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IMMUNOMODULATORS IN PREVENTING RECURRENT RESPIRATORY TRACT INFECTIONS (RRTI): A META-ANALYSIS *

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ABSTRACT

Background: **Immunomodulators (IM) in the prevention of recurrent respiratory tract infections in children and adults are being introduced now in the market. Its role remains controversial despite substantial controlled trials that claims benefit with its use.**

Objectives: **The objective of this review is to answer the following questions: (1) Does the use of immunomodulators significantly reduce the frequency of recurrent respiratory tract infections in children? (2) Does the use of immunomodulators significantly reduce the frequency of recurrent respiratory tract infections in adults? (3) Does it help in preventing exacerbations in chronic obstructive pulmonary disease (COPD)?**

Search Strategy: **Randomized controlled trials were identified by searching the Medline, Pub Med (1980-2000), Cochrane Controlled-trials register, and by manual searches and cross-references. All languages were considered.**

Data collection and analysis: **Two reviewers independently extracted data and assessed trial quality. Discrepancy in results was resolved through a third reviewer. Analysis of data was done using Review Manager (RevMan) 4.0.**

Main Outcome measures: **Reduction in the frequency of recurrent respiratory tract infections (RRTI) in healthy children and adults, including exacerbation of COPD in adults.**

Results: **In children, a total of 622 patients from the 5 RCTs were evaluated. Overall analyses showed significant reduction in the frequency of RRTI in children [OR: 0.38; 95% CI 0.27,0.55]. The absolute risk reduction (ARR) is 16.95 % and numbers needed to treat (NNT) of 6. In adults, also 5 studies out of the 11 were analyzed. Total of 1119 patients were included and 563 were treated with IM. The frequency of RRTI also showed significant reduction with pooled odds ratio at 0.37 [95% CI 0.28-0.48]. ARR is 19.67 %, NNT of 5. With regard to the effect in reduction of exacerbation in COPD, use of IM has no significant difference with placebo. The summary odds ratio is 0.95 [95% CI 0.66,1.36]. ARR is 1.38 % with NNT of 72.**

Conclusion: **Use of immunomodulators prevents recurrent respiratory tract infections in children and adults but does not reduce exacerbations in COPD patients.**

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BACKGROUND

The Growing Need for the Prevention of Recurrent Respiratory Tract Infections

Recurrent upper and lower respiratory tract infections represent a major clinical problem in both adults and children. These infections tend to occur in people with impaired host immunity such as the elderly with underlying illnesses, young individuals with immature immunity and in people in close contact with others, as in child care centers and nursing homes. They also occur during winter months when the common cold is prevalent. Other predisposing factors, namely smoking, pollution and occupation also play a role. In the Global Burden of Disease, by the year 2020, COPD and lower respiratory tract infections rank third and fourth respectively as leading causes of death.

Immunity refers to the ability of an organism to protect itself against foreign antigens that enter the body. The immune system is an interactive network of cells and intercellular communication factors involving innate or non-specific elements, and adaptive or specific elements. Whereas non-specific immunity is the initial front line of the immune response and provides a defense barrier that prevents most pathogens from causing infection, specific immunity becomes involved when this first line fails. With increasing health costs, efforts are now geared toward prevention. Preventive therapy must maintain the body's defenses at an effective level to reduce frequency, duration and severity of illnesses and thus reduce the need for drug therapy. Inducing protection at the portal of entry of microorganisms is the crux of immunotherapy.

Immunomodulators (IM) and its Mechanism of Action

One of the first events in response to bacterial infection is adhesion of circulating polymorphonuclears to the vascular endothelium via adhesion molecules. Enhancement is important for the transendothelial migration of both neutrophil and monocytes leading to phagocytic activities of these cells. Duchow and colleagues exposed murine whole blood to concentrations of an IM and demonstrated an increase in B2 integrins (LFA-1 on monocytes, p150, 95 and MAC-1 on both monocytes and granulo-

cytes) and ICAM-1 on monocytes and granulocytes stimulated in murine whole blood.[31]

When foreign organisms or particles reach the distal airways, they are phagocytized by the alveolar macrophages and are processed and eventually destroyed.[32] The study of Mauel and associates showed that both the hexose monophosphate pathway and superoxide anion and nitrite production, known as the respiratory oxidative burst, were increased with IM exposure. These reactions generate toxic metabolites that can destroy invading pathogens. Thus, increasing two important parameters for host defense against pathogens and tumors: the microbicidal and cytolytic activities of the macrophages.[33]

Oral immunomodulators are found to act on the mucosal-associated lymphoid tissue by stimulating the secretion of IgA. Secretory IgA is the most important protective element against respiratory infection. Bosch and associates compared the effects of two IMs on mice, one synthetic and the other of bacterial origin, on humoral immune response, particularly on secretory and serum IgA and IgG. Immunomodulators proved to be effective at therapeutic doses in inducing secretory IgA formation.[34]

Studies on human subjects were conducted to support the findings done on animals and showed promising results. On two separate studies by Emmerich and Lusuardi, it was demonstrated that IMs act on local airway immunity by increasing the ratio of CD4+/CD8+, macrophage activity, and secretory IgA and a decrease in serum IgE in bronchoalveolar lavage of chronic bronchitis patients (Grade II).[36,37] Local effect on immunity was confirmed by another study by Lusuardi. Blood samples of chronic bronchitis patients showed no modification in the basic immune parameters (leukocyte number, cell differentials and lymphocyte subsets), granulocyte activities (chemotactic response and superoxide anion release) and immunoglobulins after intake of an IM while BAL analysis showed otherwise.[13] These data demonstrate that IMs can increase immune defenses in the respiratory tract of patients with chronic bronchitis, without apparently altering systemic immunity.[13]

Objectives

A systematic review was undertaken to evaluate the relevant literature and assess the effectiveness of immunomodulators in: (1) reducing the frequency of recurrent respiratory tract infections in children. (2) reducing the frequency of recurrent respiratory tract infections in adults, and in (3) preventing exacerbations among COPD patients.

MATERIALS AND METHODS

Criteria for Considering Studies for the Review

Type of Studies

A literature search of MEDLINE, PUBMED, and the Cochrane Controlled Trials Register were conducted. Randomized placebo-controlled trials and existing metaanalysis published from 1980 up to December 2000 that compare the effect of IM in the frequency of RRTI in children, adults, and COPD exacerbations were obtained. The titles and abstracts of retrieved studies were assessed and copies of relevant studies were collected. The references of retrieved articles were checked to locate other relevant trials. Key journals and textbooks were hand searched in addition to the electronic database searches. Studies in all languages were considered.

Types of Participants

Adults and children with history of recurrent respiratory tract infections, including COPD patients were considered in this review. Studies were grouped according to types of participants as follows: children (0-18 y/o), adults (>18y/o), and COPD patients.

Types of Intervention

All types of immunomodulators used to prevent RRTI and/or COPD exacerbation were considered. A minimum of 6-month follow-up was included in the inclusion criteria.

Types of Outcome Measures

The frequency of RRTI was used as principal outcome measure to assess the relative effectiveness of immunomodulators among healthy adults and children and frequency of exacerbations among COPD patients.

Search Strategy for Identification of Studies

The following were the keywords used in the search strategy:

Immunomodulators
Recurrent respiratory tract infections
Chronic Obstructive Lung Disease
Randomized controlled trials
Double-blind study, Placebo-controlled,
Clinical trial, Adults (≥18 y/o)
Children (<18 y/o)

Methods of the Review

Validity Assessment

Two reviewers independently did validity assess-

ment. A third party settled the disagreement. The methodological quality (validity) of the study were assessed using the following check points: (1) Was the assignment to the treatment groups really random?; (2) Were those assessing outcomes blind to the treatment allocation? (3) Were the control and treatment groups comparable at entry? (4) Were the groups treated identically other than for the named interventions? (5) Was relatively complete follow-up achieved? and, lastly (5) Was there an intention-to treat analysis ?

All studies were classified according to an internationally established hierarchy of design in which randomized controlled trials are regarded as the least susceptible to bias.

Data Extraction

Data abstracted included the study period, baseline characteristics of the patients, inclusion/exclusion criteria, and the type and dose of the immunomodulators.

Data Synthesis

Formal meta-analysis and investigation of heterogeneity among trials was conducted using Cochrane Review Manager software program. The Peto method (fixed effects) was used to estimate summary Odds Ratios and 95% confidence intervals in evaluating the outcomes. The ARR and NNT were also computed.

Summary tables of each study were drawn up.

RESULTS

Immunomodulators in Reducing Recurrent Respiratory Tract Infections in Children

The search resulted in recovery of 20 articles [1-5,15-28] in children using the following immunomodulators: Klebsiella pneumoniae glycoprotein, Polyoxidonium, Pidotimod, Tolfa Torf Preparation and bacterial lysates- OM-85 Broncho Vaxom (Imocur) and LW 50020 (Luivac).

Only 5 met the inclusion criteria. The excluded studies were either an open trial[23,28] measured different outcomes[17,18,19,25] and had a shorter period of follow-up (< 6 months) or length of follow-up was not specified.[15,16,20,21,22, 23,24,26,27] The metaanalysis included studies by Ahrens,[1] Du Pan,[2] Jankowski,[3] Paupe[4] and Riedel-Seifert[5] (APPENDIX 2: Figure 1, Table I).

A total of 622 patients from the 5 randomized double blind placebo-controlled trials were evaluated. Three hundred nineteen (319) received immunomodulators using broncho-vaxom in 3 studies, and Tolfa Torp preparation and Luivac in the remaining 2 studies. On the other hand, three hundred three (303) subjects received placebo. About 27 %(87 out of 319) in the treatment group and 44 % (134 out of the 303) in the placebo group had recurrent respiratory tract infections. Overall analyses showed significant reduction in the frequency of RRTI in children [OR: 0.38; 95% CI 0.27,0.55] with absolute risk reduction (ARR) of 16.95 % and NNT of 5.

Comparison: Immunomodulators (IM) vs. Placebo
Outcome: Frequency of Recurrent Respiratory Tract Infections in Children.

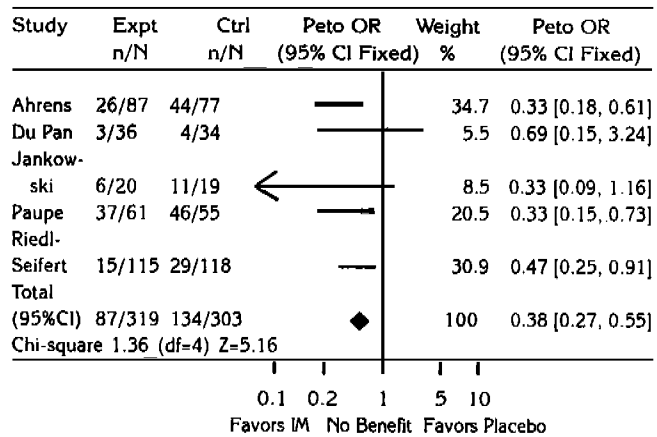

Figure 1. Immunomodulators In Reducing the Frequency of Recurrent Respiratory Tract Infections in Children.

Immunomodulators in reducing Recurrent Respiratory Tract Infections in Adults

We identified 11 studies[6-10, 13,14,16,17,23,29] in adults. Five studies were eligible. These were studies by Ahrens,[6] Derenne,[7] Fischer,[8] Per Venge[9] and Sclenter.[10] Other studies were excluded on the following reasons: open trial,[23] incomplete follow-up, [14,16,23] measured different endpoints[13,17] and no available translation of the article was obtained.[29] Total of 1119 patients were included and 563 were treated with IM. The frequency of RRTI also showed significant reduction with pooled odds ratio at 0.37 [95% CI 0.28-0.48]. ARR is 19.67%. It was also derived that in order to achieve reduction in RRTI, you need only 6 patients to treat (see Appendix 2: Table II and Figure 2).

Immunomodulators in reducing Exacerbations in COPD

We identified 7 studies. Six randomized trials and one meta-analysis. The five studies reviewed are

Table I. Studies in Children with Recurrent Respiratory Tract Infections Included in the Meta-Analysis and their Endpoints.

Study ID	Methods	Participants	Interventions	Endpoints	Study quality
1. Ahrens 1984[1]	RCT, PC DB	N:164 T: 77 P: 87 Patients suffering from chronic obstructive diseases of the respiratory tract, those treated for acute respiratory infections, or those in whom at least one infection of the respiratory tract occurred during the months of autumn and winter the previous year	Broncho-vaxom/placebo one capsule daily for 10 days for 3 consecutive months	freq of infxn; degree of severity-mild,mod. & severe; duration of antibacterial tx;overall evaluation of the therapeutic success by the doctor and the patient	A
2. RC Martin Du Pan 1982[2]	RCT; PC, DB	N:70 T: 34 P: 36 10mo-5y/o with recurrent respiratory tract infections	Broncho-vaxom/placebo 3 tsp daily for 10 days for 2 consecutive months	Frequency of respiratory infections.	A
3. Jankowski 1993[3]	RCT, PC, DB	N: 39 T: 19 P: 20 16-20 y/o with recurrent respiratory tract infections	Tolfa-Torp Preparation/ day for 3 weeks	Frequency of respiratory Infections; phagocytic activity of granulocyte	A
4. Paupe 1991[4]	RCT, PC, DB	N: 116 T: 55 P: 61 6mo-19y/o healthy children seen in 10 clinics throughout France	Broncho-vaxom/placebo one capsule once daily for the first 10 days of 3 consecutive months	Recurrent respiratory, ear, nose and throat infections	A
5. Riedl-Seifert 1995[5]	RCT, PC, DB	N: 233 T: 118 P: 115 Patients with minimum of 10 infections in the last year from children aged 4-6 years old, and 8 infections in children 7-9 years old	Administered Luivac or LW 50020 (not specified)	Frequency of respiratory tract Infections; infection severity	A

Legend:
RCT: Randomized-Controlled Trials; PC: Placebo-controlled; DB: double-blind; STUDY QUALITY: A-high quality study B- study of subtle bias; C-study of frank bias; N: total number of patients T: number of patients in the treatment group, P: number of patients in the placebo group.

included in the meta-analysis by Bergemann et al[12] Only five studies were eligible for analysis. These were studies by Cvorisec,[12] Magyar,[12] Hutas,[12] Orcel[12] and Shapiro.[11] The study by Orlandi et al[12] was excluded because it measured a different endpoint.

A total of 1013 COPD patients were included. Ninety-seven out of 522 (18.58%) in the treatment arm and 98 from 491(19.95%) who received placebo had recurrent respiratory tract infection. The summary odds ratio is 0.95 [95% CI 0.66,1.36]. ARR is 1.38 % with NNT of 72 (see Appendix 2: Table III and Figure 3).

The result showed that the use of immunomodulators in preventing exacerbation in chronic bronchitis proved to have no significant effect.

Comparison: Immunomodulators (IM) vs. Placebo
Outcome: Frequency of Recurrent Respiratory Tract Infections in Adults.

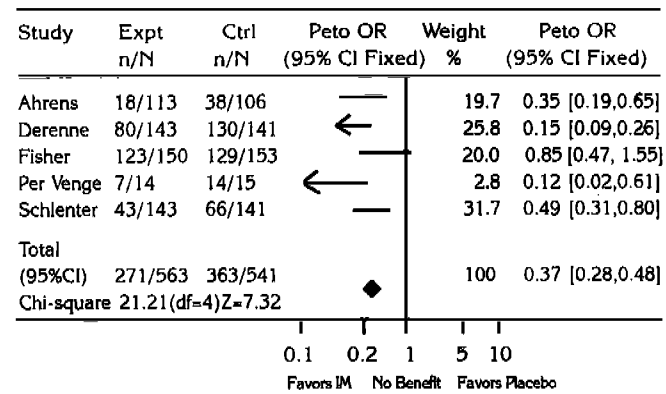

Figure 2. Immunomodulators in Reducing Recurrent Respiratory Tract Infections in Adults: Meta-analysis.

Table II. Studies in Adults with Recurrent Respiratory Tract Infections Included in the Meta-Analysis and their Endpoints.

Study ID	Method	Participants	Intervention	Endpoints	Study Quality
1. Ahrens 1983[6]	RCT, DB, PC	N: 219 T: 113 P:106 Patients with chronic obstructive diseases of the respiratory tract, who had been treated for acute respiratory tract infections, or in whom at least one infection of the respiratory tract had occurred during the months of autumn and winter of previous year	Broncho-vaxom or placebo in capsules to be taken one capsule daily for 10 consecutive days during the first 3 months	Frequency of infections; Degree of severity of infections; duration of antibacterial treatment; overall evaluation of the therapeutic success by the doctor and the patient	A
2. Derenne 1992[7]	RCT, DB, PC	N:284 T: 143 P: 141 Suffering from ENT and respiratory infections	Broncho-vaxom or placebo in capsules to be taken one capsule daily for 10 consecutive days during the first 3 months	Number of acute exacerbations of chronic bronchitis; antibiotic consumption; immunoglobulin levels	A
3. Fischer 1992[8]	RCT, DB, PC	N:303 T: 150 P: 153 18-50 y/o with at least 4 recurrencies of respiratory tract infections in the previous year which required a visit to physician	LW50020 (3mg lysates) one capsule during 3 administration periods of 28 days each separated by 28 day treatment-free intervals	Maximum severity score of the clinical symptoms; Tolerability	B
4. Per Venge 1996[9]	RCT, DB, PC Cross-over study	N: 29 T: 14 P: 15 Patients with more than 3 infectious exacerbations of their bronchitis during the preceding 2 winter seasons	Hyaluronan administration subcutaneous once every week for 24 wk, and the placebo was given the same volume of saline	Number of bacterial infections; consumption of antibiotics	A
5. Schlenter 1991[10]	RCT, DB, PC	N: 284 T: 143 P:141 Chronic purulent sinusitis of more than 6 months duration and with sinobronchitis	Broncho-vaxom or placebo in capsules to be taken one capsule daily for 10 consecutive days during the first 3 months	Headache, Nasal discharge and cough were evaluated on the basis of 5 point scale; average numbers of reinfections	A

Legend:
RCT: Randomized-Controlled Trials; PC: Placebo-controlled; DB: double-blind . STUDY QUALITY: A-high quality study, B- study of subtle bias; C-study of frank bias N: total number of patients T: number of patients in the treatment group, P: number of patients in the placebo group.

DISCUSSION

Experimental studies on both animals and humans have shown that immunomodulators affect components of the immune system in a non-specific manner (via upregulation of adhesion molecules on monocytes and granulocytes and activation of alveolar macrophages promoting phagocytosis) and specifically by increasing immunoglobulins (secretory IgA). The effects of which could either be beneficial or harmful.

The potential hazard of immunostimulating drugs was discussed in a meeting held in Geneva last 1992. On clinical grounds, it could be speculated that the use of immunomodulating drugs might trigger an underlying autoimmune disorder or induce such pathology. So far, only one single case of hemolytic

Comparison: Immunomodulators (IM) vs. Placebo
Outcome: Exacerbation in COPD

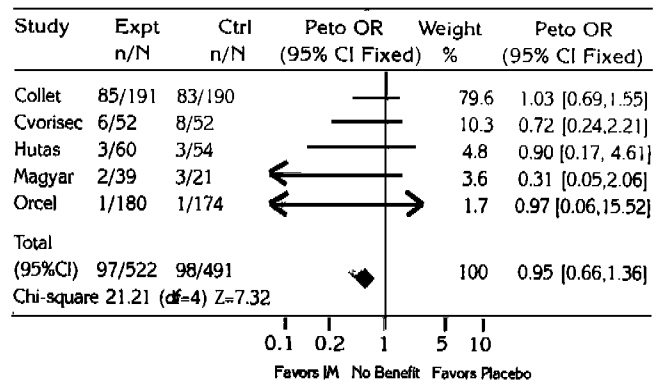

Figure 3. Immunomodulators in Preventing Exacerbation in COPD.

Table III. Studies in Adults in the Prevention of Frequent Exacerbations of COPD Included in the Meta-analysis and their Endpoints.

Study ID	Method	Participants	Intervention	Endpoints	Study Quality
1. Collet,et al 1997[11]	RCT, PC, DB	N: 381 T: 191 C: 190 Heavy smoker with FEV1 between 20 and 70% predicted w/c improved less than 15% after 200 ug of Salbutamol. Excluded: with severe concomitant disease, those prescribed medications affecting the immune system and who had an episode of acute exacerbation treated with antibiotics within the previous month	Broncho-vaxom one capsule /day for 30 days followed by a repeat course of 10 consecutive days of therapy per month for 3 months	Risk of having at least one episode of acute exacerbation; total number of days of hospitalization; risk of being hospitalized; mortality;	A
2. Cvorisec, et al 1989[12]	RCT, PC, DB	N: 104 T: 52 C: 52 Patient with chronic bronchitis according WHO definition	Administered Broncho-vaxom (not specified)	Number of acute exacerbations per 6 months; duration of antibiotic treatment of all acute exacerbations over 6 months	A
3. Hutas,et al 1993[12]	RCT, PC, DB	N: 114 T: 60 C: 54 Patient with chronic bronchitis according WHO definition	Administered Broncho-vaxom (not specified	Number of acute exacerbations per 6 months; duration of antibiotic treatment of all acute exacerbations over 6 months	A
4. Magyar, et al 1985[12]	RCT, PC, DB	N: 60 T: 39 C: 21 Patient with chronic bronchitis according WHO definition	Administered Broncho-vaxom (not specified	Number of acute exacerbations per 6 months; duration of antibiotic treatment of all acute exacerbations over 6 months	A
5. Orcel, et al 1994[12]	RCT, PC, DB	N:354 T: 180 C: 174 Patient with chronic bronchitis according WHO definition	Administered Broncho-vaxom (not specified	Number of acute exacerbations per 6 months; duration of antibiotic treatment of all acute exacerbations over 6 months	A

Legend:
RCT: Randomized-Controlled Trials; PC: Placebo-controlled; DB: double-blind. STUDY QUALITY: A-high quality study, B- study of subtle bias; C-study of frank bias N: total number of patients T: number of patients in the treatment group, P: number of patients in the placebo group.

anemia[44] has been associated with the use of such drugs and literature search has not revealed any new published cases. Tolerance to the drug was demonstrated in a study by Martin du Pan where immunomodulators proved to be acceptable to children, even to the youngest (10 months to 5 years), with no intolerance reported.[40]

The clinical use of immunomodulators has proved highly effective in preventing respiratory tract infection in a variety of individuals. Individuals with impaired or immature immune system such as the elderly and children prone to respiratory tract infections. Healthy individuals with weakened immune response due to exposure to environmental hazard. Individuals with chronic lung diseases with frequent respiratory tract infection. Lastly, immunocompromised individuals with underlying illnesses. Although, no significant benefit was achieved in reducing exacerbations of COPD patients with the use of immunomodulators, thought of viral and non-infectious causes comprising part of the triggers should be taken into consideration.

Overall duration of antibiotic and antitussive treatment was also significantly reduced in the treatment group.[38] Other similar studies had the same outcome in terms of recurrent respiratory, ear, nose and throat infections.[4,39,40,41] Incidence of absenteeism was likewise reduced.[42, 43]

A host of studies have shown that immunomodulators can positively reduce the frequency, duration and severity of recurrences of respiratory tract infections. Reduction is a sign of immune-defense activation and indicates an improvement in the general condition of a person who can respond to repeated contacts with pathogens.

CONCLUSION

Implications for Practice

There are evidences that support the use of immunomodulators in the prevention of recurrent respiratory tract infections in children and adults. However, data suggest that its use in reducing exacerbation of COPD in adults have no significant effect.

By decreasing the episodes of infections, immunomodulators may potentially reduce the number of physician consultation, laboratory investigations, and number of prescriptions for antibacterial therapy. These add to substantial savings in time, money and productivity. If used in appropriate circumstances, immunomodulators may be a valid and a cost- effective adjunctive measure in some clinical situations.

Implications for Research

In view of future research, the following are recommended: (1) The need for large multicenter studies, (2) Refining the definition of RRTI of viral or bacterial origin, lastly (3) lengthen follow-up period for at least one year.

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