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E. Serrano · J. P. Demanez · A. Morgon · C. Chastang · P. Van Cauwenberge

Effectiveness of ribosomal fractions of *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae* and the membrane fraction of *Kp* (Ribomunyl) in the prevention of clinical recurrences of infectious rhinitis

Results of a multicenter double-blind placebo-controlled study

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Abstract A multicenter, double-blind, placebo-controlled study was conducted to investigate the efficacy of an immunostimulant, Ribomunyl, in the prevention of recurrences of infectious rhinitis in adults. This trial involved 327 patients (168 Ribomunyl treated and 159 placebo cases) with an average of 4.3 ± 1.8 rhinitis episodes per patient recorded during the year preceding the study. The main criterion of efficacy was the cumulative number of recurrences of infectious rhinitis during a 6-month follow-up period, as analyzed by standard tests. An additional analysis of relative risk of recurrences used multivariate failure for time data. Ribomunyl was effective throughout the study period, starting from the first month of treatment: a mean of 1.0 ± 1.1 recurrences was recorded in the Ribomunyl group as compared to 1.5 ± 1.4 recurrences in the placebo group; this indicated one-third fewer infections ($P = 0.001$). The protective effect of Ribomunyl on the relative risk for recurrences was estimated to be 0.58 by multivariate analysis (95% CI: 0.43–0.78, $P = 0.0001$). Analysis of secondary criteria also favored Ribomunyl: 38.5% less antibiotic courses per patient (0.8 ± 1.3 vs 1.3 ± 1.6; $P = 0.002$) and the number of days with antibiotics (5.6 ± 9.3 vs 9.1 ± 12.1; $P = 0.002$).

Key words Recurrent infectious rhinitis · Treatment · Immunostimulant · Ribosomes

E. Serrano (✉)
Service ORL, Hopital Rangueil, F-31054 Toulouse Cedex, France

J. P. Demanez
Hopital Sart-Tilman, Liège, Belgium

A. Morgon
Hopital E. Herriot, Lyon, France

C. Chastang
Hopital St. Louis, Paris, France

P. Van Cauwenberge
University Hospital, Ghent, Belgium

Introduction

The airways are the main gateway to environmental pathogens. The mucous membrane carpeting them is a natural barrier equipped with highly efficient biochemical, mechanical and immunological defence systems. The immune defences of the nasal cavities are part of the mucosal associated lymphoid tissue (MALT), which comprises in particular Waldeyer's ring as an effector and informative system. Secretory IgA is the main humoral effector. Both systems appear to play a fundamental role in providing host protection [10].

If tissue defences become ineffective [2] inflammation and infection result, as typified by rhinitis or rhinopharyngitis. Persistence of infection can be complicated by sinusitis, otitis, laryngitis and bronchitis. Although viruses are usually the primary cause of pathology, superinfections with bacteria are frequent [7]. Although the usual expression of rhinitis can be mild, its recurrent nature may make it disabilitating and generate therapeutic difficulties [5]. The frequency of these recurrences may also be indicative of inadequate immune protection, suggesting that immunostimulant treatment might be effective in reducing the frequency of these recurrences.

Ribomunyl holds a unique position as an immunostimulant class because of its original composition and, therefore, its mode of action. Ribomunyl is made up of ribosomal fractions of *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae*, and membrane fractions of *Klebsiella pneumoniae*. The vaccinating properties of ribosomes were first described for *Mycobacterium tuberculosis* ribosomes [18]. Since then, a number of studies have confirmed the properties of these fractions [8, 11]. Animal studies and clinical trials have confirmed its protective function against experimental or natural infections [3].

It is now known that Ribomunyl induces the production of humoral and secretory specific antibodies [4, 19]. This has been associated with non-specific immunostimulant properties due to the membrane fractions of non-en-

capsulated *K. pneumoniae*. In addition to polyclonal stimulation of B-lymphocytes [6], it activates polymorphonuclear cells [14] as well as macrophages through phagocytosis and the production of cytokines [9, 12, 15] and stimulates natural killer cells [1]. Ribomunyl can therefore be considered to behave both like an orally effective nanoparticular vaccine and an immuno stimulant that provides protection against bacterial and viral infections, stimulating the mucosal immune system [13]. It was thus of interest to us to test whether this stimulation in immunoclinical studies could lead to a clinical efficacy in preventing recurrent nasal infections in adults, as previously demonstrated in children [16].

Materials and methods

A prospective, double-blind, randomized placebo-controlled study was carried out involving 50 French ENT specialists in private practice and 2 affiliated ENT Belgian investigators. The protocol was approved by French and Belgium ethics committees, and all patients gave written informed consent. The study was conducted in agreement with good clinical practice.

Patients

During the 2-month period from 7 September to 4 November 1994, 328 adults (ages 18–82 years old) were recruited to allow an identical follow-up during the autumn-winter season when infectious rhinitis was expected to occur. Each had to have at least three episodes of infectious rhinitis (or rhinopharyngitis or rhinosinusitis) during the preceding year. Patients with seasonal allergic or toxic rhinitis, or patients with nasal disorders likely to be cured surgically were excluded.

One patient immediately defaulted after inclusion, allowing statistical analysis to be performed on 327 patients, 137 men and 190 women. Of this group, 168 were randomly assigned to Ribomunyl and 159 to placebo. Baseline characteristics of all patients indicated that the Ribomunyl group had an average of 4.4 ± 1.9 episodes of infectious rhinitis per patient while that in the placebo group was 4.3 ± 1.7, as recorded in patient files during the year preceding the study. The underlying chronic nasal condition in the study population included pan-sinusitis (14.1%), perennial allergic rhinitis (11.3%) and vasomotor rhinitis (7.6%). All data, risk factors and socioeconomic conditions did not show any imbalance between groups except for age. The mean age was 39.5 years ± 13.8 for the Ribomunyl group versus 42.7 ± 14.3 for the placebo group ($P = 0.04$). This difference was not considered to be clinically relevant.

Treatment

One tablet of Ribomunyl or placebo was taken daily in the first month of the study for 4 consecutive days a week for 3 weeks. In the 5 following months, medication was given 4 consecutive days a month. This schedule has been used in previous clinical trials [16] and is now used in several countries. Compliance was determined by tablet counts and by using patients' diaries indicating days of treatment. Good compliance was defined as a minimum 75% correct intake of medication or placebo each month for 4 months and was greater than 90% in both groups.

Response criteria

The principal criterion for efficacy was the cumulative number of recurrences of infectious rhinitis per patient during the 6-month follow-up period. A decision tree was used to delineate precisely what episodes should be counted as recurrences of infectious rhinitis (Fig. 1). The secondary criteria were the number and duration of courses of antibiotics prescribed for recurrences, as well as subjective responses by each patient. These data were recorded during the mandatory follow-up visits at months 2, 4 and 6, or when optional visits were required.

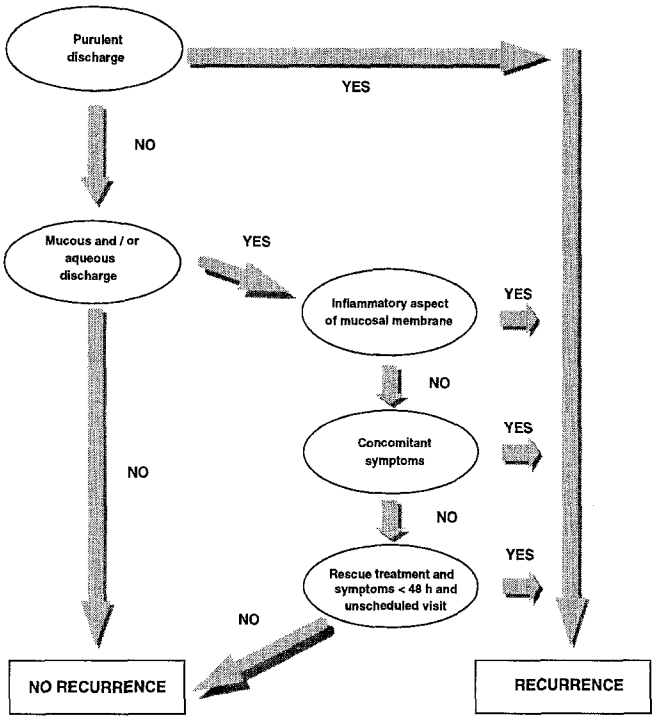

Fig. 1 Decision tree for assessing recurrences of infectious rhinitis

Statistical analysis

The sample size calculation was based upon a 30% difference of the number of recurrences between groups, with SD = 2, $\alpha = 0.05$, $\beta = 0.05$ and an expected 20% drop-out rate. The sample size was calculated for 240 patients.

Data processing was carried out using the SAS statistical package. The main analysis of the primary efficacy variable was performed by Pierre Fabre Research Institute, using standard Wilcoxon and Chi tests. An additional analysis of the cumulative incidence of recurrences used an extension of Cox's model as a censored multivariate failure time data [17] and was performed by the Department of Biostatistics of Hôpital St. Louis (Paris). This model took into account the overall observation of multiple episodes per patient, and the correlation between episodes within the same patient. A graphic representation of the cumulative incidence of recurrences used the Nelson Aalen's non-parametric estimator.

Results

Treatment efficacy

Ribomunyl and placebo-treated patients were followed for a mean duration of 172 and 173 days ± 22, respectively. Efficacy analysis showed on average a 1.0 ± 1.1 recurrence in the Ribomunyl-treated group, and 1.5 ± 1.4 in

the placebo group ($P = 0.001$). In both groups, more than 50% of the recurrences were associated with signs of sinusitis or pharyngitis. Patients treated with Ribomunyl exhibited one-third fewer recurrences of infectious rhinitis than those by the placebo recipients. As shown in Table 1, the between-groups difference became significant as early as at the end of the first month of treatment ($P = 0.05$) and was maintained throughout the study period ($P = 0.003$ at month 3 and $P = 0.001$ at month 6).

As the conclusion of the study, the number of patients free of recurrences was 65 (38.7%) in the Ribomunyl-treated group and 47 (29.6%) in the placebo group ($P = 0.08$). The number of patients with at least 3 infections was 18 (10.7%) in Ribomunyl group and 39 (24.5%) in the placebo group ($P = 0.001$). These results were consistent with our extension of Cox's model, which showed a protective effect of Ribomunyl compared to placebo, over time (0.58; 95% CI = 0.43–0.78; $P = 0.0001$). Calculation of the cumulative incidence of recurrences by the Nelson-Aalen's estimator also showed that this parameter was lower in the Ribomunyl-treated group than in the placebo group, with an intergroup difference increasing over time (Fig. 2).

Table 1 Comparison of the mean cumulative number of recurrences of infectious rhinitis per patient by study month

Time (month)	Ribomunyl ($n = 168$)			Placebo ($n = 159$)			P value
	Sum	Mean	SD	Sum	Mean	SD	
1	16	0.1	0.3	27	0.2	0.4	0.05[a]
2	56	0.3	0.5	80	0.5	0.6	0.04[a]
3	81	0.5	0.7	122	0.8	0.8	0.003[a]
4	112	0.7	0.8	156	1.0	1.0	0.002[b]
5	142	0.8	0.9	203	1.3	1.2	0.001[b]
6	170	1.0	1.1	240	1.5	1.4	0.001[b]

[a] Chi^2 test

[b] Wilcoxon test. Tests were performed on the number of recurrences as categorical data (0, 1, 2, 3, 4, 5). When the number of classes was less or equal to 4 classes, the Chi^2 test was used whereas the Wilcoxon test was used when the number of classes was > 4

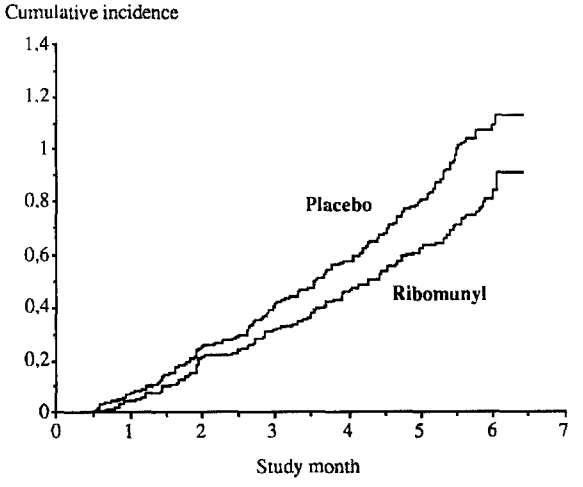

Fig. 2 Cumulative incidence of recurrences of infectious rhinitis in Ribomunyl-treated patients (Nelson-Aalen's non-parametric estimator). Addition of probabilities for a new rhinitis were conditional to the population at risk over time

Table 2 Distribution of patients according to the number of antibiotic courses required

Number of antibiotic courses per patient	Treatment group				Wilcoxon test
	Ribomunyl		Placebo		
	n	%	n	%	
0	96	57.1	66	41.5	
1	39	23.2	42	26.4	
2	18	10.7	25	15.7	$P = 0.002$
3	8	4.8	14	8.8	
4	4	2.4	2	1.3	
5	–	–	5	3.1	
6	2	1.2	3	1.9	
7	–	0.6	–	–	
8	–	–	2	1.3	
Total group	168	100.0	159	100.0	

The use of antibiotics prescribed for managing episodes of infection were analyzed (Table 2). Both the mean number of antibiotic courses per patient (0.8 ± 1.3 vs 1.3 ± 1.6; $P = 0.002$) and the number of days with antibiotics (5.6 ± 9.3 vs 9.1 ± 12.1) showed a significant difference in favor of the Ribomunyl-treated group than in the placebo group. Additionally, patients' subjective evaluations also favored Ribomunyl ($P = 0.04$).

Complications

All intercurrent events occurring during the 6-month follow-up period were documented. The numbers of patients having discontinued treatment (8 on Ribomunyl and 10 with placebo) were similar, with none stopping treatment due to intolerance. The total and per patient numbers of mild adverse events were similar between the two groups. Serious adverse events were recorded in 3 patients treated with Ribomunyl and 4 given placebo, but none of these events was deemed drug-related (hospitalizations for treatment of epiglottitis, chronic suppurative hydradenitis, surgery for snoring or sleep apnea, appendicitis, prostatic hypertrophy and coincidental trauma.

Discussion

Recurrent infectious rhinitis is a seasonal disease that is clearly recognized in children, but has been less well described in adults. During the winter period, nasal symptoms will predominate: congestion, sneezing and discharge. Sinus, pharyngeal and bronchial symptoms may also be recorded, with fever and headache commonly occurring. Many viruses and bacterial agents can also be in-

volved in this pathological process. As such, a number of drugs have been prescribed for the treatment of these episodes, including symptomatic medications (vasoconstricting and anti-inflammatory agents) and various antibiotics.

In the context of recurrent infective upper respiratory tract episodes, the immunostimulant activity of Ribomunyl represents a preventive approach that is worth further evaluation. Patient follow-up in our study was based on the documentation of all episodes of rhinitis. Investigators were requested to complete the description of each clinical presentation by recording any sinus-related, pharyngeal or bronchial symptoms, and including general signs (such as fever and headache), as well as by providing an accurate description of the rhinoscopic appearance of the nasal mucosa. Our decision tree to combine the various aspects of nasal discharge and other local or general features allowed an accurate non-biased distinction between infectious and non-infectious episodes.

The main result of our placebo-controlled study conducted over a 6-month period showed that the cumulative number of recurrences of infectious rhinitis was significantly reduced by one-third in patients treated with Ribomunyl compared with those treated with placebo. Using failure time data analysis, the relative risk for having recurrences was 0.58; i.e., 42% lower in the Ribomunyl-treated group than in our placebo group.

Our secondary criteria analysis was also consistent with our finding drawn from our primary criterion analysis, favoring Ribomunyl treatment. In particular, this included antibiotic usage showing a lesser need in the Ribomunyl-treated group than in the placebo group. These findings indicate that Ribomunyl can be an invaluable addition to the therapeutic measures now available to prevent the recurrences of infectious rhinitis.

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