

Review on immunotherapy in airway allergen sensitised patients

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ABSTRACT

Allergen immunotherapy is a more than 100-year-old treatment in particular for birch pollen, grass pollen, house dust mite and cat dander sensitised allergic patients. The mechanism of allergen-specific immunotherapy is complex. Different hypotheses have been postulated to explain the mode of action, such as a decrease of the number of tissue mast cells, eosinophils and basophils, an increase of IgG₄ and IgA synthesis, a shift from Th₂ to Th₁ cells and an increase in the number and function of IL-10 producing T-regulatory cells (T-reg). All these immunological effects may contribute to immune tolerance and long-term changes in the immune system. The efficacy and safety of subcutaneous (SCIT) and sublingual immunotherapy (SLIT) with pollen and house dust mite have been investigated in many trials, meta-analyses and reviews. Nowadays grass pollen SLIT and SCIT, and birch pollen and house dust mite SCIT are implemented in clinical practice to treat therapy-resistant patients. However, the treatment is not effective for all patients and often not without side effects. Therefore, the development of new, safer and more effective immunotherapies is needed. These are approached along novel routes, including improved administration, combined treatment with immune response modifiers, fusion with immune response modifiers, allergen coupled to adjuvants and reconstruction of natural extracts with multiple recombinant allergens or with modified allergens. These developments are promising, but more research is required to implement them in clinical practice.

KEYWORDS

Immunotherapy, SCIT, SLIT

INTRODUCTION

Immunotherapy with inhalation allergens is over 100 years old. The treatment is indicated for patients with birch pollen, grass pollen, house dust mite or cat dander allergy. The therapy induces allergen-specific immune tolerance for inhalation allergic patients and leads to a reduction of allergic symptoms in patients with rhinitis, conjunctivitis and allergic asthma. Immunotherapy is the only available effective treatment to target the disease instead of the symptoms. Whether immunotherapy is prescribed depends on the severity of symptoms, the effect of elimination measures, or medication and the desire of the patient to stop long-term pharmacological treatment. Currently, immunotherapy can be given either subcutaneously (SCIT) or sublingually (SLIT). Grass pollen has been registered for subcutaneous and sublingual administration, whereas birch pollen, house dust mite and cat dander have been registered for subcutaneous use only. Allergens are administered subcutaneously under medical supervision. The therapy has a build-up phase with, in general, weekly injections with an increasing concentration of the allergen. The duration of this build-up phase depends on the frequency of injections and ranges from 3-6 months. The build-up phase is followed by monthly maintenance injections for 3-5 years. Another option is to use an accelerated schedule (rush immunotherapy) for the build-up phase. This approach shortens the build-up phase substantially. A series of injections is administered in one visit. SLIT uses sublingual administration of drops or tablets under the tongue and is usually taken at home, except for the first dose. The safety profiles of SCIT when using the conventional schedule or the rush schedule are comparable. The safety profile of SLIT is superior to SCIT. Which route of immunotherapy is used depends on several factors such as vaccine availability, patient characteristics, cost, and physician and patient preferences.^{1,2}

MECHANISM

The mechanisms of allergen-specific immune response are complex and not fully understood. For this response, an early and a late phase can be distinguished. In the early phase of immunotherapy a decrease occurs in the number of tissue mast cells, eosinophils and basophils along with a reduction in mediator release.³ Basophil decrease is caused by up-regulation of H2 receptors, which causes inhibition of FcεRI-mediated release of histamine and other mediators. Also an increase of IgG4 and IgA synthesis is observed in the early phase of immunotherapy.⁴ IgG4 blocks the interaction between IgE and the allergen and the presentation of the allergen to T cells. In the late phase, after one to several months of immunotherapy, a shift occurs from Th2 to Th1 cells, as well as an increase in the number and function of two types of T-regulatory cells (T-reg) cells.³ The two types of T-reg cells are the natural T-reg (nT-reg) cells and inducible T-reg (iT-reg) cells. iT-reg cells are IL-10 secreting cells derived from naïve CD4⁺ T lymphocytes and are an important factor in peripheral tolerance induction.^{5,6} IL-10 inhibits the production of IgE, enhances IgG4 and is directly involved in the suppression of allergen-specific

T-effector cells.⁷ nT-reg cells (CD4⁺, CD25⁺ and FOXP3⁺ (Forkhead box protein 3)) originate from the thymus and show a corresponding function to the iT-reg cells.⁸ nT-reg cells express high levels of IL-10 and TGF-beta.⁹ T-reg cells induce IL-10 secreting dendritic cells. These dendritic cells play a role in the activation and differentiation of T-cells into different subtypes. These are able to cause inflammatory response or immune tolerance depending on their maturity stage.¹⁰ iT-reg cells induce suppression of IgE production by effector B-cells. Recently, IL-10 secreting B-cells have been detected in venom-allergic patients after immunotherapy.¹¹ IL-10 secreting natural killer cells have also been reported to play a role in the immune tolerance by antigen-specific T-cell suppression and via a decrease in IgE production. However, more research is needed to reveal their specific role.¹² All these immunological effects, i.e. decrease in the number of tissue mast cells, eosinophils and basophils, an increase of IgG4 and IgA synthesis, a shift from Th2 to Th1 cells and an increase in the number and function of IL-10 producing T-reg cells, may contribute to long-term immune tolerance and to a change in the immune system (figure 1). The immunological mechanisms in SCIT and SLIT are considered to be identical.⁹

Figure 1. The mechanism of immunotherapy is shown in this figure. The number of mast cells, basophils and eosinophils decreases and the production of IgG4 and IgA increases. A shift from Th2 cells to Th1 cells and an increase of T-reg cells occurs during immunotherapy. IL 10 plays a important role in this induction of immune tolerance

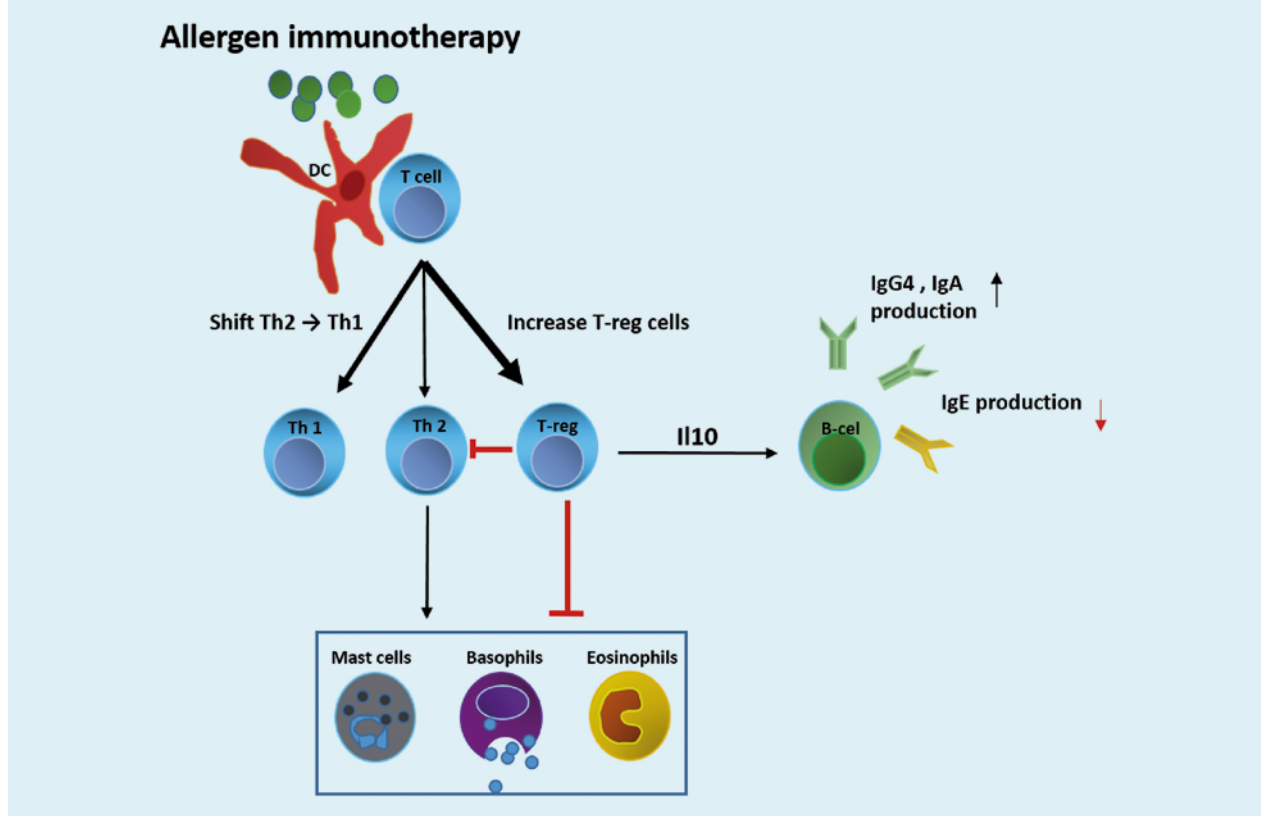


Table 1. High-evidence studies on the efficacy and safety of immunotherapy

Study year	Author	Type of article (n = studies)	Study allergen	Administration	Efficacy	Safety
2007	Calderon <i>et al.</i> ¹³	Cochrane meta-analysis (n=15)	Tree, grass and weed pollen	SCIT	Significant reduction in symptom score and medication usage	Adrenalin administered in 0.13% of actively treated group
2011	Radulovic ¹⁴	Meta-analysis (n = 49 RCTs)	Grass pollen	SLIT	Significant reduction in symptom score and medication requirement	None of the trials reported severe allergic reactions
2012	Di Bona <i>et al.</i> ¹⁵	Meta-analysis (n = 36 RCTs)	Grass pollen	SCIT	Significant clinical benefit from SCIT	0.86 AE/patient receiving SCIT, 12 anaphylactic reactions
				SLIT	Mild-to-moderate benefit from SLIT	2.13 AEs/ patient receiving SLIT; one anaphylactic reaction
2009	Compalati <i>et al.</i> ¹⁶	Meta-analysis (n = 17)	HDM	SLIT	Reduction of symptoms and medication score	
2013	Calderon <i>et al.</i> ¹⁷	Evidence-based analysis (n = 44)	HDM	SCIT	Significant favourable effect of SCIT vs placebo on symptom score	Safety aspects poorly described Serious side effects which required adrenaline were reported
				SLIT	Significant difference in symptom score in benefit of SLIT vs placebo in some studies	Safety aspects are reported very rarely
1997	Varney <i>et al.</i> ¹⁸	Double-blind, randomised, placebo-controlled study	Cat dander	SCIT	Mean number of symptoms, peak flow response, and conjunctival provocation sensitivity decreased	No serious immunotherapy-related side effects were reported

AE = adverse event; HDM = house dust mite; RCT = randomised controlled trial; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

EVIDENCE FOR EFFICACY AND SAFETY OF SCIT AND SLIT

Pollen

Many studies have been performed in patients with a seasonal allergy on the efficacy of SCIT and SLIT. Three meta-analysis on this topic have appeared (*table 1*).

The Cochrane meta-analysis of Calderon *et al.* (2007) evaluated the safety and efficacy of allergen (tree, grass and weed) SCIT for patients with seasonal allergic rhinitis.¹³ In the symptom score meta-analysis 15 studies (n = 597 immunotherapy, n = 466 placebo) and in the medication score meta-analysis 13 studies (n = 549 immunotherapy, n = 414 placebo) were included. The authors conclude that

a significant reduction in symptom score and medication usage can be achieved with immunotherapy. With regard to the safety aspects of this treatment, adrenaline was administered to only 0.13 % of the actively treated patients to cope with adverse events due to the immunotherapy.

The publication by Radulovic *et al.* (2011) is a systematic review on the efficiency and safety of SLIT.¹⁴ A total of 49 RCTs were used for the meta-analysis to evaluate the effect on symptom score ($n = 2333$ immunotherapy, 2256 placebo) and 38 RCTs ($n = 1737$ immunotherapy, 1642 placebo) to evaluate the effect on medication score. A significant reduction in symptom score and medication requirements was measured in the actively treated group compared with the placebo group. Severe systemic reactions such as anaphylaxis were not reported in any of these trials. Grazax® and oralair® are used for SLIT therapy in clinical practice since they were registered in Europe in 2006 and 2008, respectively.

The meta-analysis by Di Bona *et al.* (2012) has demonstrated the effect of grass pollen SCIT and SLIT on symptom score and medication score in 36 RCTs (immunotherapy $n = 3014$, placebo $n = 2768$).¹⁵ This study evaluated the standardised mean difference between SLIT, SCIT and placebo: there appears to be a significant clinical benefit for patients treated with SCIT and a mild-to-moderate benefit for patients treated with SLIT, both compared with placebo. Data on medication score have been analysed for 20 SLIT RCTs and 11 SCIT RCTs. These analyses showed a significantly better pooled mean estimation of treatment with SLIT and SCIT on the medication score compared with placebo. This study reported a total of 960 adverse events (AEs) due to the immunotherapy (0.86 AEs/patient for SCIT and 2.13 AEs/ patient for SLIT.) Paradoxically, the total number of AEs reported was higher in the SLIT group compared with SCIT group. However, these AEs varied from mild to severe and in total 12 anaphylactic reactions were reported for SCIT-treated patients and one for SLIT-treated patients. In summary, SCIT and SLIT generally achieve a reduction in symptom score and medication usage, but these treatments are not without local and systemic side effects. SCIT has been found effective and safe for birch pollen and grass pollen sensitised patients, whereas SLIT was only effective and safe for grass pollen sensitised patients.

House dust mites

Only a few meta-analyses have been performed on the effectiveness of house dust mite immunotherapy.

First, Compalati *et al.* (2009) performed a meta-analysis on the efficacy and safety of house mite dust SLIT in allergic rhinitis patients and allergic asthma patients.¹⁶ The data from eight of the 12 selected RCTs ($n = 382$ allergic rhinitis patients and $n = 476$ allergic asthma patients) in allergic rhinitis patients were included in

this meta-analysis, revealing a reduction of symptoms and medication score. Similar results have been found with allergic asthma patients, based on nine out of the 12 selected RCTs. These led the authors to conclude that there is promising evidence of efficacy of house dust mite SLIT for patients with allergic rhinitis and allergic asthma, but more high-quality studies are required to substantiate this. Another study was initiated as an evidence-based analysis of house dust mite allergen SLIT and SCIT for allergic asthma and allergic rhinitis patients.¹⁷ Nine out of 19 selected studies on SCIT ($n =$ between 22 and 132 randomised participants per study) in patients with allergic asthma were found to reveal a significant difference in mean \pm SD symptom score for symptom-related parameters. Unfortunately, the safety aspects were rather poorly described in these studies: nearly all serious side effects, which required adrenaline, were reported to occur during the rush dosing phase. Only two of the 14 selected studies ($n =$ between 15 and 465 randomised participants per study) on SLIT in allergic asthma patients demonstrated a significantly better symptom score of SLIT over placebo. Safety aspects were scarcely reported in these studies. However, a few studies have specifically mentioned that no adverse events occurred. Three out of seven studies ($n =$ between 32 and 145 randomised participants per study) on SCIT in allergic rhinitis patients reported a significantly favourable effect of SCIT versus placebo on the symptom score. The quality of safety reporting was low in most of these studies. However, anaphylactic reactions were reported in only one study. Two out of 15 studies ($n =$ between 15 and 257 randomised participants per study) on SLIT in allergic rhinitis patients showed significant benefit of SLIT versus placebo on symptom score. The conclusion was that there were too many shortcomings in primary and secondary efficiency criteria in all of the considered studies to allow a solid meta-analysis on the efficiency of house mite dust immunotherapy. However, they were able to establish statistically that SCIT shows a significantly favourable effect compared with SLIT and placebo. The safety aspects were described only moderately. No serious AEs due to the immunotherapy were reported in the actively treated group.¹⁷

Cat dander

To our knowledge, the only published study on the effectiveness of cat immunotherapy was performed by Varney *et al.*¹⁸ This is a double-blind, randomised, placebo-controlled study with 28 cat allergic patients, investigating the efficacy of immunotherapy with standardised cat dander extract. This study established that immunotherapy with standardised cat dander is an effective treatment for cat allergic patients. No serious immunotherapy-related side effects were reported in this study.

In conclusion, the efficacy and safety of pollen, house dust mite and cat dander SCIT and SLIT have been investigated in many trials, meta-analyses and reviews and are implemented in clinical practice to treat therapy-resistant patients, because of the good safety profile and effectiveness in most patients.

Prevention

There is evidence that immunotherapy can prevent the development of asthma and new sensitisations. The first prospective long-term follow-up study on this topic is the Preventive Allergy Treatment (PAT) study.¹⁹ Children with seasonal rhinoconjunctivitis ($n = 250$) were selected from three paediatric allergy centres and randomised into a group receiving grass and/or birch pollen specific immunotherapy (SIT) for three years and an open placebo group. The SIT group showed significantly fewer asthma symptoms and improved results of methacholine bronchial provocation testing after three years compared with the placebo group. The subsequent follow-up of the PAT study performed by Jacobsen *et al.* evaluated the even longer-term clinical effect and the preventive effect on developing asthma in 147 patients treated with grass and/or birch pollen SIT.²⁰ A significant improvement of rhinoconjunctivitis and conjunctival sensitivity persisted seven years after a three-year SIT treatment (ten-year follow-up.) Also significantly less patients in the SIT group developed asthma evaluated by clinical symptoms after ten years.

The retrospective study by Purello-D'Ambrosio *et al.* based on 8396 mono-sensitised patients, treated with immunotherapy or pharmacotherapy (groups are well balanced in numbers), demonstrated that 27% of the patients treated with immunotherapy were poly-sensitised after seven years and even 77% of the pharmacological group. Asthmatic patients were more prone to develop poly-sensitisation than rhinitis patients.²¹

New developments

Immunotherapy in its current form is not without side effects and patient adherence still remains a problem. Immunotherapy is cost-effective for both SCIT and SLIT compared with symptomatic therapy from around six years (threshold of £20,000-30,000 per quality-adjusted life years, QALY),²² but these costs remain significant. Furthermore, there are still problems with the efficacy. The extrinsic factors that might play a role in the effectiveness/ineffectiveness of immunotherapy are the doses of the allergen used, the allergens present in the preparation, the route of administration, the indication for which it is prescribed and therapy adherence. It is not clear which intrinsic factors in the immune mechanisms are important per patient for establishing whether the immunotherapy actually translates into clinical tolerance/improvement of

symptoms or failure of immunotherapy non-responders. The costs, ineffectiveness of immunotherapy in some patients and the safety aspects stimulate researchers to develop new immunotherapy strategies. Targets are numerous: novel route of administration, combined treatment with immune response modifiers, fusion with immune response modifiers and allergen coupled to adjuvants. Other targets are reconstruction of natural extracts with multiple recombinant allergens (allergens produced by recombinant DNA technology) or with modified allergens (altered composition of allergens) or the use of peptides of allergens as extracts (table 2).^{2,23}

Novel routes are, for example, intralymphatic or epicutaneous administration, which have both already scored in efficiency and safety in clinical trials.²⁴⁻²⁷ Pretreatment patients with anti-IgE omalizumab before immunotherapy, and an optional period during immunotherapy, caused a significant decrease of systemic allergic reactions and a decrease in the need for rescue medication to suppress symptoms.^{28,29} The fusion of allergens with immune response modifiers should ensure a more effective form of immunotherapy with fewer side effects. The fusion with human Fcγ receptors inhibits basophil and mast cell degranulation by cross-linking of Fcγ and FcεRI receptors.³⁰ The major cat allergen *Felis domesticus* 1 (Fel d 1) was fused to TAT peptide and to a part of the human variant chain, creating a transporter (MAT) vaccine (MAT-Fel d 1). MAT-Fel d 1 on intralymphatic administration has proved to be safe and effective for immunomodulation.²⁶ Allergens are also coupled to GpG oligonucleotide, virus-like particles, monophosphoryl lipid A, carbohydrate-based particles and hepatitis B PreS to cause a shift in immune reaction, to increase the efficiency or to decrease the side effects of the immunotherapy. These forms of immunotherapy show promising results in humans and mouse models.²³ The efficacy and safety of immunotherapy with a mixture of grass pollen components (allergenic proteins in allergens) to allergic patients demonstrated a strong IgG response.³¹ The idea behind immunotherapy with modified allergens is to induce T-cell tolerance and to avoid IgE-related side effects. The allergens can be administered in allergen fragments, fusions, hybrids or chimeras.³² Fel d 1-derived cat peptides have been proven safe and well tolerated by patients with a cat allergy.³³

In summary, these are approached along novel routes including improved administration, combined treatment with immune response modifiers, fusion with immune response modifiers, allergen coupled to adjuvants and reconstruction of natural extracts with multiple recombinant allergens or with modified allergens. These are promising new developments, but more research is required to implement these in clinical practice.

Table 2. *New developments in immunotherapy*

New methods	Specified	Expected value	Status efficacy and safety
Different routes of administration	Intralymphatic	Inducing faster immune tolerance Causing less side effects Lasting longer Improvement of compliance	Proven in humans ^{24,25}
	Epicutaneous	Improvement of compliance Reducing risk of allergen leaking into the circulation/ provoking systemic reactions	Proven in humans ^{23,26}
Allergens combined with immune response modifiers	Anti-IgE Omalizumab	Reducing systemic reactions Obtaining a higher percentage patients on maintenance target dose	Proven in humans ^{27,28}
Allergen fusion with immune response modifiers	Human Fcγ receptor	Inhibition of basophil and mast cell degranulation by cross-linking of Fcγ and FcεRI receptors	Proven in mouse models ²⁹
	Transactivator of transcription peptide	Targeting allergen to the MHC class II pathway	Proven in humans ²⁵
Allergens coupled with adjuvants	GpG oligonucleotide	Causing a shift in immune reaction to increase the efficiency and decrease the side effects	Promising results in humans and mouse models ²²
	Virus-like particles		
	Monophosphoryl lipid A		
	Carbohydrate-based particles		
	Hepatitis B PreS		
Reconstruction of natural extracts with multiple recombinant allergens	Mixture of grass pollen components	Increase efficacy and safety by inducing more specific immune tolerance	Proven in humans ³⁰
Reconstruction of natural extracts with modified allergens	Allergen fragments, fusions, hybrids and chimeras	Inducing T-cell tolerance and avoiding IgE related side effects by using more rational and safer allergen preparations	Promising results in humans and mouse models ³¹
Allergen peptides	Fel d 1 –derived cat peptides	Improvement of safety and reduce the duration of treatment	Proven in humans ³²

CONCLUSION

Allergen immunotherapy has been prescribed now over a long period for birch pollen, grass pollen, house dust mite and cat allergic patients. The efficacy and safety have been proven in many years of practice, despite the fact that the immunological reactions are not fully understood. This treatment has a lot of benefits for patients, such as decrease of symptoms, decrease of medication usage, long-term effect and prevention of new sensitisation or asthma. Therefore, immunotherapy should be prescribed more often as therapeutic option, in particular if you take

the high prevalence of airway allergy into consideration. However, the development of new immunotherapy methods will continue to improve the prolonged period of the treatment, the side effects and the ineffectiveness for some patients. Despite the fact that the results of the new developments are promising, more research is needed to implement these new techniques in clinical practice.

DISCLOSURES

The authors declare no conflicts of interest.

REFERENCES

- Burks AW, Calderon MA, Casale T, et al. Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/ European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. *J Allergy Clin Immunol*. 2013;131:1288-96 e3.
- Cox L, Compalati E, Kundig T, Larche M. New directions in immunotherapy. *Curr Allergy Asthma Reports*. 2013;13:178-95.
- Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clin Immunol*. 2014;133:621-31.
- 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.
- Aslam A, Chan H, Warrell DA, Misbah S, Ogg GS. Tracking antigen-specific T-cells during clinical tolerance induction in humans. *PLoS One*. 2010;5:e11028.
- Suarez-Fueyo A, Ramos T, Galan A, et al. Grass tablet sublingual immunotherapy downregulates the TH2 cytokine response followed by regulatory T-cell generation. *J Allergy Clin Immunol*. 2014;133:130-8.
- Akdis M, Burgler S, Cramer R, et al. Interleukins, from 1 to 37, and interferon-gamma: receptors, functions, and roles in diseases. *J Allergy Clin Immunol*. 2011;127:701-21.
- Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. *Annu Rev Immunol*. 2012;30:531-64.
- Cavkaytar O, Akdis CA, Akdis M. Modulation of immune responses by immunotherapy in allergic diseases. *Curr Opin Pharmacol*. 2014;17C:30-7.
- Saei A, Hadjati J. Tolerogenic dendritic cells: key regulators of peripheral tolerance in health and disease. *Int Arch Allergy Immunol*. 2013;161:293-303.
- van de Veen W, Stanic B, Yaman G, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J Allergy Clin Immunol*. 2013;131:1204-12.
- Deniz G, van de Veen W, Akdis M. Natural killer cells in patients with allergic diseases. *J Allergy Clin Immunol*. 2013;132:527-35.
- Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev*. 2007;CD001936.
- Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy*. 2011;66:740-52.
- Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis-based comparison. *J Allergy Clin Immunol*. 2012;130:1097-107.
- Compalati E, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. *Allergy*. 2009;64:1570-9.
- Calderon MA, Casale TB, Nelson HS, Demoly P. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. *J Allergy Clin Immunol*. 2013;132:1322-36.
- Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. *Clin Exp Allergy*. 1997;27:860-7.
- Moller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol*. 2002;109:251-6.
- Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy*. 2007;62:943-8.
- Purello-D'Ambrosio F, Gangemi S, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. *Clin Exp Allergy*. 2001;31:1295-302.
- Meadows A, Kaambwa B, Novielli N, et al. A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis. *Health Technol Assess*. 2013;17:1-322.
- Akdis M. New treatments for allergen immunotherapy. *World Allergy Organ J*. 2014;7:23.
- Agostinis F, Forti S, Di Berardino F. Grass transcutaneous immunotherapy in children with seasonal rhinoconjunctivitis. *Allergy*. 2010;65:410-1.
- Hylander T, Latif L, Petersson-Westin U, Cardell LO. Intralymphatic allergen-specific immunotherapy: an effective and safe alternative treatment route for pollen-induced allergic rhinitis. *J Allergy Clin Immunol*. 2013;131:412-20.
- Senti G, Cramer R, Kuster D, et al. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. *J Allergy Clin Immunol*. 2012;129:1290-6.
- Senti G, Graf N, Haug S, et al. Epicutaneous allergen administration as a novel method of allergen-specific immunotherapy. *J Allergy Clin Immunol*. 2009;124:997-1002.
- Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol*. 2010;125:383-9.
- Kopp MV, Hamelmann E, Bendiks M, et al. Transient impact of omalizumab in pollen allergic patients undergoing specific immunotherapy. *Pediatr Allergy Immunol*. 2013;24:427-33.
- Zhu D, Kepley CL, Zhang M, Zhang K, Saxon A. A novel human immunoglobulin Fc gamma Fc epsilon bifunctional fusion protein inhibits Fc epsilon RI-mediated degranulation. *Nature Med*. 2002;8:518-21.
- Jutel M, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol*. 2005;116:608-13.
- Akdis CA, Blaser K. Bypassing IgE and targeting T cells for specific immunotherapy of allergy. *Trends Immunol*. 2001;22:175-8.
- Worm M, Lee HH, Kleine-Tebbe J, et al. Development and preliminary clinical evaluation of a peptide immunotherapy vaccine for cat allergy. *J Allergy Clin Immunol*. 2011;127:89-97.