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Reprint (translation)

ANNALES DE PÉDIATRIE

IMOCUR® IN THE PREVENTION OF RESPIRATORY INFECTIONS IN CHILDREN BELOW SIX YEARS

Results of a multicentre double-blind, placebo-controlled study

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Expansion Scientifique Française

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PAUPE J. — Imocur® in the prevention of respiratory infections in children below six years. Results of a multicentre double-blind, placebo-controlled study.
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SUMMARY : Sixty-four children under the age of six years with recurrent ear nose and throat (ENT) and/or lower respiratory tract infections (three episodes or more during the reference period) were studied in a double-blind, placebo-controlled clinical trial of Imocur®, an orally administered bacterial immunomodulator. Imocur® provided better individual protection than the placebo throughout the three-month treatment period and the subsequent three-month follow-up period. Throughout the six-month trial period, 34 % of the Imocur®-treated patients remained infection-free and 37 % required no antibiotics compared with 3 % and 10 % respectively of the placebo-treated patients. The number of infectious episodes per patient during the six-month trial was 4.86 in the placebo group compared to 1.66 in the Imocur®-treated group. Similarly, the Imocur®-treated group required only half as much antibiotic therapy as the placebo group. Patient tolerance was excellent with no adverse effect reported in the Imocur®-treated group. Imocur® thus proved to be an effective immunomodulator in the treatment of recurrent ENT and/or lower respiratory tract infections in children.

KEY-WORDS : Imocur®. — Immunomodulator. — Bacterial extracts. — Respiratory tract infections in children.

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TABLE I. — **Physical characteristics of patients.**

Parameter	Imocur® (n = 35)	Placebo (n = 29)
Sex (M/F)	20/15	11/18
Age (years)	2,8 ± 1,5	3,5 ± 1,7
Weight* (kg)	12,7 ± 3,8	13,9 ± 4,3
Height* (cm)	88,5 ± 15,3	92,9 ± 16,6

* Weight and height data were missing for one and two patients respectively in the Imocur® group.

TABLE II. — **Distribution of patients by age.**

Age (years)	Imocur®	Placebo
(0-2)	14 (40 %)	7 (24 %)
(2-4)	14 (40 %)	11 (38 %)
(4-6)	7 (20 %)	11 (38 %)
Total	**35 (100 %)**	**29 (100 %)**

TABLE III. — **Clinical characteristics of patients.**

Parameter	Imocur® (n = 35)	Placebo (n = 29)
No. of ENT and lower-respiratory-tract infections (reference period)		
3 infections	5 (14 %)	3 (10,5 %)
4 infections	13 (37 %)	9 (31 %)
> 4 infections	17 (49 %)	17 (58,5 %)
Duration of disease (months)	21,66 ± 13,94	23,10 ± 11,13

INTRODUCTION

Bacterial immunomodulators are used to provide protection against respiratory infections in both adults and children. Imocur® Children is an immunomodulator composed of bacterial fractions. A formulation for children has been tested in various clinical trials abroad, particularly in Germany and Switzerland*.

Five double-blind placebo-controlled trials involving a total of 313 children were conducted [1, 2, 3, 4 and 6).

We coordinated the French trial [5] which involved 116 children of both sexes with recurrent ENT and lower respiratory tract infections (61 treated with Imocur® and 55 with a placebo). The study demonstrated the efficacy of this product in the prevention of infectious episodes as well as in the reduction of drug consumption (particularly of antibiotics) regardless of the age of the patients studied (the average age was 6.58 ± 5.29 years in the Imocur®-treated group and 7.60 ± 5.34 years in the placebo group).

Analysis of the subpopulation of children aged under six years, planned initially in the trial protocol, proved possible and was of particular interest. In fact, it is in this age group that the frequency of ENT and lower respiratory tract infections is highest, with rhinopharyngitis the main disease. This illness, which occurs systematically in most children, with symptoms varying from one child to another, is known to evolve favourably, in most cases, with growth. However, this misleads us into considering this immun adaptation disease to be an inevitable and benign ailment while, in fact, it can sometimes have long-term after-effects. Thus, chronic purulent bronchorrhea may induce bronchoalveolar lesions, while chronic or acute auricular symptoms may have long-term effects on auditory function.

PATIENTS AND METHODS

A total of 122 children of both sexes, aged six months to 15 years who had suffered three or more respiratory infections during the previous autumn-winter period, or during the six months preceding the trial for patients under the age of one, were studied in this multicentre trial (10 centres). The trial was reviewed by an ethical committee, and the consent of the parents or legal guardians was obtained for each of the children taking part.

The study lasted for six months (autumn-winter of 1985-1986) with the administration of an immunomodulator (Imocur® Children : 3.5 mg of bacterial fractions) or a placebo at the dose of one capsule per day for the first ten days of the first three months of the study, followed by a monitoring period of three months. After being examined for inclusion in the study, the children were re-examined every month by the investigators, which permitted a regular follow-up of the patients and the counting of infectious episodes and their treatments.

RESULTS

Description of the patient population

Of the 122 patients taking part in the trial (63 treated with Imocur® and 59 with a placebo), 116 were included in the evaluation of therapeutic efficacy (61 Imocur® and 55 placebo).

The patient population under the age of six comprised 35 children treated with Imocur® and 29 with the placebo. Both patient groups were hom-

* Imocur® Children which is marketed in France by Fournier Laboratories, Dijon is a product of OM Laboratories, Meyrin/Geneva. In Switzerland and other countries it is known under the trade-mark of Broncho-Vaxom®.

TABLE IV. — **Status of patients at entry to the study.**

Parameter		Imocur® (n = 35)	Placebo (n = 29)
No. of treated patients		23 (66 %)	22 (76 %)
No. of patients treated only once		10 (29 %)	8 (28 %)
No. of treatments		42	45
No. of treatments with antibiotics		17 (40 %)	20 (44 %)
No. of diagnoses*		67	59
No. of cases of	Rhinopharyngitis	23 (30 %)	22 (37 %)
	Bronchitis	20 (30 %)	16 (27 %)
	Otitis	19 (28 %)	12 (20 %)

* Patients could have more than one diagnosis on entry to the study.

ogeneous and comparable at the beginning of the trial for all the parameters studied, particularly as regards the physical characteristics listed in Table I.

Table II gives the distribution by age of the patients aged 0 to six years. Table III shows the clinical characteristics of the patients at the beginning of the trial, the duration of the disease and the number of infectious episodes observed during the reference period.

Table IV lists the various parameters used to assess the status of patients at entry to the study. As for the way in which the children were cared for, a factor which influenced their infectious status, 57 % (20 patients) of the Imocur®-treated children compared to 52 % (15 patients) in the placebo-treated group attended a creche or nursery regularly.

Efficacy of individual protection

Table V shows the results obtained for the main parameters used to determine efficacy : the number of patients free of ENT or respiratory infection and the number of patients having required no antibiotic therapy during the three-month treatment period, the three-month follow-up period or the whole six-month trial period.

After six months of study, statistically significant differences emerged in favour of Imocur® compared to the placebo for the two parameters considered. Whereas only one of the 29 children in the placebo group remained infection-free throughout the six-month trial period, every third child in the Imocur® group enjoyed total protection, i.e., protection was ten times greater. Similar differences were found for antibiotic therapy.

Statistical analysis revealed that this individual protection was independent of the severity of the child's condition ($\leqslant 4$ or > 4 infections during the reference period). A study of the two periods of the trial showed that the difference emerged with the passage of time, the effect of the product being more pronounced during the follow-up period. This is confirmed by the graphic representation of the percentages of infection-free patients in each group at each monthly medical examination (fig. 1).

There were always fewer protected patients in the placebo group than in the Imocur® group except between day 90 and day 120. Moreover, while the placebo-protected patients varied in their evolution from month to month, the number of infection-free patients increased steadily in the Imocur® group.

Counting of infectious episodes and antibiotic treatments

Figure 2 shows the number of infectious episodes and the number of antibiotic treatments observed during the six-month trial period.

During the trial period, the Imocur®-treated children under the age of six suffered fewer infectious episodes and required far fewer antibiotic treatments than those in the placebo group.

TABLE V. — **Number of children under the age of six who remained infection-free and required no antibiotics during the treatment period (day 0 to day 90), the followup period (day 90 to day 180) and the entire trial period (day 0 to day 180) (Imocur® n = 35 ; placebo n = 29).**

	Day 0-day 90		Day 90-day 180		Day 0-day 180	
Parameter	**Imocur®**	**Placebo**	**Imocur®**	**Placebo**	**Imocur®**	**Placebo**
No. of infection-free patients	12 (34 %)	1 (3 %) $p < 0,01$	23 (66 %)	5 (17 %) $p < 0,001$	12 (34 %)	1 (3 %) $p < 0,01$
No. of patients requiring no antibiotics	13 (37 %)	4 (14 %) $p < 0,05$	27 (77 %)	10 (34 %) $p < 0,001$	13 (37 %)	3 (10 %) $p < 0,05$

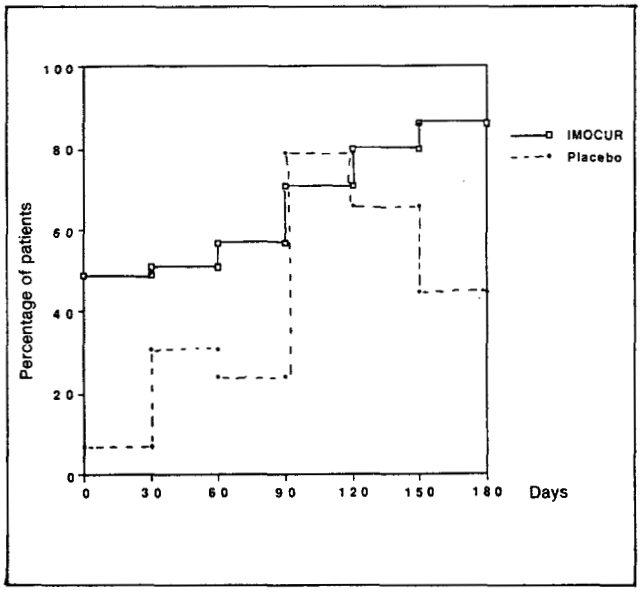

Fig. 1. — Percentage of infection-free patients at each monthly medical examination.

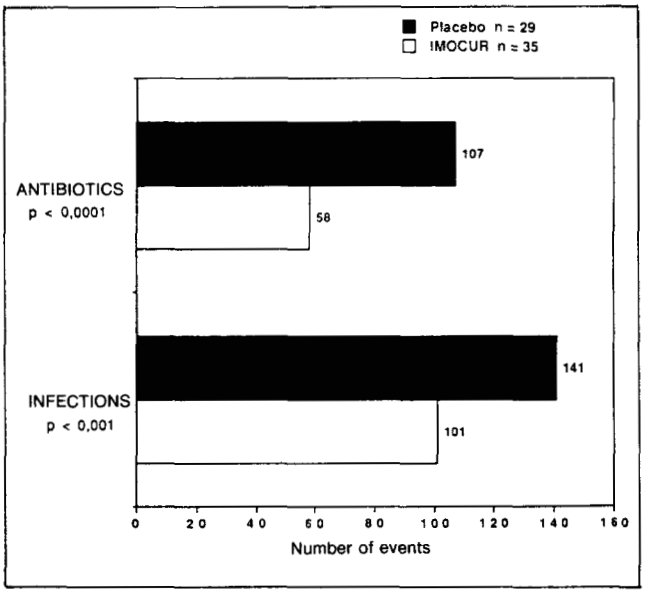

Fig. 2. — Number of infections and antibiotic treatments during the six-month trial period among patients under the age of six.

After six months, patients in the placebo group averaged 4.86 infectious episodes and 3.69 antibiotic treatments. In the Imocur® group, these averages were down to 2.89 episodes and 1.66 antibiotic treatments, a drop of 41 % in the number of infections and of 55 % in antibiotic consumption.

PATIENT TOLERANCE

Patient tolerance was excellent ; Imocur® produced no adverse effects in the children under the age of six.

DISCUSSION

The aim of this trial was to evaluate efficacy of Imocur® against respiratory infections in at-risk children recruited at outpatients pediatric clinics for ENT or pneumology. The more specific analysis of the patient population under the age of six showed that Imocur® reduced the number of infectious episodes significantly (— 41 % compared to the placebo), bringing about a proportionately greater decrease in antibiotic consumption (— 55 %).

This permits us to conclude that the infections occurring under Imocur® therapy are deemed less severe by examining physicians and require less antibiotic therapy : 57 % of the infectious episodes were treated with antibiotics in the Imocur® group compared with 76 % in the placebo group. Moreover, Imocur® provides individual protection against infections. During this trial, in fact, very little spontaneous improvement was observed in the placebo group : only one patient (3 % of the patient population) was found to be infection-free after six months of treatment, whereas 12 Imocur®-treated patients (34 % of the patient population) enjoyed total protection.

Likewise, the seasonal time effect well known in trials with immunomodulators did not seem to come into play in this study : the first three months corresponding to a winter period and the following three months to the start of spring, spontaneous improvement is generally marked in both patient groups. In this study, in fact, while the number of infection-free patients in the placebo group during these two periods rose from 3 % to 17 %, the number of patients enjoying total protection jumped from 34 % to 66 % in the Imocur® group. These results, which clearly favoured the Imocur® group during the monitoring phase, confirmed the preventive efficacy of Imocur®.

CONCLUSION

This trial demonstrated the efficacy of Imocur® in the prevention of recurrent ENT and lower respiratory tract infections in children under the age of six. Its efficacy, excellent patient tolerance and simple administration schedule (one capsule per day, ten days per month for three months) make it a therapeutic drug of choice against these recurrent infections in young children.

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