Effects of an Immunostimulating Agent on Acute Exacerbations and Hospitalizations in Patients with Chronic Obstructive Pulmonary Disease

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The PARI-IS Study is a double-blind placebo-controlled randomized clinical trial to study the effect of an immunostimulating agent to prevent acute respiratory exacerbation in patients with COPD. Three hundred eighty-one ambulatory patients (190 placebo and 191 immunostimulant) were followed at home for 6 mo by experienced research nurses. The risk of having at least one episode of acute exacerbation (primary outcome) was similar in the two groups ($p = 0.872$). In contrast, the total number of days of hospitalization for a respiratory problem was 55% less in the group treated with OM-85 BV (287 d) than in the group treated with placebo (642 d). Patients treated with OM-85 BV spent an average of 1.5 d in hospital compared with 3.4 d for patients treated with placebo ($p = 0.037$). The risk of being hospitalized for a respiratory problem was 30% lower in the treated group (16.2%) than in the placebo group (23.2%); $p = 0.089$. Eight deaths were observed: two in patients treated with OM-85 BV and six in patients treated with placebo ($p = 0.153$). During the course of the study dyspnea improved slightly in patients treated with OM-85 BV, whereas it deteriorated slightly in patients receiving placebo ($p = 0.028$). These results suggest that this immunostimulating agent may be beneficial for patients with COPD by reducing the likelihood of severe respiratory events leading to hospitalization. Collet JP, Shapiro S, Ernst P, Renzi P, Ducruet T, Robinson A and the PARI-IS Study Steering Committee and Research Group. Effects of an immunostimulating agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease.

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Chronic obstructive pulmonary disease (COPD) denotes a group of diseases that affect the respiratory tract, characterized by chronic airflow limitation, dyspnea, and hypoxemia (1), that is, unlike asthma, largely irreversible. The clinical course of COPD is one of gradual progressive impairment, which may eventually lead to oxygen dependence, respiratory failure, and cor pulmonale (1–3). On average, patients with COPD experience from one to four episodes of acute exacerbations (or acute bronchitis) per year (2). These episodes are characterized by an increase in one or several of the following: cough, sputum quantity or purulence, and dyspnea (4). During acute episodes, patients cannot perform their usual activities, and a few of them need to be hospitalized because of respiratory failure or complicating pneumonia. As a consequence, COPD is the fourth most common cause of morbidity in the United States (5), being responsible, annually, for more than 17 million office visits and 13% of all hospitalizations. In 1986 COPD and allied conditions were the fifth leading cause of

death (3.6% of all deaths) (6, 7). The above figures probably underestimate the impact of COPD on health and longevity since death certificates often cite COPD as a contributory factor rather than the principal cause of death (8–10).

The etiology of acute exacerbations remains controversial. Viruses are believed to play an important role as the primary agent, but bacteria that can be identified in sputum during exacerbation can also be readily isolated in the sputum of patients who are not experiencing such deterioration (2). Thus, sputum culture is not a useful test for the diagnosis of acute bronchitis in patients with COPD. With regard to treatment, since the study of Anthoninsen and coworkers in 1987 (11) most clinicians would advocate the use of antibiotics. The high prevalence of chronic bronchitis and the frequency of acute exacerbations result in substantial personal and health care costs. Any intervention that could reduce the incidence of acute exacerbations in patients with COPD is likely to have a major impact on the morbidity and the quality of life, as well as on the costs resulting from this disease.

Immunostimulating agents made from bacterial extracts represent a class of medications that contains antigens derived from several bacterial strains and whose potential benefit results from the stimulation of the nonspecific component of the immune system. OM-85 BV is an immunostimulating agent made from eight different species of bacteria that are frequently present in the lower respiratory tract: *Hemophilus influenzae*, *Diplococcus pneumoniae*, *Klebsiella pneumoniae* and *ozaenae*, *Staphylococcus aureus*, *Streptococcus pyogenes* and *viridans*, and *Neisseria catarrhalis*. Evidence regarding the mechanism of action of OM-85 BV is supportive of direct activation of lung macrophages and enhancement of antigen presentation to T-lymphocytes. Activation of macrophages results in an increased specific response of T-lymphocytes and B-lymphocytes, as well as a stimulation of macrophage phagocytic activity (12). Sustaining macrophage activation would maintain the immune system in a "state of alert" that would favor a rapid response to invading organism, thereby preventing clinical illness. Several randomized clinical trials (13–21) have shown that OM-85 BV can reduce the number of acute exacerbations by 25 to 50%, compared with placebo. The most recent study published in 1994 by Derenne and Delclaux (21) involved 290 elderly patients. Among those receiving placebo, 74 (51.7%) had at least one episode of acute bronchitis, whereas in the group treated with OM-85 BV only 51 (34.7%) presented such an event. Moreover, the mean number of infections was reduced by 30% in the group treated with OM-85 BV, and the frequency of use of antibiotics was 28% lower. Another recent study (17), although performed on a limited number of patients (n = 62), suggested that the drug might also improve the main symptoms that characterize COPD: patients treated with OM-85 BV had significantly decreased cough, dyspnea, and sputum after 3 mo of treatment, compared with patients treated with placebo.

The PARI-IS study (Prevention of Acute Respiratory Infections by an Immunostimulant) was implemented to assess whether OM-85 BV could protect patients with COPD against acute exacerbations thought to be related primarily to respiratory tract infections. Our objective was not only to focus on the incidence of exacerbations but also to study the effect of these episodes on both patient morbidity and consumption of health care services.

METHODS

Patients were recruited from 12 different institutions in the region of Montreal. After approval by the relevant ethics committees an initial screening of hospital charts provided the list of potential candidates for the study. Patients were contacted by mail, and those who expressed interest were seen as outpatients to assess inclusion and exclusion criteria. Eligible patients had a history of heavy smoking ($\geq$ 20 pack-years) and a FEV_1 value between 20 and 70% of predicted, which improved less than 15% after salbutamol (200 μg by inhalation). Patients with severe concomitant disease making follow-up difficult or unlikely and those who had been prescribed medications affecting the immune system (i.e., immunosupressants or systemic corticosteroids for more than 2 wks in the last month) were excluded, as well as those who had an episode of acute exacerbation treated with antibiotics within the previous month. All patients received influenza vaccination. Randomization was centralized at the SMBD Jewish General Hospital, stratified by institution and degree of ventilatory impairment (i.e., subjects were divided into those whose FEV_1 was 20 to 40% of predicted and those whose FEV_1 was greater than 40%). Block randomization in groups of four patients was carried out to insure a balanced treatment allocation within strata. The prescribed drug regimen (i.e., OM-85 BV or its placebo in capsules of identical appearance) consisted in taking one capsule per day on an empty stomach in the morning every day for 30 d followed by a repeat course of 10 consecutive days of therapy per month for 3 mo. The study drug was delivered to the patient at home by the nurse who also provided the necessary information regarding its use. Before each treatment period the patients were informed individually by their nurse of the date on which they had to resume. Patients were allowed to take any other medication required for the treatment of their condition. Compliance with the drug regimen was ascertained by the research nurses who obtained information on drug use by a structured interview of the patient and by monitoring a symptom diary in which patients had to report the use of medication. The nurses also collected the empty medication blister packs and counted leftover pills.

Information regarding acute exacerbations and other health events was collected by 10 research nurses who were each responsible for following a group of patients through monthly contacts, alternatively at home (four times) or by telephone (three times). The nurses examined the diary in which patients recorded changes in respiratory symptoms; they were taught to collect information regarding the occurrence of health events and to record symptoms in a systematic manner without interpretation. An episode was considered to represent an acute exacerbation when the patient met the following three conditions: (*1*) change in sputum (color, texture, or quantity), (*2*) occurrence of at least one additional symptom among increased shortness of breath or cough, or presence of fever, and (*3*) evidence of the nontrivial nature of the episode (as determined by either an unscheduled medical visit and/or use of antibiotics). The primary study outcome was the occurrence of at least one such episode during the 6-mo period of follow-up. Secondary outcomes included total number of acute exacerbations and hospitalization for a respiratory problem, as well as all hospitalization, change in baseline respiratory symptoms (i.e., cough, dyspnea, and sputum production), and change in quality of life (as measured with the SF-36 scale). In classifying the episodes of hospitalization according to the main reason for admission (respiratory and nonrespiratory), we sought the diagnoses from the hospital discharge summary and reviewed the hospital chart to ensure that the diagnoses were coherent with the clinical notes. This information was collected by the research coordinator (AR) who has an extensive experience of hospital charts and data abstraction. The principal reason for admission was agreed upon by a committee made of three investigators. When the clinical description raised any doubts resolution of the ambiguity was left to a reference respirologist. All this work was blind to the nature of the treatment administered. Many patients who were admitted for a nonrespiratory cause were also treated for their chronic lung condition and some developed an acute exacerbation during their hospital stay; these cases, however, were not counted as respiratory admissions for the purpose of our study.

Initially, a sample size of approximately 600 patients was targeted to provide a power of at least 80% to detect a difference in the groups at the 0.05 significance level, assuring a 25% or greater reduction in the probability of an ARI in the OM-85 BV-treated group, from an assumed probability of an ARI of 45% in the control group. For administrative reasons the beginning of the trial was postponed to November 7, 1994. Because of the delay, only two-thirds of the target

TABLE 1

COMPARISON OF THE TWO GROUPS AT BASELINE

Variables	OM-85 BV (*n = 191*)	Placebo (*n = 190*)
Male sex, (%)	69.6	71.1
Age, yr*	65.3 (7.7)	66.9 (7.7)
Education, yr*	8.8 (4.0)	8.9 (3.6)
Still smoking, %	40.8	31.1
Past hospitalization, %	62.8	68.4
Dyspnea†	45.3 (17.9)	46.4 (19.0)
FEV_1, L*	1.08 (0.41)	1.10 (0.36)
FEV_1, % pred*	42.3% (11.6)	44.0% (11.5)
FVC_1, L*	2.44 (0.79)	2.48 (0.84)
FVC, % pred*	67.7% (15.3)	68.4% (15.6)
Shortness of breath in the last month		
None, %	2.1	2.6
Less than every day, %	15.2	10.5
Every day, %	22.5	23.7
Many times a day, %	44.0	45.3
All the time, %	14.7	17.4
Unscheduled visit to doctor in last 6 mo for respiratory problem*	0.68 (1.05)	0.64 (1.07)
At least one use of antibiotics for a respiratory problem in last 6 mo, %	38.7	35.8

* Values are means with SD shown in parentheses.

† Values are mean distances on Oxygen Cost Diagram in millimeters with SD shown in parentheses.

population could be included before the end of December. To know whether it would be necessary to resume recruitment in the Fall of 1995 an interim analysis was performed in July 1995 focusing on the primary outcome only. Interpretation of interim analysis results and decisions were taken by an independent committee. Statistical analyses were carried out according to the intention-to-treat principle. Primary analyses of the incidence of one or more ARI and other categorical variables was carried out by chi-square tests. Continuous variables were compared using *t*-tests. SF-36 Quality of Life scores and comparison were computed using software provided by J. Ware (22). Secondary analysis allowed for estimation of effects both in selected subgroups and through regression models after adjustment for baseline factors. All analyses were carried out using the SAS (6-07) statistical package.

RESULTS

A total of 382 patients were randomized during a 6-wk period from November 7 to December 20, 1994. One patient was eliminated immediately after randomization because she lived too far from Montreal to be followed according to the protocol. Of the 381 patients, 191 were allocated to OM-85 BV and 190 to placebo. The comparability of the two groups with regard to most important characteristics at baseline is shown in Table 1. More patients in the placebo group than in the treated group had been hospitalized before the trial: 68.4 versus 62.8%, but examination of the cause of these previous hospitalization showed that the two groups did not differ in any substantive or systematic manner. During the course of the study eight patients died: two receiving OM-85 BV and six receiving placebo, and one left Canada. Among the 372 remaining patients, only six could not be interviewed at the last visit (1.6%) because they were hospitalized (n = 2), could not be reached (n = 2), or were not willing to be interviewed (n = 2). All these patients, however, had been interviewed the month before, thereby providing valid information for the study. On average, patients had 5.7 interviews out of a maximum of six during the study.

The primary outcome, occurrence of one or more episodes of acute exacerbation, did not differ between the two groups: 44.5% in the OM-85 BV-treated group, compared with 43.7% in the placebo-treated group ($p = 0.872$). The mean number of acute exacerbation episodes was the same in the two groups and equal to 0.57. On the basis of these results, the executive committee decided to stop the study and perform a complete analysis. In contrast to the absence of effect on the occurrence of acute exacerbations, the total number of days of hospitalization for a respiratory problem, which reflects both the number of episodes of hospitalization and the duration of stay, was 55% less in the group treated with OM-85 BV (287 d) than in the group treated with placebo (642 d) (Table 2). During the study period we observed 101 episodes of hospitalization for a respiratory problem (44 in the treated group and 57 in the reference group); patients in the group treated with OM-85 BV spent on average 1.5 d in the hospital for respiratory problems compared with 3.4 d in the group receiving placebo ($p = 0.037$). The risk of being hospitalized for a respiratory problem was 30% less in the group treated with OM-85 BV (16.2%) than in the group treated with placebo (23.2%); $p = 0.089$. Eleven of the 12 centers showed a decreased risk of hospitalization in the treated group compared to the reference group (Table 3). In contrast, the risk of being hospitalized for reasons other than a respiratory problem was similar in the two groups: 11.0% in patients treated with OM-85 BV versus 12.1% in those treated with placebo ($p = 0.74$). Duration of hospital stay is presented in Table 4; hospitalization for a respiratory reason was shorter in the group receiving OM-85 BV (mean duration, 6.5 d; SD, 8.3 d; median, 4 d) than in the group allocated to placebo (mean duration, 11.3 d; SD, 16.1 d; median, 6 d); $p = 0.058$.

Analysis by degree of initial lung function impairment ($FEV_1 > 40\%$ and $20\% < FEV_1 \leq 40\%$ of predicted) showed that the risk of hospitalization was higher in the more severe group and that the protective effect was present in both groups (Table 5).

A comparison of the change from baseline respiratory symptoms showed that cough and sputum production, measured on a 5-point scale did not differ. Change in dyspnea measured with the Oxygen Cost Diagram (23) showed that the group treated with placebo deteriorated slightly (on aver-

TABLE 2

CUMULATIVE NUMBER OF DAYS OF HOSPITALIZATION

Reason for Hospitalization	OM-85 BV (*n = 191*) (*days*)	Placebo (*n = 190*)	Difference (*days*)	Percentage Difference (%)
Respiratory problems	287	642 days	−355	−55
Nonrespiratory	189	255 days	−66	−26
All	476	897 days	−421	−47

TABLE 3

RISK OF HOSPITALIZATION IN EACH PARTICIPATING CENTER

Center	Broncho-Vaxom	Placebo	Relative Risk
1 Hôpital Maisonneuve Rosemont	5/32 (15.6%)	5/32 (31.3%)	1.0 (0.3–3.9)
2 Centre Hospitalier de Verdun	6/27 (29.6%)	7/27 (29.6%)	0.9 (0.3–2.2)
3 Hôpital Notre Dame	5/16 (31.3%)	4/17 (41.2%)	1.3 (0.4–4.1)
4 Hôpital Saint Luc	2/22 (9.1%)	6/23 (30.4%)	0.3 (0.1–1.5)
5 Hôtel Dieu de Montréal	5/20 (45.0%)	8/19 (47.4%)	0.6 (0.2–1.5)
6 Montreal Chest Hospital	1/14 (14.3%)	3/16 (25.0%)	0.4 (0.05–3.3)
7 SMBD Jewish General Hospital	2/6 (50.0%)	3/5 (60.0%)	0.4 (0.1–1.9)
8 Montreal General Hospital	0/8 (0.0%)	0/6 (0.0%)	—
9 Hôpital Sacré Coeur de Montréal	1/18 (11.1%)	2/18 (22.2%)	0.5 (0.05–5.0)
11 Lakeshore Clinic	3/8 (62.5%)	2/7 (28.6%)	1.3 (0.3–5.7)
14 Hôpital Charles Lemoine	0/5 (0.0%)	2/6 (33.3%)	—
15 Hôpital Le Gardeur	1/10 (20.0%)	2/12 (25.0%)	0.6 (0.1–5.7)
Total	31/191 (23.6%)	44/190 (31.1%)	0.7 (0.5–1.1)

TABLE 4

DURATION OF HOSPITAL STAY IN DAYS

	OM-85 BV				Placebo				
Reason for Hospitalization	(*n*)*	(*mean*)	(*SD*)	(*median*)	(*n*)*	(*mean*)	(*SD*)	(*median*)	p Value
Respiratory problems	44	6.4	8.3	4	57	11.3	16.1	6	0.058
Nonrespiratory	29	6.5	7.3	4	31	8.2	10.8	5	0.47
All	73	6.5	7.9	4	88	10.2	14.4	6	0.043

* Number of episodes.

TABLE 5

FREQUENCY OF RESPIRATORY HOSPITALIZATIONS ACCORDING TO INITIAL SEVERITY OF VENTILATORY IMPAIRMENT

	Risk of ⩾ 1 Hospitalization for Respiratory Problem		
Initial FEV_1	OM-85 BV	Placebo	p Value
20 to 40% of predicted, n = 170	20/87 (23%)	27/83 (32.5%)	0.164
> 40% of predicted, n = 211	11/104 (10.6%)	17/107 (15.9%)	0.256

age, −2.33 mm; SD, 18.3), whereas the group treated with OM-85 BV improved slightly (on average, +1.56 mm; SD, 15.4); this difference was significant ($p = 0.028$). FEV_1 decreased in both groups (on average, 5.5 ml; SD = 29.1 in the treatment group and 7.5 ml; SD, = 22.1 in the placebo group; $p = 0.54$). With regard to quality of life, change in the eight subscales and the two summary scales of the SF-36 questionnaire was, on average, minimal and not different between the two groups.

With regard to safety, 289 health events were reported (Table 6): 138 in the OM-85 BV-treated group and 151 in the placebo-treated group. Most of these events were not severe and consistent with what might be expected among a population of sick elderly patients. The number of abdominal and skin problems was slightly higher in the OM-85 BV-treated group, whereas the number of respiratory problems (mainly acute attacks of shortness of breath that did not meet the definition of acute exacerbation) was more frequent in the placebo-treated group. Eight deaths were observed during the course of the trial, six in the group treated with placebo and two in the group treated with OM-85 BV ($p = 0.153$). Four of these deaths were related to a respiratory infection, three in the placebo group.

DISCUSSION

This trial showed that the occurrence of acute exacerbation (measured by monthly patient interview) was not affected by the use of OM-85 BV. This trial also demonstrated that both

TABLE 6

ADVERSE HEALTH EVENTS IN THE STUDY POPULATION (SOME PATIENTS MAY HAVE HAD MORE THAN ONE EVENT)

	Number of Events		
Adverse Health Events Grouped by Category	OM-85 BV (*n = 191*)	Placebo (*n = 190*)	p Value
Abdominal with gastroenteritis	34	20	0.042
Pulmonary and respiratory	26	39	0.073
Cardiac	10	6	0.31
Skin	8	4	0.24
Falls	8	7	0.80
Vertigo	7	11	0.33
Urological	8	3	0.13
Musculoskeletal	3	1	0.32
Ocular	7	5	0.56
Miscellaneous	27	55	0.001
Total	138	151	

the number and length of hospital admissions were less in the group treated with OM-85 BV. As a consequence, the mean number of days spent in hospital for a respiratory problem was 55% shorter in the group treated with OM-85 BV (1.5 d) than in the group treated with placebo (3.4 d); $p = 0.037$. The beneficial effect on our secondary outcome, hospitalization, was in the direction hypothesized and had been specified a priori in the protocol. However, we expected to find a significant effect of OM-85 B on occurrence of acute exacerbation as well.

The absence of effect on occurrence of acute exacerbation contrasts with the results from previous studies (12–21) and especially the most recent one performed by Derenne and Delclaux in France (21). We propose two explanations for the discrepancy. The first relates to the mechanism of drug action, which might more conspicuously alter the development of overt diseases by stimulating the immune system to rapidly clear microorganisms rather than prevent the infection entirely. The fact that nurses were highly trained to collect any change in respiratory symptoms without interpretation, associated with the fact that patients with COPD were quickly treated with antibiotics (even when changes in symptoms were minor to prevent further development of the disease) may have resulted in our protocol being very sensitive to detect all exacerbations, even minor ones. Such minor episodes may not have been counted as acute exacerbations in previous studies using a doctor-based diagnosis (12–21). Second, there may have been misclassification of acute infectious events as suggested by the more frequent recording of respiratory problems not meeting the definition of an acute exacerbation in the placebo group (39 events) as compared with the occurrence of only 26 such events in the OM-85 BV group (Table 6). If all these respiratory events were all episodes of acute exacerbations, the group treated with OM-85 BV would have experienced less episodes than the group treated with placebo.

The risk of being hospitalized for respiratory difficulty is 30% smaller in the group treated with OM-85 BV (16.2%) than in the reference group (23.2%), whereas the risk of being hospitalized for a nonrespiratory reason is similar in the two groups: 11.0 and 12.1%, respectively. The shorter duration of stay in patients hospitalized for a nonrespiratory reason (Table 4), although not significant, may be of interest. It might be explained by the fact that whatever the reason for hospitalization, our patients also require treatment of their chronic lung condition, which may have been less severe in those receiving the immunostimulant. Moreover, the group treated by OM-85 BV may have been less susceptible to hospital-acquired respiratory infections (also responsible for increased duration of stay).

Our results suggest that OM-85 BV is effective in the prevention of severe respiratory events by helping the airways to get rid of the infecting agent more rapidly, hence, reducing the risk of hospitalization and the duration of the stay in hospital. These results are in accord with what is known about OM-85 BV. Pharmacodynamic studies provide evidence that the drug acts primarily on a variety of functions of the nonspecific immune system rather than provoking specific immune responses to the various bacterial antigens it contains. *In vitro* it has been demonstrated that OM-85 BV increases the secretion of prostaglandin E_2, interleukin-1 and -2, and tumor necrosing factor-alpha in cultured macrophages (24–26). The metabolic (production of toxic oxygen metabolites) and functional (lytic) activities in murine macrophages are increased by OM-85 BV (12) as are the antigen processing (27) and the expression of adhesion molecules in human PMNs and monocytes (28). Studies in animals have shown that OM-85 BV compensates the immunosuppressive activity of cyclophosphamide (29) and increases the secretion of prostaglandin E_2 and interleukin-1 on Peyer's patches (30). The phagocytotic activity of PMNs in a diffusion chamber implanted into the peritoneum of rabbits was stimulated with OM-85 BV (31), and the survival of experimentally infected mice was significantly improved (32). Emmerich and coworkers (33) showed that the secretion of salivary gland IgA was significantly increased in humans after OM-85 BV administration. Finally, it has been shown that gamma-interferon and macrophage activity are increased, and that the helper T-cell/suppressor T-cell ratio is modified in the bronchoalveolar lavage fluid of treated patients (33, 34).

We did not observe any change in SF-36 Quality of Life scale during the trial. This is likely related to the fact that quality of life measured at a time distant from the exacerbation is not sensitive to the effect of the drug on decreasing the severity of infections. The positive effects on dyspnea and FEV_1 are interesting to consider but difficult to interpret because they represent the change measured on a continuous scale over a 6-mo period. These results are consistent with those observed by Xinogalos and coworkers in 1992 (17) and might be related to a decrease in chronic infection. The absence of effect observed on the other major symptoms (i.e., cough and sputum production) may be partly due to the fact that this information was measured on a 5-point categorical scale, not designed to detect a change in symptoms over time. Change in symptoms (if present) might not have been great enough to provoke a change of category on the scale.

OM-85 BV has been used for more than 20 yr worldwide and has a good safety profile. Our trial confirms this profile. Most of the documented health events reported in Table 6 were of limited duration and had a favorable outcome. The total number and the distribution of events were similar in the two groups and quite compatible with what would have been observed in a population of elderly patients with a chronic disease and followed for 6 mo during the winter. The group treated with OM-85 BV experienced more gastroenteritis and less respiratory problems than the group treated with placebo. Gastroenteritis was not severe and resolved without hospitalization. It is difficult to relate this problem to the use of the medication as other trials did not report an excess of gastrointestinal problems in patients treated by OM-85 BV. The excess of nonspecific respiratory problems in the group treated by placebo may well reflect a beneficial effect of the drug; a proportion of these problems may represent real acute exacerbations although not meeting the study definition chosen a priori for the study. The number of deaths was three times lower in the group treated with OM-85 BV than in the control group: six versus two ($p = 0.153$).

In summary the results of this study are quite consistent with the mechanism of action of OM-85 BV. The drug seems to decrease the severity of exacerbations and, hence, the risk of being hospitalized and the length of stay in hospital. This effect is consistent across different degrees of severity of lung impairment (Table 5). The absence of effect on occurrence of acute episodes could be due to the definition used and the way data were collected. The fact that the protective effect of OM-85 BV is obtained through the stimulation of nonspecific immunity gives it great potential to become an important complement to regular vaccines; theoretically, it has the advantage of protecting against a large variety of microorganisms that are not covered by regular vaccines.

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