

Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.58, No.6(2018). p. 280-5; doi: <http://dx.doi.org/10.14238/pi58.6.2018.280-5>

Original Article

Immunotherapy and probiotic treatment for allergic rhinitis in children

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Abstract

Background Allergic rhinitis is a global health problem that is increasing in prevalence. Many kinds of therapy have been tried, such as antihistamines, probiotics, and immunotherapy. Immunotherapy may restore the patient's normal immunity against the specific allergen, while probiotics may modify the natural course of allergy.

Objective To evaluate probiotics and immunotherapy for improving clinical symptoms of allergic rhinitis.

Methods This randomized controlled trial (RCT) involved 64 patients, aged 3-18 years, and diagnosed with persistent allergic rhinitis in the Department of Child Health, Sardjito General Hospital from April 2016 until May 2017. Patients were randomly allocated into three therapy groups: group A (standard therapy/cetirizine only), group B (standard and probiotic therapy), and group C (standard therapy and immunotherapy). Clinical symptoms of allergic rhinitis including sneezing, rhinorrhea, and itchy nose, were evaluated for 7 weeks and classified as improved or not improved. The significance of the data was analyzed using proportion test.

Results Sixty-four patients completed 7 weeks of therapy, 15 subjects in group A, 26 in group B, and 23 in group C. Group C showed significantly more improvement of sneezing and rhinorrhea compared to both group A ($Z=5.71$; $Z=7.57$, respectively) and group B ($Z=2.82$; $Z=6.90$, respectively). However, itchy nose was not significantly improved in group C compared to group B ($Z=0.50$), but was significantly improved in group C compared to group A ($Z=10.91$). Group B had significant improvement of sneezing, rhinorrhea, and itchy nose compared to group A ($Z=3.81$, $Z=2.86$, and $Z=10.91$, respectively).

Conclusion The combined standard-immunotherapy group has significantly superior improvement compared to the combined standard-probiotic group and the standard therapy group, in terms of sneezing and rhinorrhea in children with persistent allergic rhinitis. [Paediatr Indones. 2018;58:280-5; doi: <http://dx.doi.org/10.14238/pi58.6.2018.280-5>].

Keywords: allergic rhinitis; immunotherapy; probiotics

Allergic respiratory diseases are major health problems in the pediatric population due to their high prevalence and chronicity, as well as the costs for treatment and effect on quality of life. One of the most important risk factors for the development of airway diseases in children and adolescents is atopy.¹ This condition predominates during the childhood years, with 25% classified as having severe allergic rhinitis.² The prevalence of asthma and allergies has increased over the last few decades. Allergic diseases are multifactorial illnesses determined by a complex interplay between genetic and environmental factors.³ A prevalence and comorbidity study of allergy in children in our previous study on 2014 revealed that 33.8% were diagnosed with allergic rhinitis, 17.3% with atopic dermatitis, and 9.1% with asthma.⁴ House dust mites were the most common aeroallergen.⁵

Allergic rhinitis is defined as a type I hypersensitivity allergic reaction with the predominance of Th2 cells and characterized by high IgE levels.⁶ The standard therapy for allergic rhinitis is second generation antihistamines, but additional therapy

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may be needed in persistent or severe cases.⁷ Probiotic treatment has a unique, disease-modifying effect, as it manipulates the normal flora ecosystem in the gastrointestinal tract, induces the stability of Th1 and Th2 immune responses, and stimulates T-regulators to inhibit excessive Th1 and Th2 reactivity.⁸ Probiotic supplementation was shown to be beneficial for decreasing nasal eosinophil percentages in children with allergic rhinitis.⁹

Immunotherapy is given with the aim of modifying the pathogenesis of allergic rhinitis. By giving increasing amounts of allergens to modify the biological response, long-term tolerance may be induced, even after the treatment has ended. This treatment approach has been shown to decrease symptoms and improve quality of life, while being cost-effective for a large number of patients. In addition, it is considered to be the only treatment that can influence the natural course of the disease by targeting the cause of the allergic inflammatory response.^{9,10} In allergic rhinitis, the effectiveness of immunotherapy has been demonstrated in many carefully conducted placebo-controlled trials.¹¹ Skin test sensitivity decreases and allergen-specific IgG increases with immunotherapy.¹² Immunotherapy has also been demonstrated to be quite effective in both seasonal and perennial allergic rhinitis.^{10,13} Immunotherapy treatment using house dust mite allergen has been used widely in developed countries for treating allergic rhinitis and asthma, but rarely used in Indonesia.^{14,15} The frequency of symptoms has been used as a predictor of immunotherapy effectiveness in asthma patients.¹⁵ Administration of immunotherapy and probiotic adjuvants can improve clinical scores and quality of life in asthmatic children, despite a lack of significant differences in immunological parameters such as IFN γ and eosinophils.¹⁷⁻¹⁹ These treatments may increase the CD4+/CD8+ T-cell ratio as well, which may lead to remarkable improvement of clinical symptoms in asthmatic children.¹⁴ This study aimed to evaluate probiotics and immunotherapy for improving clinical symptoms of allergic rhinitis.

Methods

This RCT was conducted from April 2016 to May 2017, on subjects who were diagnosed with persistent

allergic rhinitis and treated as outpatients in the Allergy and Immunology Division, Department of Child Health, Dr. Sardjito General Hospital. The inclusion criteria were children aged 3-18 years with persistent allergic rhinitis, at least one positive skin prick test result, and parental written informed consent. Diagnoses were based on the 2016 *Allergic Rhinitis and Its Impact on Asthma* (ARIA) classification with symptoms present at least 4 days/week for at least 4 weeks.²¹ We excluded those who did not complete 7 weeks of therapy, those with unusual skin prick test results (wide skin lesions or severe dermatographism), antihistamin-dependent,²⁰ and uncooperative patients.

Subjects were allocated into three groups using a randomized block design and followed up until the 7th week of therapy. The 3 groups were group A (standard therapy/cetirizine only), group B (standard and probiotic therapy), and group C (standard therapy and immunotherapy). We used cetirizine 10mg as standard therapy, a sachet of *Protexin*® for probiotic and a house dust mite allergen with 0.001 concentration from Pharmacy in Dr. Soetomo General Hospital. The improvement of each clinical symptom was evaluated by comparing the frequency of the symptom before and after 7 weeks of therapy. The significance of the data was analyzed using the proportion test. The study protocol was approved by the Medical Research Ethics Committee of the Universitas Gadjah Mada Medical, Public Health, and Nursing School.

Results

A total of 64 subjects aged 3 to 18 years were included in the study and randomly allocated into three groups: 15 in group A, 26 in group B, and 23 in group C. Most subjects were male (10 in group A, 16 in group B, and 16 in group C). The subjects were predominantly between 3 and 12 years of age in group A (12) and group B (20), but group C subjects were mostly >12-18 years of age. Most subjects had a history allergic rhinitis prior to the study, with symptoms of sneezing, rhinorrhea, and itchy nose. The baseline characteristics of subjects are shown in **Table 1**.

The improvement of each clinical symptom was evaluated by comparing the frequency before and after the 7th week of therapy. The comparisons of clinical

Table 1. Baseline characteristics of study subjects

Characteristics	Group A (n=15)	Group B (n=26)	Group C (n=23)
Sex, n			
Male	10	16	16
Female	5	10	7
Age, n			
3-12 years	12	20	10
>12-18 years	3	6	13
Nutritional status, n			
Underweight	0	1	1
Normal	15	21	21
Overweight	0	4	1
History of sneezing, n			
Present	12	24	23
Not present	3	2	0
History of rhinorrhea, n			
Present	10	19	20
Not present	5	7	3
History of itchy nose, n			
Present	8	20	18
Not present	7	6	5
History of atopy, n			
Present	12	22	18
Not present	3	4	5

Table 2. Clinical symptom improvement after 7 weeks of therapy in the standard vs. combined standard-probiotic (groups A and B)

Parameter	Standard (A) (n=15)	Standard+probiotic (n=26)	Z score
Sneezing, n			
Improved	9	18	3.81
Not improved	6	8	
Rhinorrhea, n			
Improved	10	19	2.86
Not improved	5	7	
Itchy nose, n			
Improved	7	19	10.91
Not improved	8	7	

symptom improvement between groups are shown in **Tables 2, 3, and 4**. **Table 2** shows that group B had significantly improved clinical symptoms compared to group A. Sneezing improved in 18/26 of subjects in group B vs. 9/15 in group A ($Z=3.81$). Rhinorrhea improved in 19/26 of subjects in group B vs. 10/15 in group A ($Z=2.86$). Itchy nose improved in 19/26 of group b vs. 7/15 in group A ($Z=10.91$).

Table 3 shows that clinical symptoms of sneezing and rhinorrhea significantly improved in group C compared to group B [sneezing: 17/23 group C vs.

18/26 group B ($Z=2.82$); rhinorrhea: 19/23 group C vs. 19/26 group B ($Z=6.90$)]. However, while itchy nose symptoms showed vast improvement in both groups B and C, there was no significant difference between groups, with 17/23 of group C vs. 19/26 of group B showing improvements ($Z=0.50$).

Table 4 shows the clinical symptom improvements between groups A and C. Group C had significantly more improvement of clinical symptoms compared to group A [sneezing: 17/23 group C vs. 9/15 group A ($Z=5.71$); rhinorrhea: 19/23 group C

Table 3. Clinical symptom improvement after 7 weeks of therapy in the combined standard-probiotic vs. combined standard-immunotherapy (groups B and C)

Parameter	Standard+probiotic (B) (n=26)	Standard+immunotherapy (C) (n=23)	Z score
Sneezing, n			
Improved	18	17	2.82
Not improved	8	6	
Rhinorrhea, n			
Improved	19	19	6.90
Not improved	7	4	
Itchy nose, n			
Improved	19	17	0.50
Not improved	7	6	

Table 4. Clinical symptom improvement after 7 weeks of therapy in the standard vs. combined standard-immunotherapy (groups A and C)

Parameter	Standard (A) (n=15)	Standard+immunotherapy (C) (n=23)	Z score
Sneezing, n			
Improved	9	17	5.71
Not improved	6	6	
Rhinorrhea, n			
Improved	10	19	7.57
Not improved	5	4	
Itchy nose, n			
Improved	7	17	10.91
Not improved	8	6	

vs. 10/15 group A (Z=7.57); itchy nose: 17/23 group C vs. 7/15 group A (Z=10.91)].

Discussion

Children with persistent allergic rhinitis who received standard (antihistamine) therapy combined with immunotherapy had significantly superior improvement of sneezing and rhinorrhea compared to those who received standard therapy combined with probiotics, and those who received standard therapy alone. Similarly, an RCT by Karakoc-Aydiner *et al.* concluded that house dust mite-sensitized children with asthma and/or rhinitis treated with either subcutaneous injection immunotherapy or sublingual immunotherapy showed better clinical outcome improvements than children who got antihistamine alone.²² Another study by Smith *et al.* in 2004 also showed significant improvement of reduction in runny nose and sneezing compared between immunotherapy and placebo.²³

Similar study was done as well by Palma-Carlos *et al.* and showed significant improvement of rhinorrhea, sneezing, and conjunctivitis compared with placebo after one year therapy.²⁴

Probiotic are beneficial microbes that give benefit to the host, such as normalize the dysbiotic microbiota, which will associate with immunopathology.⁹ It is described in a review by Hardy *et al.* in 2013 that probiotic has the ability as immunomodulatory on the cells, molecules and immune response in the gut mucosae.⁷

Subcutaneous injection immunotherapy has been demonstrated to be efficacious in the management of allergic rhinitis and asthma, even in multi-allergen situations. This therapy has been effective in the prevention of new sensitizations and progression of rhinitis to asthma.¹³ Immunotherapy acts on the T helper cells type 1 (Th1/Th2) axis to shift the T cell phenotype away from the allergic Th2 phenotype. More recently, some evidence has emerged to suggest that immunotherapy may promote regulatory T cells action in attenuating allergic symptoms.¹⁰

From our study, we conclude that immunotherapy combined with antihistamine has better improvement compared with antihistamine only or antihistamine with probiotic.

Conflict of Interest

None declared.

Funding

This work was supported by “Dana Masyarakat” Funding from Universitas Gadjah Mada Medical, Public Health, and Nursing School.

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