984; Sledge, 1986; Sledge 1987; Jones, 1993; Barnes, 1994; Clunie, 1996; Asavatanabodee, 1997; Jahangier, 1997; O´Duffy, 1999].

Chemical synovectomy refers to the intra-articular administration of a chemical agent capable of destroying the synovial membrane by metabolic or abrasive action on the cells or extracellular material. Osmic acid is the most commonly used agent [Bontoux, 1978].

CHAPTER 8. EXTRA-ARTICULAR COMPLICATIONS OF RHEUMATOID ARTHRITIS

8.1 Amyloidosis

8.1.1 Secondary amyloidosis should be suspected in RA patients who develop proteinuria, renal failure, gastrointestinal symptoms, myocardiopathy and/or hepatomegaly, and in those having elevated phase reactants concurrent with little clinical activity.

8.1.2 The recommended treatment is chlorambucil at a dosage of 0.1-0.2 mg/kg/day [Berglund, 1993; David, 1993].

Background:
Amyloidosis is a syndrome characterized by the presence of insoluble deposits of normal serum proteins in the extracellular material of one or more organs. Secondary amyloidosis, produced by the serum amyloid A, a phase reactant, is the most frequent form of amyloidosis. It occurs in association with a large number of chronic inflammatory diseases such as RA. The inflammatory response tends to increase the production of serum amyloid A in the liver, which is broken down in the circulating macrophages into smaller fragments that are deposited in the tissues [Glenner, 1980]. Amyloidosis increases RA mortality by causing organ dysfunction.

When to suspect:
Secondary amyloidosis should be suspected in RA patients who develop proteinuria, renal failure, gastrointestinal symptoms, myocardiopathy and/or hepatomegaly [Okuda, 1994; Hazenberg, 1994], as well as in those having elevated phase reactants concurrent with little clinical activity.

Clinical description:
The prevalence of amyloidosis in RA in post-mortem studies ranges between 10 and 25% [Husby, 1985; Pai, 1993]; it becomes symptomatic in only 2-10 %. It is more frequent in patients with severe long-standing disease [Okuda, 1994]. One of the most frequent indicators of amyloid deposits in RA patients is the presence of proteinuria, which may progress to nephrotic syndrome. Other organs that may be affected are the heart, liver, spleen, gut, and skin.

Diagnosis:
The diagnosis of amyloidosis requires documentation of an extracellular fibrillar deposit with green birefringence under polarized light in biopsies stained with Congo red [Glenner, 1980]. It is recommended that biopsies be made of abdominal fat [Duston, 1989] or of rectal or gingival mucosa [Kyle, 1983], which is safe and accessible. It has recently been suggested that scintigraphy with serum amyloid P component (a phase reactant that coprecipitates in all forms of amyloidosis) marked with iodine-123 may be a reliable alternative to biopsy in the diagnosis of secondary amyloidosis [Tan, 1995].

Treatment:
Treatment should always aim to suppress RA activity [Gerts, 1991; Berglund, 1993; David, 1993; Lovat, 1997]. Chlorambucil at a dosage of 0.1-0.2 mg/kg/day has been shown to play a beneficial role in the treatment of secondary amyloidosis in patients with chronic arthritis [Berglund, 1993; David 1993].

8.2 Anemia

8.2.1 Anemia in RA is usually asymptomatic, therefore periodic blood cell counts should be obtained including erythrocyte, leukocyte, and platelet counts; calculation of the mean corpuscular volume (MCV); reticulocyte count; and general liver and kidney function tests.

8.2.2 There is no specific treatment for anemia in RA. It should be considered for possible changes in RA treatment guidelines.

Background:
Anemia is one of the hematologic disorders that can appear during the course of RA. It may be related with the disease's inflammatory character and chronic nature, with associated iron-deficiency, or it may be an undesired effect of treatment. The severity depends on its intensity.

If the anemia is severe (hemoglobin less than 80 g/l), not only iron deficiency, but also other, infrequent causes of anemia should be considered, such as autoimmune hemolytic anemia and drug-induced aregenerative anemia. In the absence of blood loss, the diagnosis of hemolytic anemia is based on reticulocytosis, and the diagnosis of aregenerative anemia is based on the drug used in treatment and its association with leukopenia and thrombocytopenia.

When to suspect:
The anemia is usually moderate and asymptomatic, and is detected in routine tests. Typical symptoms may also develop at times, such as fatigue, increasing difficulty in normal physical exertion, palpitations, and/or pale skin and mucosa. The range of symptoms depends on the intensity of the anemia and on the organism's possible development of adaptive mechanisms.

Diagnosis:
A blood count should be obtained, including erythrocyte, leukocyte, and platelet counts; calculation of the mean corpuscular volume (MCV); reticulocyte count; and general liver and kidney function tests. If anemia exists, a second round of tests may be obtained to diagnose its etiology. These tests may include:

- Determination of the serum levels of ferritin and transferrin and their saturation index, indicated to evaluate associated iron deficiency (Table 25). Iron deficiency is also accompanied by elevated transferrin levels, with a low saturation index (less than 16%).
- Myelogram. Indicated only in cases where there is unconfirmed suspicion of coexisting iron-deficiency anemia.
- Bone marrow biopsy. Only if aregenerative anemia is suspected.

Table 25. Definition and characteristics of anemia in RA

DEFINITION	
Hemoglobin	<130 g/l (men); <120 g/l (women)
CHARACTERISTICS	
Normocytic	MCV: 83-97 fl
Normochromic	MCH: 27-33 pg
Transferrinemia	Slightly reduced saturation index
Reticulocytes	Normal or low
Ferritin (serum values)	>60 ng/ml <12 ng/ml (iron deficiency anemia) 12-60 ng/ml (anemia associated with iron deficiency)

Treatment:
Transfusions of concentrated red blood cells are contraindicated, except in exceptional cases of severe anemia with high cardiocirculatory risk. Iron (oral ferrous salt compounds) should only be administered when there is evidence of coexisting iron-deficiency anemia. The cause of blood loss should also be investigated.

The usefulness of administering erythropoietin has not been defined, although it could be indicated prior to surgery, particularly before joint prosthesis. The treatment required for pure red cell aplasia is complex and should be carried out in a hematology unit.

8.3 Cardiological complications

8.3.1 Cardiac involvement should be suspected if there is pericardial pain, heart failure, or conduction abnormalities. The two most frequent complications are pericarditis and myocarditis.

8.3.2 Pericarditis should be treated with full doses of NSAIDs (150 mg/day of indomethacin). If this treatment is not effective, prednisone (1 mg/kg/day) is useful to control symptoms. Myocarditis is treated with high-dose steroids, diuretics, digitalis, vasodilatador agents, and antiarrhythmia drugs.

Background:
The heart and adjacent structures (pericardium and vessels) may be affected by nodular lesions or fibrosis in RA patients. In these patients, however, heart involvement is likely to be due to causes other than rheumatoid disease itself. The cardiac lesions derived from RA have little clinical expression, and are usually mild alterations not requiring treatment.

When to suspect:
Pericardial-type pain, heart failure, or conduction abnormalities should be a warning of possible cardiac involvement in an RA patient. The two types of cardiac involvement in RA patients are

pericarditis and myocarditis.

Pericarditis

Clinical description:
This is the most frequent type, with an annual incidence of 0.3-0.4% [Jurik, 1986]. Echocardiographic studies show asymptomatic pericardial effusion in over 30% of RA patients. In some exceptional cases of massive effusions or rapid onset, cardiac tamponade manifesting as shock is produced. Most RA patients with symptomatic pericarditis are males with positive RF.

Diagnosis:
Pericardial effusion seen on echography.

Treatment:
Full doses of NSAIDs (150 mg/day of indomethacin). If this is not effective, prednisone (1 mg/kg/day) is useful to control symptoms. Cases of cardiac tamponade should be treated with evacuation by pericardiocentesis.

Myocarditis

Clinical description:
Myocarditis may be interstitial or granulomatous and is rare in RA [Lebowitz, 1963]. The granulomatous variety is highly specific in RA, while the interstitial variety is more frequent in lupus. Myocarditis presents as progressive shortness of breath. The physical examination reveals tachycardia, reduced differential blood pressure, and frequently a third heart sound. The coronary valves may be affected by granulomas leading to valve insufficiency and affecting, in this order, the mitral, aortic, tricuspid, and pulmonary valves. The coronary arteries may be affected in RA, especially the small intramyocardial vessels. Coronary arteritis is not usually expressed clinically, thus the presence of symptoms of ischemia in RA patients is practically always due to associated coronary arteriosclerosis.

Diagnosis:
Reduced contractility shown on echocardiography. Biopsy of the right ventricle may be indicated in these patients.

Treatment:
High-dose steroids, combined with diuretics, digitalis, vasodilators, and antiarrhythmia drugs.

8.4 Osteoporosis

8.4.1 Osteoporosis should be suspected in the presence of vertebral or peripheral fractures not due to trauma. When RA is first diagnosed, all patients should be evaluated for the main risk factors for fracture and loss of bone mass; this analysis should include both RA-associated and independent risk factors (Tables 26 and 27).

8.4.2 First-line agents for the specific treatment of osteoporosis are alendronate, risedronate, or hormone replacement therapy or, alternatively, cyclical etidronate or calcitonine.

Background:
A large percentage of RA patients have low bone mass in the axial and peripheral skeleton. These patients are considered to have twice the risk of the general population for developing fractures of the vertebra and femur, with a relative risk of 2.1 for fracture of the vertebra and 1.5-2.1 for fracture of the femur, rising to 4.4 in patients with marked alternation of functional capacity.

Many risk factors are involved in the development of osteoporosis: age, post-menopause (in women), disease activity, functional capacity, immobility, and the influence of drugs used in treatment, especially the corticosteroids. Major bone mass loss has been described even in the initial phases of RA. Despite this evidence, no CPG for osteoporosis treatment in RA has been developed to date.

When to suspect:
Vertebral or peripheral fractures, excluding those caused by trauma.

Diagnosis:
At the initial examination an analysis should be made of the main risk factors for fracture and loss of bone mass, both risk factors that are associated with RA and those that are independent of the disease (Tables 26 and 27). If one or more of these factors is present, a bone densitometry of the lumbar spine and femur is indicated, according to the recommendations of the National Osteoporosis Foundation (US), the International Committee for Osteoporosis Clinical Guidelines in post-menopausal women, the ACR (US), and the National Osteoporosis Society (Great Britain) for the prevention and treatment of corticosteroid-induced osteoporosis.

Since a large percentage of vertebral fractures are asymptomatic, a lateral radiograph should be made of the dorsal and lumbar spine to evaluate the existence of vertebral fractures in accordance with the following criterion for fracture: a 20% or greater reduction of the anterior, mid, or posterior height of the vertebral body. Laboratory tests will usually also be obtained to rule out associated processes that may be causing the osteoporosis.

Table 26. RA-independent risk factors for osteoporosis

- Age over 65 years
- History of fracture due to bone fragility after 40 years of age
- Body weight under 58 kg
- Fractures due to bone fragility in nuclear family members
- Smoking
- Early menopause
- Prolonged amenorrhea
- Hypogonadism in males
- Other predisposing diseases

Table 27. RA-associated risk factors for osteoporosis

- Active disease
- HAQ >1.25
- Treatment with corticosteroids >7.5 mg/day for over 6 months, or cumulative doses over 30 g
- Treatment with methotrexate

In accordance with the WHO criteria for the diagnosis of osteoporosis in women, osteopenia or osteoporosis is considered to exist when the T-scale value is between -1 and -2.5, or is less than -2.5, respectively. Although there is no official consensus, these diagnostic criteria appear to be valid in men.

Treatment:
Since all RA patients are at risk for osteoporosis, the following recommendations for preventive treatment are made for all such patients:

- Stop smoking and excessive alcohol consumption.
- Maintain physical activity.
- Take necessary precautions to avoid falls.
- Calcium supplements sufficient to reach a daily intake, including diet, of 1,500 mg, plus 400-800 IU of vitamin D3.
- If hypercalciuria is present, thiazides should be administered.

Begin specific treatment of osteoporosis if:

- There is a history of fracture of the vertebra or femur.
- Bone mineral density is less than -1.5 on the T scale.
- The patient is over 65 years of age.
- The dose of corticosteroids is higher than 7.5 mg/day of prednisone for more than 6 months, and there are other risk factors (Tables 26 and 27).

Treatment with alendronate, residronate, or hormone replacement therapy (estrogens either alone or in association with progestogens - depending on whether or not the uterus is intact - in postmenopausal women, or testosterone in hypogonadal men). If contraindicated, cyclical etidronate or calcitonine can be used as an alternative.

At the time this guideline was written, no information was available on the efficacy of raloxifene in secondary osteoporosis.

Monitoring:
Patients who have a baseline densitometry should repeat the test one year later, and every 1-3 years thereafter. If annual bone loss is more than 4% in the lumbar spine or 7% in the femur, treatment should be initiated or modified.

8.5 Lung complications

8.5.1 The appearance of pleuritic pain, shortness of breath (either progressive or of recent onset), or hemoptysis suggests pulmonary disease in RA patients. Lung complications may include pleural disease, rheumatoid nodules, interstitial fibrosis, or bronchiolitis obliterans with organizing pneumonia (BOOP).

8.5.2 Treatment for pleural disease includes thoracocentesis to obtain an exudate and rule out other pathologies (infection or neoplasm), NSAIDs at full doses, or steroids at half doses (10-20 mg/day of prednisone). Rheumatoid nodules do not require treatment in the absence of complications. Recent onset (acute) interstitial involvement is treated with prednisone (1-1.5 mg/kg/day). If there is no response, patients may be treated with cyclophosphamide or azathioprine. BOOP is treated with prednisone (1.5 mg/kg/day).

Background:
It is not clear how pulmonary disease is associated with RA [Kelly, 1993]. Pleuritis (with or without effusion), pulmonary nodules (with or without cavitation), rheumatoid pneumoconiosis (Caplan's syndrome), and BOOP are accepted rheumatoid manifestations. The association of RA with bronchiectasis or with diffuse interstitial fibrosis, however, is questionable [McMahon, 1993; Shadick, 1994]. In any case, the appearance of pulmonary lesions in a patient with RA makes it necessary to rule out the presence of a neoplastic process, infection, or a drug side effect (pneumonitis due to gold salts or methotrexate).

When to suspect:
Pulmonary disease should be suspected in the event of pleuritic pain, shortness of breath, either progressive or of recent onset, or hemoptysis.

Pleural disease:
Clinical description: The incidence of pleuritis in RA patients is nearly 20% [Jurik, 1982]. It is usually asymptomatic and especially affects male patients with seropositive and nodular RA. When it is symptomatic, it manifests as pleuritic pain and pleural effusion.
Diagnosis: Low cell count in the pleural fluid (<5,000 leukocytes/mm^3), low concentration of glucose (<40 mg/dl) and complement, together with a high total protein content.
Treatment: Treatment includes thoracocentesis to obtain an exudate and rule out other pathologies (infection or neoplasm), full doses of NSAIDs, and half-doses of steroids (10-20 mg/day of prednisone).

Rheumatoid nodules:
Clinical description: Intrapulmonary rheumatoid nodules usually remain asymptomatic, except when they cavitate, in which case they may become superinfected or produce hemoptysis. The presence of pulmonary nodules has most frequently been described in RA patients exposed to inorganic dust (Caplan's syndrome in coal miners). All pulmonary nodules should be biopsied to rule out neoplasia.
Diagnosis: The only certain diagnosis of rheumatoid nodules is histological.
Treatment: The nodules have not been shown to respond to pharmacological treatment, nor do they usually require surgical treatment unless complications occur (pneumothorax).

Interstitial fibrosis:
Clinical description: Diffuse interstitial fibrosis affects 10% of patients with RA [Jurik, 1982]. Its clinical presentation is no different from the idiopathic syndrome, and it presents as a slowly progressing shortness of breath.
Diagnosis: In all RA patients with pulmonary findings on the physical examination (fine basal crepitations) or on the radiography (reticular or reticulo-nodular pattern), the physician should request blood gas analysis and respiratory function tests (diffusion test). High resolution tomography, although it does not detect pulmonary inflammation, is a highly specific and sensitive technique for the diagnosis of pulmonary interstitial fibrosis.
Treatment: Interstitial disease of recent onset (acute) is an indication for prednisone therapy (1-1.5 mg/kg/day). Patients who do not respond can be treated with cyclophosphamide or azathioprine, although there is no evidence that these agents reduce the progression of fibrosis.

Bronchiolitis obliterans with organizing pneumonia (BOOP):
Clinical description: BOOP is a rare pulmonary disease that has been related with RA [Rees, 1991]. It presents with cough and severe shortness of breath of recent onset.
Diagnosis: Chest X-ray shows bilateral opacities of the pulmonary parenchyma without loss of volume. High resolution tomography reveals patchy areas in the pulmonary parenchyma, which are

usually peripheral. A definitive diagnosis requires thoracoscopic lung biopsy, with the observation of intraluminal plugs in the bronchioles.
Treatment: Oral prednisone (1.5 mg/kg/day) in a single daily dose for 4-6 weeks, then slowly tapering off until discontinuing the drug in 4-6 months.

8.6 Felty's syndrome

8.6.1 Felty's syndrome is characterized by the presence of splenomegaly, leukopenia (<3,500/mm^3), and neutropenia (<2,000/mm^3) in patients meeting RA criteria.

8.6.2 The use of filgastrim is recommended when the absolute neutrophil count is less than 1,000/mm^3 and the patient has a history of associated severe infection.

Background and diagnosis:
Felty's syndrome is an infrequent but serious extra-articular manifestation of RA. Patients with this syndrome meet the criteria for RA and in addition have splenomegaly, leukopenia (<3,500/mm^3), and neutropenia (<2,000/mm^3). Its prognosis is largely governed by the higher incidence of systemic manifestations, mainly bacterial infections. This higher incidence of infection is due both to neutropenia and to defective functioning of the neutrophils.

Treatment:
There are no controlled studies showing the efficacy of any specific treatment for Felty's syndrome, thus the patient should be managed the same as for RA, together with prophylactic measures against infection and empirical treatment for fever the same as those used in patients with secondary neutropenia due to the use of cytotoxic drugs. These recommendations will vary in each center depending on the frequency of isolation of particular infectious agents, thus each center should use its own guidelines.

Filgastrim is recommended when the absolute neutrophil count is lower than 1,000/mm^3 and the patient has a history of severe infection associated with the course of Felty's syndrome. A bone marrow biopsy should be performed before using filgastrim, since myeloid processes may simulate Felty's syndrome. In refractory cases surgical splenectomy or embolization of the splenic artery is indicated.

8.7 Secondary Sjögren's syndrome

8.7.1 A patient with RA is considered to have secondary Sjögren's syndrome (SSS) if there are signs and symptoms indicative of xerophthalmia and xerostomia.

8.7.2 There are no specific recommendations for modifying the course of SSS in RA. This guideline recommends symptomatic treatment of xerophthalmia and xerostomia. Dental and ophthalmological examinations are recommended every 6 months.

Background and diagnosis:
An RA patient is considered to have SSS if there are objective signs and symptoms of xerophthalmia together with objective signs and symptoms of xerostomia.

Objective signs of xerophthalmia are considered to be an altered Schirmer test, together with a diagnosis of keratoconjunctivitis sicca by rose Bengal staining or fluorescein.

Objective signs of xerostomia are considered to be reduced production of saliva measured by Lashley cup or other methods, together with a positive minor salivary gland biopsy and a lymphoid foci count of 2 or higher, measured as the average of four salivary gland lobules.

A differential diagnosis should be made in patients with sarcoidosis, lymphoma, AIDS, hepatitis, autonomous neuropathy, and salivary gland hypertrophy.

Treatment:
There are no specific recommendations for modifying the course of SSS in RA.

Dryness of the eyes should be treated with:

- Withdrawal, if possible, of drugs that produce ocular dryness, such as drugs for hypertension, diuretics, and psychotropic drugs
- Use of artificial tears
- Avoidance of dry areas, those that are excessively warm, or contain irritating gases, including tobacco smoke

- Temporary or permanent surgical occlusion of the tear duct.

Dryness of the mouth should be treated with:

- Withdrawal, if possible, of drugs that produce mouth dryness, such as drugs for hypertension, diuretics, and psychotropic drugs
- Use of artificial saliva
- Use of sugar-free lemon drops
- Use of oral pilocarpine (5 mg/6 h).

Multidisciplinary teams should be created consisting of a rheumatologist, a dentist, and an ophthalmologist. Dental and opthalmological examinations are recommended every 6 months.

8.8 Vasculitis

8.8.1 Rheumatoid vasculitis is understood to be a set of vascular processes (periungual splinter hemorrhages, palpable purpura, polyarteritis nodosa) with variable prognosis and treatment.

8.8.2 Palpable purpura should be treated with full doses of NSAIDs and medium to low doses of prednisone (15-30 mg/day). Polyarteritis nodosa is treated initially with high- dose steroids (40-120 mg/day of prednisone). If there is no response, cyclophosphamide can be added, either 2-3 mg/kg/day orally or 0.5-1 g/m^2 in intravenous pulses of 2 to 4 weeks.

Background:
Rheumatoid vasculitis is an infrequent extra-articular manifestation of RA. It appears in RA of long evolution, often with little or no joint inflammation. Risk factors for rheumatoid vasculitis are male gender, positive RF, the presence of other extra-articular manifestation of RA, and time of disease evolution.

Palpable purpura:
Diagnosis: Diagnosed clinically. Systematic skin punch biopsy is not recommended for histopathological confirmation, unless a vascular process other than small vessel leukocytoclastic vasculitis is suspected. Recently prescribed drugs should be reviewed to identify a possible pharmacological cause of the palpable purpura.
Treatment: Generally disappears spontaneously. The most important factor in treatment is rest. If it does not disappear, palpable purpura should be treated with full doses of NSAIDs and medium to low doses of prednisone, beginning with 15 to 30 mg/day and progressively reducing the dosage depending on disease evolution.

Polyarteritis nodosa-type rheumatoid vasculitis:
Diagnosis: This is the most severe form of rheumatoid vasculitis and is life threatening in many patients. Histopathological confirmation is recommended whenever possible, since treatment of this form of vasculitis is frequently accompanied by severe adverse effects. Nevertheless, the physician can initiate treatment without histopathological confirmation in the most common and typical clinical presentations such as distal necrosis, skin ulceration, or multiple mononeuritis. Depending on the clinical manifestations, various complementary studies should be made, such as liver and kidney tests, arteriography, electromyogram-electroneurogram, skin biopsy, subcutaneous tissue biopsy, or biopsy of the sural nerve.
Treatment: Initial treatment is with high-dose steroids: from 40 to 120 mg of prednisone or its equivalent, in single or divided doses. The dosage selected for a particular patient will depend on the severity of the process and the threat to life. If the clinical manifestations are not controlled with high-dose prednisone or if they reappear when trying to reduce the dosage, cyclophosphamide can be added, either 2-3 mg/kg/day orally or 0.5 to 1 g/m^2 in intravenous pulses every 2 to 4 week.

Periungual splinter hemorrhages:
Although periungual splinter hemorrhages are traditionally included in the vascular manifestations associated with RA, they are not histologically related with vasculitis.
Diagnosis: They are diagnosed clinically and do not require complementary examinations.
Treatment: No specific treatment is required. Close clinical monitoring is recommended for the early identification and treatment of vascular phenomena that may develop in the future.

ACRONYMS

ACR	American College of Rheumatology
AIMS	Arthritis Impact Measurement Scales

APR	Acute phase reactants
ARA	American Rheumatism Association
ASA	Acetylsalicylic acid
AUR	Auranofin
AZA	Azathioprine
BNCS	*Biblioteca Nacional de Ciencias de la Salud* (National Library of the Health Sciences)
BOOP	Bronchiolitis obliterans with organizing pneumonia
BP	Blood pressure
CLQ	Chloroquine
CPA	Cyclophosphamide
CPG	Clinical practice guideline
CRP	C-reactive protein
CS	Corticosteroids
CSA	Cyclosporin A
DAS	Disease activity score
DAS 28	Disease activity score counting 28 joints
DP	D-penicillamine
ESR	Erythrocyte sedimentation rate
ETN	Etanercept
EULAR	European Leagues Against Rheumatism
FDA	Food and Drug Administration
FIdeM	*Fundación Ignacio de Mercado* (Ignacio de Mercado Foundation)
GUIPCAR	*Guía de Práctica Clínica para el manejo de Artritis Reumatoide en España* (Clinical Practice Guideline for the Mangement of Rheumatoid Arthritis in Spain)
HAQ	Health Assessment Questionnaire
HCQ	Hydroxychloroquine
IFM	Infliximab
IG	Injectable gold
ILAR	International Leagues Against Rheumatism

IOM	Institute of Medicine (National Academy of Sciences)
ISCIII	*Instituto de Salud Carlos III* (Carlos III Health Institute)
LEF	Leflunomide
MCH	Mean corpuscular hemoglobin
MCP	Metacarpophalangeal joint
MCV	Mean corpuscular volume
MHAQ	Modified Health Assessment Questionnaire
MTP	Metatarsophalangeal joint
MTX	Methotrexate
NIWI	*Nederlands Instituut voor Wetenschappelijke Informatiediensten* (Netherlands Institute for Scientific Information Services)
NPJ	Number of painful joints
NPJ28	Number of painful joints out of 28 joints
NPJ44	Number of painful joints out of 44 joints
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSJ	Number of swollen joints
NSJ28	Number of swollen joints out of 28 joints
NSJ44	Number of swollen joints out of 44 joints
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
OR	Odds ratio
PCB	Placebo
PGA	Patient's global assessment (of disease or health)
PIP	Proximal interphalangeal joint
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RI	Ritchie index
SER	*Sociedad Española de Reumatología* (Spanish Society of Rheumatology)
SSS	Secondary Sjögren's syndrome
SSZ	Sulphasalazine

TAISS	*Técnicas Avanzadas de Investigación en Servicios de Salud* (Advanced Research Techniques in the Health Services)
TB	Tuberculosis
TNF	Tumor necrosis factor
UISS	*Unidad de Investigación en Servicios de Salud* (Health Services Research Unit)
VAS	Visual analog scale
WHO	World Health Organization

APPENDICES

Appendix 1. Data collection instruments for parameters used in initial evaluation and monitoring of RA patients

This appendix contains a model data collection sheet for the evaluation and monitoring of RA patients. This model can be adapted to each specialist's needs in accordance with the way the particular hospital or clinical practice is run, and can be added to the patient's usual clinical record.

First, there are three scales that the patient should fill out with reference to the previous week: change with respect to the last visit, pain, and global assessment of disease. The bottom half is for the physician. It is useful to mark the swollen joints with a dot (•) and the painful joints with an **X**.

The usual procedure is to give this sheet to the patient at the end of the visit, and ask the patient to fill it out at home the day before returning for the next appointment. The physician should emphasize that this is not to be done any sooner, and that the patient should fill out the form thinking only of the previous 7 days. The bottom half is for the physician's evaluation.

The HAQ, also included in this appendix, should be printed on the back of the same sheet.

Finally, this appendix also includes instructions on how to correct the HAQ, the most commonly used joint indices, and different ways of calculating the DAS.

Patient Home Worksheet

Complete this section only

Clinical History |__|__|__|__|__| **Date** _____

Please answer the following questions **<u>one day before</u>** your appointment with the rheumatologist.

1. How is your **arthritis** in comparison with your **last visit**?

☐ Much better ☐ Somewhat better ☐ The same ☐ Somewhat worse ☐ Much worse

2. How much **pain** have you noted during this **past week**?

No pain Worse pain

1 2 3 4 5 6 7 8 9 10

3. In general, how has your **arthritis** been during this **past week**?

Very good Very bad

PGA (0-100)

1 2 3 4 5 6 7 8 9 10

Physician

Physician's global assessment of disease.

Very good Very bad

1 2 3 4 5 6 7 8 9 10

- NSJ:
- NPJ:
- RI:
- ESR: /CPR:

DAS=0.54(√R1)+0.065(NSJ)+0.33(In ESR)+0.0072(PGA)

DAS28=0.56(√NPJ28)+0.28(√NSJ28)+0.70(In ESR)+0.014(PGA)

NOTE: Original Spanish evaluation sheet provided by Enrique Batlle Gualda. University General Hospital of Alicante.

Health Assessment Questionnaire (HAQ)

Name _____ **Date** _____

We are interested in learning how your illness affects your ability to function in daily life.
Please feel free to add any comments at the end of this form.

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
	Score = 0	*Score = 1*	*Score = 2*	*Score = 3*
DRESSING AND GROOMING - Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
- Shampoo your hair?	☐	☐	☐	☐
ARISING - Are you able to:				
- Stand up from a straight chair?	☐	☐	☐	☐

- Get in and out of bed?	☐	☐	☐	☐
EATING - Are you able to:				
- Cut your meat?	☐	☐	☐	☐
- Lift a full cup or glass to your mouth?	☐	☐	☐	☐
- Open a new milk carton?	☐	☐	☐	☐
WALKING - Are you able to:				
- Walk outdoors on flat ground?	☐	☐	☐	☐
- Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Cane	☐ Devices used for dressing (buttonhook, zipper pull, long handled shoe horn, etc.)
☐ Walker	☐ Built up or special utensils
☐ Crutches	☐ Special or built up chair
☐ Wheelchair	☐ Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming	☐ Eating
☐ Arising	☐ Walking

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do
	Score = 0	*Score = 1*	*Score = 2*	*Score = 3*
HYGIENE - Are you able to:				
- Wash and dry your entire body?	☐	☐	☐	☐
- Take a tub bath?	☐	☐	☐	☐
- Get on and off the toilet?	☐	☐	☐	☐
REACH - Are you able to:				
- Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐

- Bend down to pick up clothing from the floor?	☐	☐	☐	☐

GRIP - Are you able to:

- Open car doors?	☐	☐	☐	☐
- Open jars which have been previously opened?	☐	☐	☐	☐
- Turn faucets on and off?	☐	☐	☐	☐

ACTIVITIES - Are you able to:

- Run errands and shop?	☐	☐	☐	☐
- Get in and out of a car?	☐	☐	☐	☐
- Do chores such as vacuuming or yardwork?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of these activities:

☐ Raised toilet seat
☐ Bathtub seat
☐ Jar opener (for jars previously opened)
☐ Bathtub bar
☐ Long-handled appliances for reach
☐ Long-handled appliances in bathroom
☐ Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene
☐ Reach
☐ Gripping and opening things
☐ Errands and chores

SCORING OF HAQ
Add the maximum score for each of the 8 sections and divide by 8 to give a score between 0-3.
If aid/device or help is needed the score for that activity automatically = 2 *(unless 3 has already been ticked).*
Normal function = 0
Most affected function = 3

Indices for the evaluation of joint inflammation and pain

	ACR (66/68)	Ritchie (53)	NSJ (44)	Fuchs (28)
Cervical spine	-	+*m	-	-

Temporomandibular	+	+*	-	-
Sternoclavicular	+	+*	+	-
Acromioclavicular	+	+*	+	-
Shoulder	+	+	+	+
Elbow	+	+	+	+
Wrist	+	+	+	+
Metacarpophalangeal	+	+*	+	+
Proximal interphalangeal	+	+*	+	+
Distal interphalangeal	+	-	-	-
Hip	+	+m	-	-
Knee	+	+	+	+
Ankle	+	+	+	-
Subtalar	+	+m	-	-
Midtarsal	+	+*m	-	-
Metatarsophalangeal	+	+*	+	-
Interphalangeal (foot)	+	-	-	-
- The joints marked with an asterisk (*) are counted as a single joint. - In the ARA/ACR index the subtalar and midtarsal joints are counted as a single joint. - The Ritchie index counts (0-3) the presence of tenderness or pain on motion (**m**)				

Disease Activity Score

Ranges from 0 (no disease activity) to 10 (maximum disease activity)

DAS28 with four variables:

$$DAS28=0.56(\sqrt{NPJ28})+0.28(\sqrt{NSJ28})+0.70(\ln ESR)+0.014(PGA)$$

DAS28 with three variables:

$$DAS28=0.56\ (\sqrt{NPJ28}) + 0.28\ (\sqrt{NSJ28}) + 0.70\ (\ln ESR) + 1.08 + 0.16$$

Formula to transform original DAS to DAS28:

$$DAS28 = 1.072\ (DAS) + 0.938$$

Original DAS with four variables:

$$DAS=0.54(\sqrt{RI}) +0.065(NSJ44) + 0.33(In\ ESR) + 0.0072(PGA)$$

Original DAS with three variables:

$$DAS = 0.54\ (\sqrt{RI}) + 0.065\ (NSJ44) + 0.33\ (In\ ESR) + 0.224$$

NPJ28: Number of painful joints based on a count of 28 joints
NSJ28: Number of swollen joints based on a count of 28 joints
ln: Natural logarithm
ESR: Erythrocyte sedimentation rate
PGA: Patient's global assessment of health or disease on a VAS from 0 (very good) to 100 (very poor). Either of the two scales produces the same results, although the latter one is preferable.
RI: Ritchie index
NSJ44: Number of swollen joints based on a count of 44 joints

Appendix 2. Initial RA treatment with DMARDs, according to the complete classification scheme (144 patient scenarios)

The following list shows how the 144 different patient scenarios were classified as a function of disease characteristics, together with the recommended treatment/s in each case.

I. PATIENT WITH <6 SWOLLEN JOINTS

A.1. No erosions and has NOT taken NSAIDs and/or corticosteroids during the last 3 months

1. Normal acute phase reactants

a. HAQ <1

- RF <40 — NSAIDs and/or corticosteroids
- RF 40-100 — NSAIDs and/or corticosteroids or chloroquine
- RF >100 — NSAIDs and/or corticosteroids or chloroquine or sulphasalazine

b. HAQ ≥1

- RF <40 — NSAIDs and/or corticosteroids
- RF 40-100 — NSAIDs and/or corticosteroids or chloroquine or sulphasalazine
- RF >100 — NSAIDs and/or corticosteroids or chloroquine or sulphasalazine

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 — NSAIDs and/or corticosteroids or chloroquine or sulphasalazine
- RF 40-100 — NSAIDs and/or corticosteroids or chloroquine or sulphasalazine
- RF >100 — NSAIDs and/or corticosteroids or methotrexate

b. HAQ ≥1

- RF <40 NSAIDs and/or corticosteroids or methotrexate or chloroquine
- RF 40-100 NSAIDs and/or corticosteroids or methotrexate
- RF >100 NSAIDs and/or corticosteroids or methotrexate

A.2. No erosions and HAS taken NSAIDs and/or corticosteroids during the last 3 months

1. Normal acute phase reactants

a. HAQ <1
- RF <40 Chloroquine
- RF 40-100 Chloroquine or methotrexate
- RF >100 Chloroquine or methotrexate

b. HAQ ≥1
- RF <40 Methotrexate or sulphasalazine or chloroquine
- RF 40-100 Methotrexate or sulphasalazine
- RF >100 Methotrexate or sulphasalazine

2. Elevated acute phase reactants

a. HAQ <1
- RF <40 Chloroquine or sulphasalazine or methotrexate
- RF 40-100 Methotrexate or sulphasalazine
- RF >100 Methotrexate

b. HAQ ≥1
- RF <40 Methotrexate or sulphasalazine
- RF 40-100 Methotrexate
- RF >100 Methotrexate

B. From 1 to 3 erosions

1. Normal acute phase reactants

a. HAQ <1
- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

b. HAQ ≥1
- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

C. More than 3 erosions

1. Normal acute phase reactants

a. HAQ <1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

II. PATIENT WITH 6-10 SWOLLEN JOINTS

A.1. No erosions and has NOT taken NSAIDs and/or corticosteroids during the last 3 months

1. Normal acute phase reactants

a. HAQ <1

- RF <40 — NSAIDs and/or corticosteroids or methotrexate
- RF 40-100 — NSAIDs and/or corticosteroids or methotrexate
- RF >100 — NSAIDs and/or corticosteroids or methotrexate or injectable gold

b. HAQ ≥1

- RF <40 — NSAIDs and/or corticosteroids or methotrexate
- RF 40-100 — NSAIDs and/or corticosteroids or methotrexate
- RF >100 — NSAIDs and/or corticosteroids or methotrexate or injectable gold

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 — NSAIDs and/or corticosteroids or methotrexate
- RF 40-100 — NSAIDs and/or corticosteroids or methotrexate or injectable gold
- RF >100 — Methotrexate

b. HAQ ≥1

- RF <40 — Methotrexate
- RF 40-100 — Methotrexate
- RF >100 — Methotrexate

A.2. No erosions and HAS taken NSAIDs and/or corticosteroids during the last 3 months

1. Normal acute phase reactants

a. HAQ <1

- RF <40 — Methotrexate
- RF 40-100 — Methotrexate
- RF >100 — Methotrexate or injectable gold

b. HAQ ≥1

- RF <40 — Methotrexate
- RF 40-100 — Methotrexate or injectable gold
- RF >100 — Methotrexate or injectable gold

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 — Methotrexate
- RF 40-100 — Methotrexate
- RF >100 — Methotrexate

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

B. From 1 to 3 erosions

1. Normal acute phase reactants

a. HAQ <1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

C. More than 3 erosions

1. Normal acute phase reactants

a. HAQ <1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate

- RF >100 Methotrexate

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

III. PATIENT WITH >10 SWOLLEN JOINTS

A.1 No erosions and has NOT taken NSAIDs and/or corticosteroids during the last 3 months

1. Normal acute phase reactants

a. HAQ <1

- RF <40 NSAIDs and/or corticosteroids or methotrexate or injectable gold
- RF 40-100 NSAIDs and/or corticosteroids or methotrexate or injectable gold
- RF >100 NSAIDs and/or corticosteroids or methotrexate or injectable gold

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 NSAIDs and/or corticosteroids or methotrexate or injectable gold
- RF 40-100 NSAIDs and/or corticosteroids or methotrexate or injectable gold
- RF >100 NSAIDs and/or corticosteroids or methotrexate or injectable gold

b. HAQ ≥1

- RF <40 NSAIDs and/or corticosteroids or methotrexate or injectable gold
- RF 40-100 Methotrexate or injectable gold
- RF >100 Methotrexate or injectable gold

A.2 No erosions and HAS taken NSAIDs and/or corticosteroids during the last 3 months

1. Normal acute phase reactants

a. HAQ <1

- RF <40 — Methotrexate
- RF 40-100 — Methotrexate
- RF >100 — Methotrexate

b. HAQ ≥1

- RF <40 — Methotrexate
- RF 40-100 — Methotrexate
- RF >100 — Methotrexate

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 — Methotrexate
- RF 40-100 — Methotrexate
- RF >100 — Methotrexate

b. HAQ ≥1

- RF <40 — Methotrexate
- RF 40-100 — Methotrexate
- RF >100 — Methotrexate

B. From 1 to 3 erosions

1. Normal acute phase reactants

a. HAQ <1

- RF <40 — Methotrexate
- RF 40-100 — Methotrexate
- RF >100 — Methotrexate or injectable gold

b. HAQ ≥1

- RF <40 — Methotrexate
- RF 40-100 — Methotrexate or methotrexate + injectable gold
- RF >100 — Methotrexate or methotrexate + injectable gold

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 — Methotrexate or leflunomide
- RF 40-100 — Methotrexate or leflunomide

- RF >100 Methotrexate or leflunomide

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate or methotrexate + injectable gold
- RF >100 Methotrexate or methotrexate + injectable gold

C. More than 3 erosions

1. Normal acute phase reactants

a. HAQ <1

- RF <40 Methotrexate
- RF 40-100 Methotrexate
- RF >100 Methotrexate or injectable gold or leflunomide

b. HAQ ≥1

- RF <40 Methotrexate
- RF 40-100 Methotrexate or methotrexate + injectable gold
- RF >100 Methotrexate or methotrexate + injectable gold

2. Elevated acute phase reactants

a. HAQ <1

- RF <40 Methotrexate or methotrexate + sulphasalazine
- RF 40-100 Methotrexate or leflunomide
- RF >100 Methotrexate or leflunomide

b. HAQ ≥1

- RF <40 Methotrexate or injectable gold
- RF 40-100 Methotrexate or methotrexate + injectable gold
- RF >100 Methotrexate or methotrexate + injectable gold

TABLES

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2.3. Articles that complement one of the articles on the clinical trials (Tables 7, 8, and 9)

Complement of 21

C1. Weinblatt ME, Polisson R, Blotner SD, Sosman JL, Aliabadi P, Baker N, et al. The effects of drug therapy on radiographic progression of rheumatoid arthritis: results of a 36-week randomized trial comparing methotrexate and auranofin. Arthritis Rheum 1993; 36(5): 613-9.

Complement of 22

C2. Lopez-Mendez A, Daniel WW, Reading JC, Ward JR, Alarcon GS. Radiographic assessment of disease progression in rheumatoid arthritis patients enrolled in the cooperative systematic studies of the rheumatic diseases program randomized clinical trial of methotrexate, auranofin, or a combination of the two. Arthritis Rheum 1993; 36(10): 1364-9.

Complement of 30

C3. Ward JR, Williams HJ, Boyce E, Egger MJ, Reading JC, Samuelson CO. Comparison of auranofin, gold sodium thiomalate, and placebo in the treatment of rheumatoid arthritis: subsets of responses. Am J Med 1983; 75(6A): 133-7.

Complement of 33

C4. Davis P, Menard H, Thompson J, Harth M, Beaudet F. One-year comparative study of gold sodium thiomalate and auranofin in the treatment of rheumatoid arthritis. J Rheumatol 1985; 12(1): 60-7.

Complement of 37

C5. Van Riel PLCM, Larsen A, Van de Putte LBA, Gribnau FWJ. Effects of aurothioglucose and auranofin on radiographic progression in rheumatoid arthritis. Clin Rheumatol 1986; 5(3): 359-64.

Complement of 39

C6. Schattenkirchner M, Kaik B, Muller-Fassbender H, Rau R, Zeidler H. Auranofin and sodium aurothiomalate in the treatment of rheumatoid arthritis: a double-blind, comparative multicenter study. J Rheumatol Suppl 1982; 8: 184-9.

Complement of 47

C7. Rau R, Herborn G, Menninger H, Sangha O. Progression in early erosive rheumatoid arthritis: 12 month results from a randomized controlled trial comparing methotrexate and gold sodium thiomalate. Br J Rheumatol 1998; 37(11): 1220-6.

C8. Rau R, Herborn G, Menninger H, Blechschmidt J. Comparison of intramuscular methotrexate and gold sodium thiomalate in the treatment of early erosive rheumatoid arthritis: 12 month data of a double-blind parallel study of 174 patients. Br J Rheumatol 1997; 36(3): 342-52.

Complement of 49

C9. Porter D, Madhok R, Hunter JA, Capell HA. Prospective trial comparing the use of sulphasalazine and auranofin as second line drugs in patients with rheumatoid arthritis. Ann Rheum Dis 1992; 51(4): 461-4.

Complement of 50

C10. Capell HA, Marabani M, Madhok R, Torley H, Hunter JA. Degree and extent of response to sulphasalazine or penicillamine therapy for rheumatoid arthritis: results from a routine clinical environment over a two-year period. Q J Med 1990; 75(276): 335-44.

Complement of 52

C.11. Heijde DM, Riel PL, Nuver-Zwart IH, Gribnau FW, Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989; 1(8646): 1036-8.

C12. Van der Heijde DM, Van Riel PLCM, Van de Putte LBA. Sensitivity of a Dutch Health Assessment Questionnaire in a trial comparing hydroxychloroquine vs sulphasalazine. Scand J Rheumatol 1990; 19(6): 407-12.

2.4. Articles that are redundant with one of the articles on clinical trials (Tables 7, 8, and 9)

Redundant with 1

R1. Woodland J, Mason RM, Harris J, Dixon AS, Currey HL, Brownjohn AM, et al. Trial of azathioprine, cyclophosphamide, and gold in rheumatoid arthritis. Ann Rheum Dis 1974; 33(4): 399-401.

Redundant with 7

R2. Berry H, Liyanage S, Durance R, Barnes CG, Berger L. Trial comparing azathioprine and penicillamine in treatment of rheumatoid arthritis. Ann Rheum Dis 1976; 35(6): 542-3.

Redundant with 19

R3. Strand V, Tugwell P, Bombardier C, Maetzel A, Crawford B, Dorrier C, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Arthritis Rheum 1999; 42(9): 1870-8.

Redundant with 24

R4. Jeurissen MEC, Boerbooms AMT, Van de Putte LBA, Doesburg WH, Lemmens AM. Influence of methotrexate and azathioprine on radiologic progression in rheumatoid arthritis: a randomized, double-blind study. Arch Intern Med 1991; 114: 999-1004.

R5. Kerstens PJSM, Boerbooms AMT, Jeurissen MEC, Westgeest TAA, Van Erp A, Mulder J, et al. Antiperinuclear factor and disease activity in rheumatoid arthritis: longitudinal evaluation during methotrexate and azathioprine therapy. J Rheumatol 1994; 21(12): 2190-4.

Redundant with 25

R6. Willkens RF, Stablein D. Combination treatment of rheumatoid arthritis using azathioprine and methotrexate: a 48-week controlled clinical trial. J Rheumatol 1996; 23(Suppl 44): 64-8.

R7. Willkens RF, Urowitz MB, Stablein DM, McKendry RJR, Berger RG, Box JH, et al. Comparison of azathioprine, methotrexate, and the combination of both in the treatment of rheumatoid arthritis: a controlled clinical trial. Arthritis Rheum 1992; 35(8): 849-56.

Redundant with 30

R8. Williams HJ, Ward JR, Egger MJ, Reading JC, Samuelson CO, Altz-Smith M, et al. Auranofin, gold sodium thiomalate, and placebo in the treatment of rheumatoid arthritis: cooperative systematic studies of rheumatic diseases. Clin Rheumatol 1984; 3(suppl.1): 39-50.

R9. Williams HJ, Ward JR. Comparison of oral and parenteral gold therapy and placebo in the treatment of rheumatoid arthritis. Scand J Rheumatol Suppl 1983; 51: 92-9.

Redundant with 39

R10. Schattenkirchner M, Bröll H, Kaik B, M¨ller-Fassbender H, Rau R, Zeidler H. Auranofin and gold sodium thiomalate in the treatment of rheumatoid arthritis: a one-year, double-blind, comparative multicenter study. Klin Wochenschr 1988; 66(4): 167-74.

Redundant with 41

R11. Huskisson EC, Gibson TJ, Wykeham Balme H, Berry H, Burry HC, Grahame R, et al. Penicillamine or gold for rheumatoid arthritis?: multicentre trial using 'blind' observers: the first six months. Ann Rheum Dis 1974; 33(4): 399.

Redundant with 52

R12. Van der Heijde DMFM, Van Riel PLCM, Nuwer-Zwart IH, Van de Putte LBA. Alternative methods for analysis of radiographic damage in a randomized, double blind, parallel group clinical trial comparing hydroxychloroquine and sulfasalazine. J Rheumatol 2000; 27(2): 535-8.

Redundant with 63

R13. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999; 354(9194): 1932-9.