

USE OF BACTERIAL LYSATES IN SUBJECTIVE IMPROVEMENT OF CLINICAL RESPONSE IN ALLERGIC RHINITIS PATIENTS

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ABSTRACT

BACKGROUND

Allergic rhinitis is known to be one of the most common chronic diseases in the world. In this study, we provide an overview of allergic rhinitis responding to immunostimulating agents. According to the concept that allergic rhinitis patients generally suffer from an immune deficit in order to stimulate their immune system specifically or nonspecifically, immunomodulating agents from various sources such as synthetic compounds, tissue extracts or a mixture of bacterial extracts have been used.

MATERIALS AND METHODS

The aim of the present trial is to evaluate the efficacy of the treatment with an immunostimulating agent consisting of a freeze dried bacterial lysates (Ismigen) and analyse the improvement in clinical response in allergic rhinitis patients. 50 allergic rhinitis patients were enrolled. For all patients, after 3 months of PMBL (polyvalent mechanical bacterial lysates) treatment clinical response was analysed.

RESULTS

A clinical improvement in subjective symptoms was observed in 43 of the 50 patients treated with bacterial lysates (85.6%). The results are as follows- 45 patients (91.8%), we noticed a decrease in symptoms of nasal blockage and 38 patients (90.4%) were relieved from rhinorrhea; purulent nasal discharge was reduced in 13 cases (81.5%), 30 patients (90.9%) had a large improvement in nasal/palate itching and 15 patients (75%) with headache were relieved.

CONCLUSION

From this study, bacterial lysates have shown to have a protective effect, which induces a significant reduction of the symptoms and duration related to allergic rhinitis. No negative side effects or worsening of the symptoms have been observed with this medication.

KEYWORDS

Bacterial Lysates, Allergic Rhinitis, Freeze Dried Bacterial Lysates, Polyvalent Mechanical Bacterial Lysates.

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BACKGROUND

Rhinitis is defined by a combination of two or more nasal symptoms- runny nose, blocking, itching and sneezing. Allergic rhinitis occurs when these symptoms are the result of IgE mediated by inflammation following exposure to

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allergen.¹ Bacterial lysates are constituted by a mixture of bacterial antigens derived from different bacterial species. The more often included species are- Staphylococcus aureus, Streptococcus viridans, Streptococcus pneumoniae (6 strains), Streptococcus pyogenes, Klebsiella pneumoniae, Klebsiella ozenae, Moraxella catarrhalis and Haemophilus influenzae. Bacterial lysate is both a specific and nonspecific immunostimulating agent indicated for the prevention and treatment of respiratory infections including sequelae to common cold and influenza. In particular, it is useful for the treatment of acute and chronic bronchitis, tonsillitis, pharyngitis, laryngitis, allergic rhinitis, sinusitis and otitis media. It can also be used for infections resistant to common



antibiotics and for the sequelae to bacterial and viral infections.²

The effects of bacterial lysate as an immunostimulatory agent have been debated in many clinical trials. By performing a simple research on PubMed directory of the terms³ "bacterial lysate" and limiting the search only to randomised clinical trials. It is possible to find more than 30 papers. The aim of those studies, all published during the last 20 years is to evaluate the effects of this class of drugs in maintaining the immune system in a state of alert and in raising a defence against microbial infections eventually leading to a reduction in their number. Those studies are very different and heterogeneous. In fact, the populations and samples of those trials are various being representative of diverse diseases such as- recurrent respiratory infections of upper and/or lower airways, chronic bronchitis, rhinosinusitis, allergic rhinitis and other ENT infections. Even the age of patients included is different- many trials are conducted on paediatric patients (Braido et al).⁴

A recent study, a RCT involving 140 patients with a history of recurrent respiratory infections, compared the effects of bacterial lysate obtained through mechanical lysis (patients in the first group) to the effects of bacterial lysate obtained through chemical lysis (patients in the second group) and to the effects of no treatment at all (patients in the third group, control); the endpoints were- the number of upper respiratory tract infections, the number of patients free from disease, the duration of infectious episodes, the number of working days lost because of the disease and the need for antibiotic treatment. The results for each one of the endpoints showed the efficacy of the two treatments, but the best results were achieved with the treatment with the bacterial lysate obtained through mechanical lysis and were significantly superior to those achieved with placebo and also with the bacterial lysate obtained through chemical lysis.⁵

One trial was designed to test the efficacy of bacterial lysate in treating patients suffering from chronic purulent sinusitis. This study carried over on 284 patients for a duration of six months showed the efficacy of treatment in reducing cough, purulent nasal discharge and headache on the basis of the score of symptoms.⁶

Mode of Action of Bacterial Lysate

The capacity of a virtually intact microbe to activate resting monocytic/macrophage cells is strictly linked to the presence of structures belonging to the bacterial cell wall (for example, protido-glycane or lipopolysaccharide) against which some receptor structures (such as the so called toll like receptors-TLR) are specific directed. TLR are expressed on the surface of monocyte membrane. The interaction between bacterial structures and TLR results in the activation of monocytes, their differentiation to immature dendritic cells and the following maturation to mature dendritic cells, able to be considered a suitable antigen presenting cell. The use of bacterial antigens obtained by mechanical or chemical lysis is thus able to activate monocytic-macrophagic cells of the submucosa inducing the

differentiation through immature dendritic cells and their maturation in mature dendritic cells. The activation of such a mechanism results in a suitable stimulation of the immune-response.

The presentation of bacterial antigens on mature dendritic cells results in the stimulation of the T cell compartment (with a consequent induction of a powerful helper function) and of the B cell compartment of the immune response with a following maturation to plasma cells and secretion of antibodies specifically directed to the administered antigen. The administration of bacterial lysate is thus able to induce a T helper function and a maturation of B specific lymphocytes resulting in the production of IgA salivary antibodies directed to the administered mixture of antigens.

The secretion of antibodies directed to bacterial antigens has a positive function only in the case of these antibodies having the capability to opsonise living bacterial cells, thus favouring the phagocytosis and the killing mediated by professional phagocytes, such as granulocytes.

All these findings indicate that the maturation of dendritic cells, the specific activation of the T and B cell population of lymphocytes and the resulting production of IgA in the respiratory mucosa specifically directed to the antigens administered characterised by the capacity of opsonising living bacteria, thus allowing their engulfment and killing in phagocytes represent the actual pathway for the potentiation of a both nonspecific (dendritic cells and phagocytes) and specific (T and B cells) immune response resulting in a prophylactic effect on recurrent infections of the respiratory tract.⁴

Hygiene hypothesis is a hypothesis that states a lack of early childhood exposure to infection agents, symbiotic microorganism and parasites increases susceptibility to allergic diseases by suppressing the natural development of the immune system.

Basically, Th1 (T-helper (cell) type 1), Th2 (T-helper (cell) type 2) deviation was the first major candidate mechanism for explaining the protective influence of infectious agents from immunological disorders. Th1 T-cells produce inflammatory cytokines such as IL-2, interferon (IFN)- γ and Tumour Necrosis Factor (TNF)- α that are operational in cell-mediated immunity (including autoimmune diabetes). In contrast, Th2 T-cells that produce IL-4, IL-5, IL-6 and IL-13 contribute to IgE production and allergic responses. Given the reciprocal down regulation of Th1 and Th2 cells, some authors suggested initially that in developed countries the lack of microbial burden in early childhood, which normally favours a strong Th1-biased immunity, redirects the immune response towards a Th2 phenotype and therefore predisposes the host to allergic disorders.⁷ So, here the bacterial lysates help in increasing the population of Th1 as mentioned above.

OBJECTIVES

To see the subjective response in clinical improvement of symptoms in allergic rhinitis patients.

MATERIALS AND METHODS

Before starting the study, an approval certificate from ethical committee and consent from the patients has been taken. Bacterial lysate preparation, the immunostimulating vaccine (ISMIGEN- PMBL supplied by Zambon Italia SRL (Bresso/Milan, Italy)) is the product of mechanical lysis through sonication of 8 different bacterial strains (6 x 10⁹ bacteria for each strain) selected among those most frequently responsible for respiratory tract infection, i.e. *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Streptococcus pneumoniae* (6 different serotypes- TY1/EQ2, TY2/EQ22, TY3/EQ14, TY5/EQ15, TY8/EQ23 and TY47/EQ24), *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Haemophilus influenzae* serotype B and *Moraxella catarrhalis*. The product is formulated in tablets containing 7 mg of freeze-dried lysate of 48 billion bacteria and 43 mg of excipients.

Patients

From 2015 (January) to 2016 (January), the patients suffering from allergic rhinitis attending to our outpatient department have been selected. All their symptoms were noted and analysed.

A group of 50 patients with allergic rhinitis were selected of which 27 (54%) patients were males and 23 (46%) patients were females (figure 1). Age between 5 to 15 years, 5 patients (3 males and 2 females); 16 to 25 years, 11 patients (males 7 and females 4); 26 to 35 years, 19 patients (males 10 and females 9); 36 to 45 years, 11 patients (5 males and 6 females) and 46-50 years, 4 patients (2 males and 2 females) (Table 1). All these patients were given freeze dried bacterial lysates tablet along with allergic rhinitis pharmacological treatment.

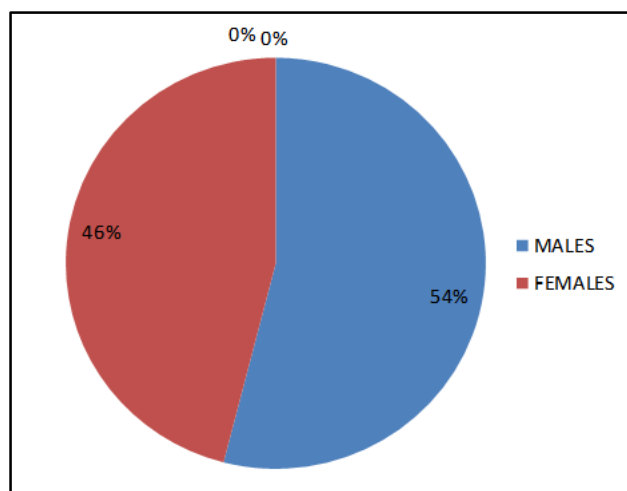


Figure 1. Showing Sex Distribution

Age Group	Males	Females
5-15 years	3	2
16-25 years	7	4
26-35 years	10	9
36-45 years	5	6
46-50 years	2	2

Table 1. Age Distribution

Inclusion Criteria

We have included patients who are suffering from allergic rhinitis, allergic rhinitis with sinusitis, both males and females who are suffering for a period of one year or more. Patients between 5 years to 50 years of age have been studied in this study.

Exclusion Criteria

Patients with ocular and asthmatic symptoms, non-allergic rhinitis, acute rhinosinusitis, nasal polyposis, episodes of allergic rhinitis for less than a year, associated chronic illness (hypertension, diabetes, chronic granulomatous infections etc.) have been excluded along with patients with age below 5 years and above 50 years.

The treatment schedule for freeze dried bacterial lysate is the following-

One tablet per day to dissolve under the tongue for 10 consecutive days followed by 20 days rest. The cycle is repeated for three consecutive months.

The clinical assessment of the treatment efficacy was made on a range of commonly accepted subjective symptoms determined during and after treatment. At the last visit, the patients were asked some questions about any eventual subjective improvement in their allergic symptoms. During the period of treatment, the patients were followed for six months.

RESULTS

Before PMBL therapy, there was a 1 month period of observation for all patients to assess the clinical picture (Table 2).

A clinical improvement in subjective symptoms was observed in 43 of the 50 patients treated with bacterial lysates (85.6%). The results are as follows- 45 patients (91.8%), we noticed a decrease in symptoms of nasal blockage and 38 patients (90.4%) were relieved from rhinorrhea; purulent nasal discharge was reduced in 13 cases (81.5%), 30 patients (90.9%) had a large improvement in nasal/palate itching and 15 patients (75%) with headache were relieved. Improvement was not immediately observed, but started almost 2-3 weeks or later after the beginning of treatment for all symptoms. 7 out of 50 patients showed a stationary response. In no case, negative side effects associated with the medication or worsening were recorded. At the end of a 6-month follow up period, the clinical variables only were checked. The overall frequency and duration of the symptoms have been drastically reduced. However, the treatment has to be repeated once in every one year for better results.

	Before	After
Nasal blockage	49	04
Rhinorrhea	42	04
Purulent nasal discharge	16	03
Nasal/palate itching	33	03
Headache	20	05

Table 2. Allergic Rhinitis Patient Symptoms Before and After Treatment

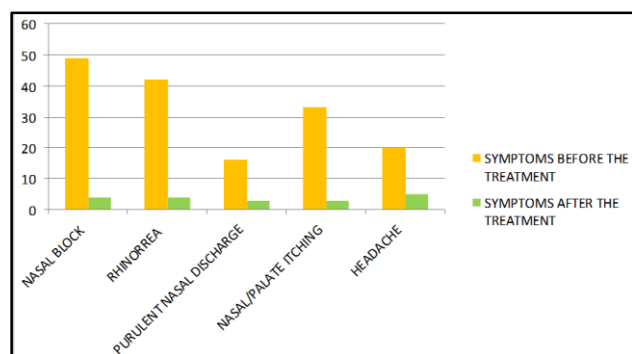


Figure 2. Showing the Symptoms Before and After Treatment

DISCUSSION

Bacterial lysate is both a specific and nonspecific immunostimulating agent indicated for the prevention and treatment of respiratory infections including squal to common cold and influenza. They enhance the concentration of antibodies directed to antigenic structures of bacteria most commonly observed during infections of the upper respiratory tract. Those antibodies have the capability of opsonising living bacteria, thus allowing the engulfment and killing mediated by human phagocytes, such as granulocytes. This activity is linked to the capacity of inducing a significant reduction (or a complete disappearance) of signs and symptoms related to respiratory infections. There is a positive trend in the results- a general reduction of infection rates, a reduction of their duration, a beneficial effect on symptoms and a reduction in the use of antibiotics.

These effects also have as a direct consequence, important economic implications. In this case of allergic rhinitis, a reduction in the number of acute exacerbations or a shorter duration of symptoms and use of antibiotics could represent an actual opportunity for curtailing costs of management of such patients. Therefore, the use of bacterial lysate could represent an important means to achieve this prominent result.

Other studies, instead, revealed the benefits of bacterial lysates use. In a randomised clinical trial where children with rhinosinusitis underwent a treatment with bacterial lysate (OM-85BV), a decrease in infectious episodes incidence and duration, their number and the duration of concomitant treatments; furthermore, the clinical response showed a correlation with an increase in serum levels of IgA (active 6.53 ± 0.96 vs. placebo 6.81 ± 0.8).⁸

A RCT including 232 children aged 3-5 years showed that the treatment with PMBL significantly reduced the rate of upper respiratory tract infections (16% decrease in pharyngitis and otitis media), being this reduction higher in children affected more frequently by this kind of infections; the drug was also safe and well tolerated compared with placebo ($P < 0.05$).⁹

In a study conducted by G. Banche et al, considerable improvement was observed in 16 of the 26 PMBL-treated patients (61.5%). These results were evaluated by means of the 0-3 grading scale for the symptoms scores- especially in 14 patients (53.8%), they noticed a relevant decrease in

nasal blockage and rhinorrhea, ocular symptoms in 13 cases (50%) almost disappeared and 10 patients (38.4%) had a large improvement in asthmatic symptoms. Improvement was not immediately observed, but started almost 2-3 weeks or later after the beginning of treatment for all symptoms. A stationary clinical response was registered in 10 of 26 patients (38.4%). In no case, negative side effects associated with the medication or worsening were recorded.

CONCLUSION

This study has shown a significant decrease in the symptoms, duration and frequency of allergic rhinitis. Bacterial lysates have also shown a reduction in infection rates and repeated use of antibiotics. Not only in allergic rhinitis, but bacterial lysates can also be used in other chronic diseases like chronic obstructive pulmonary disease, chronic rhinosinusitis, etc., but further studies have to be conducted with larger population to support this.

REFERENCES

- [1] Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol* 2001;108(1 Suppl):S2-S8.
- [2] Braido F, Tarantini F, Ghiglione V, et al. Bacterial lysate in the prevention of acute exacerbation of COPD and in respiratory recurrent infections. *Int J Chron Obstruct Pulmon Dis* 2007;2(3):335-345.
- [3] Banche G, Allizond V, Mandras N, et al. Improvement of clinical response in allergic rhinitis patients treated with an oral immunostimulating bacterial lysate: in vivo immunological effects. *Int J Immunopathol Pharmacol* 2007;20(1):129-138.
- [4] Braido F, Tarantini F, Ghiglione V, et al. Bacterial lysate in the prevention of acute exacerbation of COPD and in respiratory recurrent infections. *Int J Chron Obstruct Pulmon Dis* 2007;2(3):335-345.
- [5] Macchi A, Vecchia LD. Open comparative, randomized controlled clinical study of a new immunostimulating bacterial lysate in the prophylaxis of upper respiratory tract infections. *Arzneimittelforschung* 2005;55(5):276-281.
- [6] Heintz B, Schlenter WW, Kirsten R, et al. Clinical efficacy of Broncho-Vaxom in adult patients with chronic purulent sinusitis-a multi-centric, placebo-controlled, double-blind study. *Int J Clin Pharmacol Ther Toxicol* 1989;27(11):530-534.
- [7] Okada H, Kuhn C, Feillet H, et al. The hygiene hypothesis for autoimmune and allergic diseases: an update. *Clin Exp Immunol* 2010;160(1):1-9.
- [8] Zagar S, Lofler-Badzek D. Broncho-Vaxom in children with rhinosinusitis: a double-blind clinical trial. *ORL J Otorhinolaryngol Relat Spec* 1988;50(6):397-404.
- [9] Schaad UB, Mutterlein R, Goffin H, et al. Immunostimulation with OM-85 in children with recurrent infections of the upper respiratory tract: a double-blind, placebo-controlled multicenter study. *Chest* 2002;122(6):2042-2049.