Allergology International. 2010;59:15-19
DOI: 10.2332/allergolint.09-RAI-0150

REVIEW ARTICLE

Allergen Immunotherapy in Asthma: Current Status and Future Perspectives

Makoto Nagata[1,2] and Kazuyuki Nakagome[1,2]

ABSTRACT
Allergen immunotherapy targets Th2 cells activated by specific allergens, which constitutes the basis of allergic disease. Therefore, this approach has therapeutic potential for a variety of allergic diseases, including asthma, and may modify their natural course. Immunotherapy results in systemic immunological changes to allergens, thereby providing clinical benefits in allergic asthma. For example, immunotherapy attenuates T-cell-mediated airway inflammation by down-modulating Th2 and inducing Th1 differentiation. In addition, immunotherapy induces regulatory T cells, which produce IL-10. Meta-analysis has demonstrated that allergen immunotherapy improves clinical symptoms and non-specific airway hyperresponsiveness in asthma, and decreases drug requirements. Clinical studies have supported the usefulness if immunotherapy in mild to moderate asthma cases, particularly in patients with concomitant rhinitis. Several promising novel approaches have emerged as future immunotherapeutic strategies for the treatment of asthma. Current pharmacotherapy, including inhalational corticosteroids, provides powerful anti-symptomatic benefits in asthma; however, pharmacotherapy cannot cure or modify the natural course of asthma. As immunotherapy targets the background immunological state in asthma, it is expected to lead to long-term amelioration or cure. It is hoped that the positioning of allergen immunotherapy as a treatment option will allow the comprehensive management of symptoms in allergic individuals, and the modification of disease course.

KEY WORDS
allergic asthma, allergic conjunctivitis, allergic rhinitis, immunotherapy, Th2 responses

INTRODUCTION

Allergen immunotherapy constitutes a treatment method that modifies immunoreactive responses to specific allergens by administrating allergens that cause allergic diseases such as asthma. According to the WHO position paper,[1] immunotherapy is effective for diseases that are associated with type I allergic reactions, such as allergic rhinitis and allergic bronchial asthma. As a result of anti-symptomatic therapies, including the use of inhalational corticosteroids (ICS), management of asthma has markedly improved. Consequently, the use of allergen immunotherapy has been reduced. However, there is increasing evidence that ICS does not affect the natural course of asthma.[2-4] Furthermore, ICS does not provide therapeutic benefits for symptoms caused by rhinoconjunctivitis, which is commonly observed in asthmatic patients. In contrast to ICS, allergen immunotherapy targets the Th2 cells pathophysiologically activated by specific allergens, thus providing therapeutic potency for the variety of allergic diseases observed simultaneously in allergic individuals, and possibly modifying the natural course of allergic diseases.[1] In this article, the authors review the current understanding of the role of allergen immunotherapy in asthma and discuss future perspectives of this treatment modality in this field.

MECHANISMS OF ALLERGEN IMMUNOTHERAPY

Airway inflammation is a key feature of asthma. For example, infiltration of activated eosinophils is an important factor and is known to be associated with disease severity. In successful cases of immunotherapy in asthma, indexes of airway inflammation, including

[1]Department of Respiratory Medicine and [2]Allergy Center, Saitama Medical University, Saitama, Japan.
Correspondence: Makoto Nagata, MD, Department of Respiratory Medicine, Saitama Medical University, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama 350–0495, Japan.
Email: favre4mn@saitama–med.ac.jp
Received 3 October 2009.

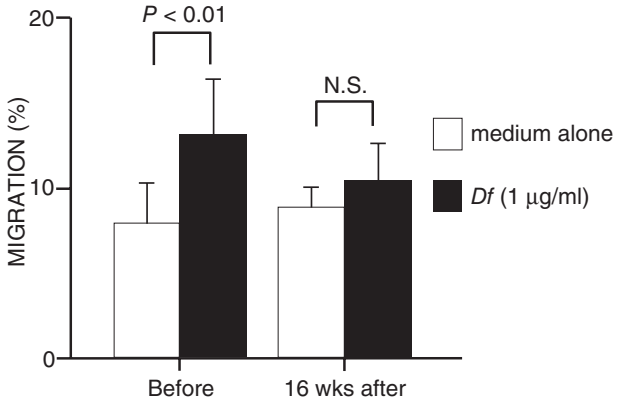

Fig. 1 Eosinophil transendothelial migration induced by culture supernatants of peripheral blood mononuclear cells (PBMC) obtained from *Dermatophagoides farinae* (*Df*)-sensitive atopic asthmatics treated by rush immunotherapy (n = 5). *Df* (-); eosinophil migration in response to supernatants of PBMC cultured with medium alone. *Df* (+); eosinophil migration in response to supernatants of PBMC cultured with *Df*-antigen. Data are expressed as mean ± SEM.

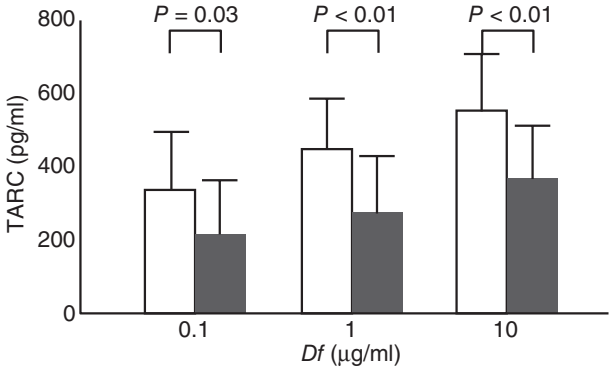

Fig. 2 Effects of rush immunotherapy on production of TARC by peripheral blood mononuclear cells obtained from house dust mite-sensitive asthmatics. Open bars represent data before immunotherapy, and closed bars represent data at 16 weeks following induction of allergen immunotherapy. Data are expressed as mean ± SEM from 8 donors.

the number of infiltrated eosinophils and/or concentrations of eosinophil specific-granule proteins, are reduced.[5-7] For circulating eosinophils to accumulate in asthmatic airways, they must adhere to and then migrate across vascular endothelial cells. These processes are largely regulated by cytokines/chemokines produced by various cells, including Th2 cells. During the allergen exposure period in birch pollen asthma, increased adhesiveness of peripheral blood eosinophils and increased chemotactic activity for eosinophils in bronchoalveolar lavage fluid are observed, and these actions are blocked by immunotherapy.[5,8]

The authors previously confirmed that stimulation of mononuclear leukocytes from house dust mite-sensitive allergic asthmatics with mite-allergen results in productions of eosinophil adhesion-inducing activity, eosinophil chemotactic activity, and eosinophil transendothelial migration-inducing activity and the increases of those parameters were attenuated in patients treated with allergen immunotherapy (Fig. 1).[9-11] These findings suggest that modification of the responsiveness of T cells, particularly Th2 cells, to specific allergens by immunotherapy results in the suppression of eosinophil accumulation in the airways. These effects are likely to involve down-regulation of Th2 cells.

It has been demonstrated that the production of Th2 cytokines, such as IL-4 and IL-5, is decreased by immunotherapy.[8,12] We recently found that immunotherapy attenuates the house dust mite allergen-specific production of TARC, a potent chemokine activator of Th2 cells, from peripheral blood mononuclear cells obtained from patients with house dust mite-sensitive allergic asthma, thus suggesting that immunotherapy can reduce accumulation of Th2 cells during allergen exposure (Fig. 2). Therefore, immunotherapy results in systemic immunological changes in response to allergens, and provides some clinical benefits in allergic asthma. In addition to modulating effects on the Th2 cascade, immunotherapy induced differentiation to the Th1, rather than the Th2, phenotype in Th0 cells.[13]

It has been reported[13] that allergen-challenge-induced expression of IL-12 mRNA in the skin was augmented by immunotherapy. These findings support the notion that immunotherapy attenuates T-cell-mediated airway inflammation via down-modulation of Th2 and induction of Th1 differentiation. There is also increasing evidence that immunotherapy induces regulatory T cells (Treg), which produce IL-10 and down-modulate allergic inflammation.[14-16] For example, in bee venom allergy, immunotherapy increases the production of IL-10, which is associated with inhibitory effects in response to specific allergens. However, recent investigations using immunotherapy with Th1 adjuvants, such as CpG-motif, have shown some clinical benefits without production of IL-10, thus indicating the need for further research to elucidate the significance of Treg/IL-10. Involvement of Treg/IL-10 in immunotherapy for Th2 suppression may be regulated by multiple factors, including allergen, adjuvant and time of assessment.

CURRENT STATUS OF ALLERGEN IMMUNOTHERAPY IN ASTHMA

The clinical indications for immunotherapy in asthma are not fully established; however, this therapy should be considered for allergic asthma patients who have identified environmental aero allergens that

Table Clinical effects in terms of step-down rate after rush immunotherapy in house dust mite-sensitive asthmatics

	FEV_1%		Duration	
	≥70%	<70%	≥10 y	<10 y
Unchanged:	15 (39.5%)	8 (66.7%)	18 (54.5%)	5 (29.4%)
Improved:	23 (60.5%)	4 (33.3%)	15 (45.5%)	12 (70.6%)
	$P = 0.009$		$P = 0.043$	

are difficult to avoid or for cases that are not severe and present normal pulmonary function. This approach was outlined in the recent US asthma guideline Expert Panel 3.[17] In asthma, meta-analysis has demonstrated that allergen immunotherapy improves clinical symptoms and non-specific airway hyperresponsiveness, and decreases drug requirements.[18] For immunotherapy to be successful, the maintenance allergen dose to be administered should be sufficiently high. In rush immunotherapy, patients are hospitalized and repeatedly injected under clinically controlled conditions, and the target concentration is easily achieved in several days, with clinical effects being seen rapidly[19]; improvement in symptom medication scores and allergen-specific bronchial hyperresponsiveness typically appears within several weeks. Using this method, we observed that clinical effects, based on the rate of obtaining step-down of asthma severity, is significantly less in patients with more than 10 years of disease or FEV1% of less than 70% (Table). Therefore, it is conceivable that immunotherapy would be beneficial for asthmatics with early-stage allergic asthma, without development of airway remodeling.

What happens if immunotherapy is prescribed in addition to ICS? Current pharmacotherapy, including ICS, recommended by the latest guidelines tends to rapidly improve symptoms in mild to moderate asthma. Maestrelli *et al.*[20] investigated the additional effects of immunotherapy when it was combined with pharmacotherapy according to the Global Initiative for Asthma (GINA) guidelines in mild to moderate disease in mite-sensitive asthmatic patients. The immunotherapy group showed partial suppression in mite-induced immediate skin reactions, decreased frequency of rescue use of short-acting β2-agonist, and improved peak expiratory flow rate, thus suggesting immunotherapy provides additive effects in patients treated with ICS. More recently, Garcia-Robaina *et al.*[21] investigated the effects of a depigmented polymerized allergen vaccine containing a 50% mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* on mild to moderate asthma, and found that the median improvement in total symptom and medication scores in the active versus placebo group was 53.8% and 58.1%, respectively. This study also demonstrated that this immunotherapy improves symptoms of rhinoconjunctivitis, thereby confirming that immunotherapy acts as an active systemic therapy for allergic individuals. In this context, Marogna *et al.*[22] compared the effects of sublingual immunotherapy (SLIT) and ICS in patients with mild asthma and concomitant rhinitis due to grass pollen allergy. After a run-in season, patients were randomized to either 800 μg/day budesonide, an ICS, during the pollen season or continuous grass SLIT for 5 years. Asthma symptoms decreased significantly in both groups; however, improvements were greater in the SLIT patients at 3 and 5 years. Furthermore, a decrease in both nasal symptoms and nasal eosinophils was observed only in the SLIT group. These results indicate that SLIT is equally effective as ICS in treating seasonal asthma and provides benefits in treating rhinitis symptoms.

Taken together, these clinical studies confirmed the rationale of current US guideline EPR3, and support the usefulness of immunotherapy in mild to moderate asthma, particularly in those with rhinoconjunctivitis.

MODIFICATION OF NATURAL HISTORY BY IMMUNOTHERAPY

What about the significance of immunotherapy in its original role of modification of the natural history of allergic diseases such as asthma? The approaches described in the following section provide promising data. As noted above, it is speculated that immunotherapy would be less effective in asthmatic patients with longer disease period because of development of airway remodeling. Moller *et al.*[23] investigated the effects of immunotherapy on onset of asthma in pollen allergy rhinitis patients. Non-specific airway hyperresponsiveness during the pollen season improved only in the active treatment group. After three years of follow up, the ratio of asthma development was significantly lower in the immunotherapy treatment group (21%) than in the control group (44%). These results suggest that immunotherapy is more effective when introduced at early stages.

Thus, Di Rienzo *et al.*[24] investigated whether mite-allergen immunotherapy using SLIT can improve the natural course of children suffering from mite allergy. At the end of a 4- to 5-year course of SLIT treatment and a further 4 to 5 years after SLIT discontinuation, there was a significant reduction in the presence of asthma in the treated patients, as compared with baseline. On the other hand, in the control group, no clinical changes were observed after 5 and 10 years of follow-up. There was a highly significant difference between the two groups, at both the end of SLIT and after 5 years. This study demonstrates that SLIT improves the prognosis of children with mite allergy, and that clinical efficacy is maintained for 4 to 5 years after discontinuation.

NEW APPROACHES FOR ALLERGEN IMMUNOTHERAPY

The following novel approaches constitute promising future immunotherapy modalities for asthma. It has been demonstrated that Th1 adjuvants, such as liposome, monophosphoryl lipid A (MPL) or the immunostimulatory DNA sequence CpG motif, may facilitate the action of allergen immunotherapy. For example, Basomba *et al.*[25] conducted a double blinded comparative study of immunotherapy using liposomal mite allergen on mild to moderate asthma. Approximately half (46%) of the immunotherapy group showed a decrease in symptom-medication scores of more than 60%, while fewer patients (only 12%) in the placebo group showed such improvement. In the active treatment group, mite-specific IgG4 was increased, while allergen-specific bronchial responsiveness was improved. It was meaningful to demonstrate that liposome, which is known to be a Th1 adjuvant, can be used for allergen immunotherapy in asthma; however, it is unclear whether this modification can overcome current treads in conventional immunotherapy.

Drachenberg *et al.*[26] examined whether a grass pollen-specific vaccine containing MPL, a potent Th1 adjuvant and a ligand for toll-like receptor 4, would modify allergic symptoms in grass pollen-sensitive subjects. Tyrosine-absorbed glutaraldehyde-modified grass pollen extract containing MPL adjuvant was used. After only four preseasonal injections, the vaccine containing MPL reduced nasal symptoms, ocular symptoms, and combined symptom and medication scores.

Tulik *et al.*[27] investigated whether a conjugate of the major ragweed allergen Amb a 1 and CpG motif (A1C) would modify asthma and rhinitis due to ragweed hay fever. No severe side effects were observed, and the active treatment was well tolerated. In the active group, nasally administered allergen induced IL-4 producing cells were blocked while IFN-γ was increased, confirming an immunological shift from the Th2 to Th1 system. During the pollen season, the AIC group showed significantly fewer asthma and rhinitis symptoms as compared with the control group. Creticos *et al.*[28] also reported that a 6-week regimen of the AIC vaccine appeared to offer long-term clinical efficacy in the treatment of ragweed allergic rhinitis: During the first ragweed season, the AIC group had better peak-season rhinitis scores than the placebo group and a clinical benefits were again observed in the subsequent ragweed season. These studies are important for demonstrating that induction of Th1 and reduction of Th2 response act as mechanisms of immunotherapy, thus raising the future possibility of additional Th1 adjuvants.

There is increasing evidence that recombinant DNA technology has the potential to produce allergen-specific immunotherapy vaccines.[29,30] Pauli *et al.*[29] evaluated the effectiveness of a recombinant birch pollen allergen vaccine in patients with birch pollen allergy. A randomized, double-blind, placebo-controlled trial was undertaken in order to compare the following three vaccines in 134 adults with birch pollen allergy: recombinant birch pollen allergen vaccine (rBet v 1a), licensed birch pollen extract, natural purified birch pollen allergen (nBet v 1), and placebo. Significant reductions (about 50%) in rhinoconjunctivitis symptoms, rescue medication, and skin sensitivities were observed in the three actively treated groups, as compared with the placebo. No severe systemic adverse events were observed in the rBet v 1-treated group. These results indicate that the rBet v 1-based vaccine is safe and effective in treating birch pollen allergy.

FUTURE PERSPECTIVES

Application of immunotherapy upon onset of asthma is clinically feasible in Japan with the aim of prevention. Patients with Japanese cedar pollinosis, for example, may be candidates for immunotherapy in terms of preventing development of asthma. The present study also suggests the usefulness of early intervention in producing improvements. The study on mite allergy using SLIT strongly suggests that immunotherapy can improve the natural course of allergic diseases, including asthma, in children. However, it remains to be elucidated whether such effects can also be achieved in adult asthmatics.

Among recent progress and newly developed approaches regarding allergen immunotherapy, liposomal allergen vaccination is promising; however, it should be clarified whether this method is better than conventional allergen immunotherapy. On the other hand, selective Th1 adjuvants, such as CpG motif or MPL, have the potential to become useful therapies for allergic asthma, such as in mite allergy. In any case, the application of Th1 system adjuvant may be useful as a modified vaccine approach in immunotherapy. Immunotherapy using recombinant allergen would provide a further possibility to improve this form of therapy. The results of a study by Pauli *et al.*[29] are extremely promising, and suggest the possible use of this approach in dust mite allergy.

Current pharmacotherapy, such as ICS, provides powerful anti-symptomatic benefits in asthma; however, it does not cure or modify the natural disease course. As immunotherapy targets the immunological background in asthma, including pathological activation of Th2 cells, it is expected to lead to long-term amelioration of asthma. It is hoped that the novel approaches described in this article will become more sophisticated and provide better efficacy, and that the positioning of allergen immunotherapy as a treatment option for comprehensive management of allergy symptoms and for modification of disease course.

REFERENCES

1. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998;**102**:558-62.
2. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;**354**:1998-2005.
3. Guilbert TW, Morgan WJ, Zeiger RS *et al*. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;**354**:1985-97.
4. Busse WW, Pedersen S, Pauwels RA *et al*, and START Investigators Group. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. *J Allergy Clin Immunol* 2008;**121**:1167-74.
5. Rak S, Bjornson A, Hakanson L, Sörenson S, Venge P. The effect of immunotherapy on eosinophil accumulation and production of eosinophil chemotactic activity in the lung of subjects with asthma during natural pollen exposure. *J Allergy Clin Immunol* 1991;**88**:878-88.
6. Furin MJ, Norman PS, Creticos P *et al*. Immunotherapy decreases antigen-induced eosinophil cell migration into the nasal cavity. *J Allergy Clin Immunol* 1988;**88**:27-32.
7. Kohno Y, Minoguchi K, Oda N *et al*. Effect of rush immunotherapy on airway inflammation and airway hyperresponsiveness after bronchoprovocation with allergen in asthma. *J Allergy Clin Immunol* 1998;**102**:927-34.
8. Hakanson L, Heinrich C, Rak S, Venge P. Priming of eosinophil adhesion in patients with birch pollen allergy during pollen season: Effect of immunotherapy. *J Allergy Clin Immunol* 1997;**99**:551-62.
9. Nagata M, Shibasaki M, Sakamoto Y *et al*. Specific immunotherapy reduces the antigen-dependent production of eosinophil chemotactic activity from mononuclear cells in patients with atopic asthma. *J Allergy Clin Immunol* 1994;**94**:160-6.
10. Nagata M, Tabe K, Choo JH, Sakamoto Y, Matsuo H. Effect of immunotherapy on the production of eosinophil adhesion-inducing activity from mononuclear cells in house-dust-mite-sensitive bronchial asthma. *Int Arch Allergy Immunol* 1998;**117** (Suppl 1):20-3.
11. Nagata M, Saito K, Kikuchi I *et al*. Immunotherapy attenuates eosinophil transendothelial migration induced by the supernatants of antigen-stimulated mononuclear cells from atopic asthmatics. *Int Arch Allergy Immunol* 2004;**134** (Suppl 1):21-4.
12. Durham SR, Till SJ. Immunologic changes associated with allergen immunotherapy. *J Allergy Clin Immunol* 1998;**102**:157-64.
13. Hamid QA, Schitman E, Jacobson MR, Walker SM, Durham SR. Increases in IL-12 messenger RNA+ cells accompany inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy. *J Allergy Clin Immunol* 1997;**99**:254-60.
14. Francis JN, James LK, Paraskevopoulos G *et al*. Grass pollen immunotherapy: IL-10 induction and suppression of late responses precedes IgG4 inhibitory antibody activity. *J Allergy Clin Immunol* 2008;**121**:1120-5.
15. Radulovic S, Jacobson MR, Durham SR, Nouri-Aria KT. Grass pollen immunotherapy induces Foxp3-expressing CD4+ CD25+ cells in the nasal mucosa. *J Allergy Clin Immunol* 2008;**121**:1467-72.
16. Akdis CA, Akdis M. Mechanisms and treatment of allergic disease in the big picture of regulatory T cells. *J Allergy Clin Immunol* 2009;**123**:735-67.
17. U.S. Department of Health and Human Services. National Heart, Lung, and Blood Institute. *National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma*. 2007.
18. Abramson MJ, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995;**151**:969-74.
19. Nagata M, Yamamoto H, Tabe K *et al*. Effects of rush immunotherapy in house-dust-mite (HDM)-sensitive adult bronchial asthma: Changes *in vivo* and *in vitro* responses to HDM. *Intern Med* 1993;**32**:702-9.
20. Maestrelli P, Zanolla L, Pozzan M, Fabbri LM, and Regione Veneto Study Group on the "Effect of immunotherapy in allergic asthma". Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. *J Allergy Clin Immunol* 2004;**113**:643-9.
21. Garcia-Robaina J, Sanchez I, de la Torre F, Fernandez-Caldas E, Casanovas M. Successful management of mite-allergic asthma with modified extracts of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* in a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2006;**118**:1026-32.
22. Marogna M, Spadolini I, Massolo A *et al*. Long-term comparison of sublingual immunotherapy vs inhaled budesonide in patients with mild persistent asthma due to grass pollen. *Ann Allergy Asthma Immunol* 2009;**102**:69-75.
23. Moller C, Dreborg S, Ferdousi HA *et al*. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjuctivitis (the PAT-Study). *J Allergy Clin Immunol* 2002;**109**:251-6.
24. Di Rienzo V, Marcucci F, Puccinelli P *et al*. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. *Clin Exp Allergy* 2003;**33**:206-10.
25. Basomba A, Tabar AI, de Rojas DHF *et al*. Allergen vaccination with a liposome-encapsulated extract of *Dermatophagoides pteronyssinus*: A randomized, double-blind, placebo-controlled trial in asthmatic patients. *J Allergy Clin Immunol* 2002;**109**:943-8.
26. Drachenberg KJ, Wheeler AW, Stuebner P, Horak F. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. *Allergy* 2001;**56**:498-505.
27. Tulic MK, Fiset PO, Christodoulopoulos P *et al*. Amb a 1-immunostimulatory oligodeoxynucleotide conjugate immunotherapy decreases the nasal inflammatory response. *J Allergy Clin Immunol* 2004;**113**:235-41.
28. Creticos PS, Schroeder JT, Hamilton RG *et al*, and Immune Tolerance Network Group. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med* 2006;**355**:1445-55.
29. Pauli G, Larsen TH, Rak S *et al*. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2008;**122**:951-60.
30. Purohit A, Niederberger V, Kronqvist M *et al*. Clinical effects of immunotherapy with genetically modified recombinant birch pollen Bet v 1 derivatives. *Clin Exp Allergy* 2008;**38**:1514-25.