Efficacy of over-the-counter immunostimulants in the prevention of paediatric recurrent acute respiratory tract infections. Criticisms and pitfalls of available metaanalyses

Introduction

Clinical Scenario

Sofia is four years old. One year ago, after starting kindergarten, she had monthly acute respiratory tract infections (ARTIs) from October to April. Now she is about to start her second year of kindergarten. Her mother, a single employed as a sales-person lacking the possibility to keep the girl at home, is concerned about possible new ARTIs and asks whether it is possible to treat Sofia with over-the-counter immunostimulants (ISs).

Summary

Preschool children frequently suffer from acute respiratory tract infections (ARTIs). Immunostimulants (ISs) are often administered to reduce their impact. This study aimed to establish the efficacy of ISs in the prevention of pediatric ARTI through the analysis of systematic reviews (SRs). We explored Medline database in October 2010 limiting our search to SRs, that included studies on the effectiveness of ISs in the prevention of pediatric ARTI. Six SRs with meta analysis (MA) were found. The studies included showed a low methodological quality and a high statistical heterogeneity. All papers published on journals with impact factor > 1 and a Jadad score > 3 reviewed the efficacy of OM-85. The number needed to treat (NNT) was between 2 and 11, depending on the setting. Conclusions. Pediatric ARTI are a social and health care problem. When they impair the quality of life of the family a course of OM-85 might be warranted. Although scientific knowledge of clinicians may be improved by SRs, MA and aggregation of results may not always be the best way to accomplish this.

Clinical Question

Is there any scientific evidence that the preventive use of ISs vs a placebo reduces the number of ARTIs in preschool and school-age children? And if so, to what extent? Sistematic Reviews (SRs) with or without Metanalysis (MA) are the mainstay for any clinical decision as they summarize the current knowledge and the quality of evidence about a certain issue. MA is a popular technique in medical research, whereby all data from all available studies of something are combined. The technique is used by researchers to get a maximum amount of statistical infor-
Materials and methods

Research Strategy

We explored Medline through PubMed, the search was closed on 2nd October 2010. We chose a single keyword (“Immunostimulant”) to improve the sensibility of the research. We defined some limits: review, meta-analysis, all child. We have not consulted other database (i.e. EMBASE, Cochrane Library). We analyzed the bibliography of articles found and personal literature of the authors about this topic. Finally we consulted a mailing list of pediatric allergology and immunology (www.apalweb.it) to obtain information about any other publications on the subject, without finding additional titles. Seven hundred and five studies were found; 6 were relevant for us (1-6) but 4 had a restricted compass: three SRs were about one single IS (1, 5, 6), and another one was about ISs used in a restricted geographic area (3). So, only two SRs with MA (2, 4) were left.

Results with some comments

Berber et al (2) found that the treatment with ISs produced a significant relative reduction rate (42.7%) of ARTIs. The authors reported that only five studies were of good quality (Jadad score ≥ 3), three of them were about OM-85, a purified bacterial extract. The authors underlined that many studies included in the SR had common methodological deviations: definition of end points were missing, sample size was not calculated, sample size was small, there were misuse of statistical tests, underreport of adverse effects, and confounding factors were not controlled or even reported... They concluded: “This is the first critical review and meta-analysis of RCT on the prevention of ARTI in children using immunostimulants. Further high-quality RCT are required to demonstrate the effect and the size of the effect of each individual immunostimulant”. The authors aggregated the results of all studies included regardless of the IS. Can we trust these results in clinical practice, since we usually give just one IS at a time? Del Rio Navarro co-signed the SR of 2001 (2) and five years later published another SR with MA (4). The authors wrote that:

- thirty-four placebo controlled trials (3877 participants) provided data in a suitable form to be included in the MA
- when compared to placebo the use of ISs allows an average reduction of 1.3 ARTI, with 39.7% relative risk reduction
- the methodological quality of clinical trials was poor and they had a high degree of statistical heterogeneity.

The study of Collet et al published in 1993 (7) wasn’t included in this MA, due to lack of means and standard deviations of ARTIs. But in the previous SR (2), the same study was included and considered as one of the few manuscripts of good methodological quality. In our opinion, the study (7) was rightly excluded but by doing so the authors didn’t let the readership know about some important results that could have been relevant for clinical decisions. Moreover, other studies with significant methodological problems, such as the study of Del Rio Navarro et al (8), were included in the MA; that study (8) showed a drop out rate > 20% and included children with IgG subclasses deficiency. The authors of this SR (4) admitted that, due to significant heterogeneity and poor quality of RCT, the positive results of their MA should be interpreted with caution.

Comment. We understood that ISs had some positive effects, but we didn’t get which one is better. Since these two SRs with MA (2, 4) were not satisfying due to the aggregation of studies carried out on different ISs, with different methodological quality and with a high statistical heterogeneity, we examined one (3) of the SRs excluded before.

The study by De la Torre Gonzales et al (3) was about ISs sold in Mexico and we noticed that Blanca Del Rio Navarro also co-authored this paper. This time each IS was analyzed separately, as suggested by Berber and Del Rio Navarro (2). The authors found that (3):

- all studies of pidotimod were published in one edition of a German magazine
- some ISs sold in Mexico were not supported by any clinical trial
- the methodological quality of the studies was generally poor
- only 4 studies, all about OM-85, were published in scientific journals with Impact Factor >1 (7, 9-11)

The authors included the studies by Collet et al (7) and Schaad et al (11) among the 4 most valid studies. These two manuscripts were excluded from SR published in 2006 (4). The results of the SR by De La Torre Gonzales et al (3) can be summarized as follows: D53, OM-85 and
pidotimod are able to reduce ARTIs rate (32%, 39% and 31% relative reduction in risk respectively). If the absolute number of ARTIs spared was considered, statistical significance was achieved only for D53 and OM-85, with -0.92 and -1.2 ARTI respectively.

Comment. After our analysis OM-85 is the most effective IS. However, the global reduction rate of ARTIs was 39% by aggregating studies on OM-85 of different methodological quality. On the contrary, we want to make a decision relying only on the best studies. Then, we decided to examine the last two SRs (5, 6). Since they are focused only on OM-85, they could provide more details about each study, allowing us to identify best studies on this IS.

Steurer-Stey et al (5) selected 13 studies and assessed their methodological quality. Five had Jadad score ≥ 3. Four of them (7, 9-11) had been considered by the Mexican authors (3) as well. Another study was the one by Del Rio Navarro et al (8); we have already highlighted the high percentage of children excluded from the final analysis of data. Surprisingly the authors assigned a Jadad score of 3 to the study by Collet et al (7), considered one of the best published by the three SRs previously reported (2-4). They justified the score with the lack of the blindness, in contrast with what was written in the other SRs (2-4) where it is described as double blind randomised vs placebo. While the authors declared they could not aggregate data from multiple studies because “patients and outcome differed substantially”, they put together manuscripts showing heterogeneous methodological quality, i.e. Schaad et al (11), with Jadad score 5, and Maestroni et al (12), with Jadad score 2. We wonder whether this will reduce the reliability of the results of the MA. They summarized: “Evidence in favour of OM-85 in the prevention of ARTI in children is weak. There is a trend for shorter and fewer infections and a reduction of antibiotic use.” To our surprise, the Swiss authors did not find statistically significant differences in favour of OM-85 by analysing the same studies considered by the Mexican reviewers (3) two years before.

Unlike Steyer Steyer et al (5), Schaad (6) defined four works as studies of good methodological quality (Jadad score > 3), the same manuscripts had been published before the publication of Swiss authors’ research. This different way of evaluating papers may generate confusion in the readership. Thus, we examined these four works. The first one is by Schaad himself (13). It is in Dutch and it is not available on line. The authors didn’t find statistically significant differences between the group of children treated with OM-85 and the placebo group, in the frequency of recurrent respiratory infections and in the other outcomes. This study had been included in the SRs described above, too (2-5). In particular, de La Torre Gonzales et al (3) and del Rio Navarro et al (4) SRs underlined that “It is not stated that the trial is randomised, flow diagram of patients is not provided, allocation concealment is unclear”. Also Steurer Stay et al (5) in their SR found no clear description of randomizations and blindness, and therefore they gave to Schaad et al (13) SR a Jadad score of 2. The study of Zagar et al (14) regarded patients with a peculiar allergic pathology, such as chronic rhinosinusitis, and it evaluated the reduction of rhinosinusitis episodes after OM-85 treatment, which is not exactly the same problem that Sofia had. Steurer Stey et al (5) assigned it a score of 2. Paupe’s (15) study also included adult patients (until 19 years old), therefore it’s a different population compared with the one we are talking about. Steurer Stey et al (5) assigned a Jadad score of 2 to this work. Gomez Barreto et al (16) studied the safety and efficacy of OM-85-BV or placebo (in association with amoxicillin/clavulanate) in the treatment of subacute sinusitis in 56 children. Sofia is not affected by sinusitis and, moreover, Steurer Stey et al (5) assigned it a Jadad score of 1 to this study. Thus, we decided to exclude these 4 studies from our analysis.

The last check. Schaad (6) concluded his research on April 2009 therefore we looked for relevant studies about our clinical question published in the last 2 years. We explored Medline through PubMed, used OM-85 as keyword and defined the limit “published in the last 2 years”. We found 29 titles and one of them was quite relevant to our study. Razi et al (17) published a randomized double-blind placebo-controlled trials of good methodological quality (Jadad score = 4) about the efficacy of OM-85 in the prevention of preschool viral recurrent wheezing. They found a statistically significant reduction rate of 30% in the active group, with 2 wheezing attacks spared per patient in 12 months. Also ARTI showed a 37% reduction rate in the treated group.

We decided to deeply analyze only the 5 studies (7, 9-11, 17) of better methodological quality about OM-85 that are synthesized in Box 1.

Final remarks

We ended our research and tried to give a reasonable answer to Gaia, Sofia’s mother. We must consider that:
Box 1 - Summary of the studies of best quality on OM-85

Collet et al, Pediatr Infect Dis J 1993 (6)
Population. Four hundred and twenty three children (6-36 months) attending day-care centres were enrolled to assess whether stimulating non specific immunity would reduce the incidence of ARTI. ARTI was defined by acute respiratory symptoms lasting for at least 2 days which required treatment.
Intervention. OM-85 or placebo, 1 capsule per day for 10 days per month for 3 months. Follow up period: 3 months with treatment and 4.5 months without.
Results. Primary outcome: the risk of ≥4 episodes of upper respiratory infections was not significantly lower in the treated group than in the placebo group (26.7% vs. 33.8%). But with a subgroup analysis, it was noted that during the 3 months treatment, 9.5% children in the active group had >3 ARTI vs 18.3% in the placebo group, p <0.05, ARR = 8.8%, NNT = 11.3.

Jara-Perez et al, Clin Ther 2000 (8)
Population. Two hundred girls (mean age 9.8 +/- 1.9 years, age range 6 to 13 years) living in an orphanage with at least 3 ARTI in the 6 months entered the trial. An upper ARTI was defined as the presence of more than one of the following signs: rhinorrhea, sore throat, or cough without signs of a lower ARTI for ≥ 48 hours. A lower ARTI was defined as the presence of more than one of the following signs: rales or crepitations, wheezing, stridor, respiratory rate >50 per minute, cyanosis, or chest indrawing (depression of intercostal spaces) for ≥48 hours. Otitis was defined as earache with erythema and limited mobility of the tympanic membrane determined by pneumatic otoscopy.
Intervention. OM-85, 1 capsule per day for 10 days per month for 3 months. Follow up period: 3 months with treatment and 3 months without.
Results. The girls in the active group presented an average episodes of ARTI of 1 vs 3 in the placebo group, p <0.001. In the active group 80% of girls had <3 ARTI vs 20% of those in the placebo group, p <0.001, RAR = 60%, NNT = 2.

Gutiérrez-Tarango et al, Chest 2001 (9)
Population. Fifty-four susceptible children from 1 to 12 years with an average of 12 ARTI/year were selected. An upper ARTI was defined as the presence of at least one between runny nose, sore throat or cough, a lower ARTI was defined as the presence of more than one of the following signs: crackling rales, wheezing, stridor, cyanosis over 48h. Otitis was defined as earache with erythema and limited mobility of the tympanic membrane determined by pneumatic otoscopy.
Intervention. OM-85, 1 capsule per day for 10 days per month for 3 months, repeated after 6 months.
Results. In the active group 5 ARTI per child per year were observed vs 8 in the placebo group, p <0.001. Seventy percent of children in the active group had <6 ARTI vs 30% in the placebo group, p = 0.001, NNT = 2.5.

Schaad et al, Chest 2002 (10)
Population. Two hundred and thirty two children (age 3-8 years) with > 3 upper ARTI/year were enrolled. Upper ARTI was defined by the presence of at least two of the following: rhinitis, pharyngitis, cough, hoarseness, temperature ≥ or = 38.5 degrees C.
Intervention. OM-85, 1 capsule per day for the first month followed by 1 capsule for 10 days per month from 3rd to 5th months. Study duration: 6 months.
Results. In the period of 6 months ARTIs were in the active group 2.1 vs 2.5 in the placebo group, p <0.05. Stratified by the number of febrile episodes in the previous year, a greater reduction occurred in those children with 6 or more upper ARTI (- 0.56 ARTI) than those with 2-5 ARTIs (-0.28 ARTI without statistical significance). In the first 5 months of the study (period in which OM-85 was administered) the percentage of children with >3 ARTI was 25.6% in the active group vs 40.4% in the placebo group (p<0.05, NNT = 7). At 6 months the percentage of children with >3 ARTI was 35.9% vs 46.5% (p = not significant).

Razi et al, JACI 2010 (17)
Population. The study included 75 children with recurrent wheezing who were 1 to 6 years old.
Intervention. Participants were given either OM-85 or a placebo (1 capsule per day for 10 days each month for 3 consecutive months) at the start of the trial. Participants were followed for 12 month.
Results. Subjects given OM-85 BV had a lower rate of wheezing attacks. The cumulative difference in wheezing attacks between the 2 groups was 2.18 wheezing attacks per patient in 12 months; there was a 37.9% reduction in the group given OM-85 compared with the group given placebo (p < .001). The duration of each wheezing attack was 2 days shorter in the group given OM-85 BV than in the group given placebo (p < 0.001). Cumulative number of ARTIs per patient in the 2 groups: OM-85 = 5.31 +/- 1.79, placebo = 7.75 +/- 2.68, mean difference = -2.44 (-3.50 to -1.36), cumulative % difference = 31.4%, p<0.001.
• the reliability of the results of a study is directly proportional to its methodological quality
• who works to provide a summary of the scientific evidence currently available on a particular issue must also highlight the methodological quality of each study
• it is not correct, in our opinion, to aggregate studies with different methodological quality
• the clinical relevance of a result can change on the basis of the setting and it is important as well as its statistical significance

In summary we must combine the best available evidence with the needs of each patient, as suggested by the Evidence Based Medicine (EBM).

OM-85 is the IS supported by the best scientific evidence and the greatest effectiveness (see box 1). The closer situation to Sofia’s one is represented by the population studied by Schaad et al (11): 25.6% of children in the active group had >3 ARTI in 5 months vs 40.4% of those in the placebo group, p<0.05, Absolute Risk Reduction = 14.8%, Number Needed to Treat (NNT) = 7, we would take it as our NNT. It may be that OM-85 has a protective effect as long as treatment is given (see the study of Collet et al and Schaad et al in Box 1) and only in children with many ARTIs (see the study of Schaad et al in Box 1). In Italy, thirty doses of pediatric OM-85 cost 20 euros, therefore a 6 months, daily treatment cost 120 euros per child. This is the cost to have one chance out of seven to get less than three Sofia’s ARTIs. Is it too expensive for her mother? The decision is up to her, it is important to involve the patient in decision making. We have the duty to provide informations derived from examination of the best scientific evidence available at the moment, about a particular topic and to adjust them to the needs of each patient and its peculiar context.

Our analysis had another aim: to verify if the answer to Sofia’s clinical question was available only by reading SRs with MA, since we know that they are a valid tool for “the busy medical doctor”. We must admit that we did not have positive results about this second aim. In fact by reading 5 out of 6 SRs we didn’t obtain our answer and we had to analyze the 5 studies of better methodological quality. The aggregation of the results of heterogeneous studies is the main problem we underlined.

References