

The relationship between autoimmunity and specific immunotherapy for allergic diseases

Andrzej Bozek^{1,*}, Krzysztof Kołodziejczyk², and Piotr Bednarski³

¹Clinical Department of Internal Disease; Dermatology and Allergology; Medical University of Silesia; Zabrze, Poland; ²Allergy Outpatient Clinic; Katowice, Poland; ³Institute of Rheumatology; Warszawa, Poland

Keywords: autoimmunity, allergy, asthma, IgE, immunotherapy

Abbreviations: SIT, specific immunotherapy; SLE, systemic lupus erythematosus; TU, therapeutic units

The aim of this study was to perform a 20-year post-specific immunotherapy (SIT) observational evaluation for an assessment of any manifestations of autoimmune disease or the appearance of autoantibodies in serum. In total, 1,888 patients (902 women and 986 men) were observed. The mean age of the patients was 34.1 ± 12.4 y at the start of the prospective observation after finishing SIT. New incidences of autoimmune disease and/or the presence of autoantibodies in serum were monitored. The SIT group was compared with control groups consisting of allergic patients who had very received SIT and with non-allergic subjects. There were no significant differences in the autoimmune disease prevalence between the allergic patients with or without SIT. However, significantly higher prevalence of 4 different autoimmune diseases (AID) were observed in the non-allergic patients during the same period. Additionally, the incidence of 8 different autoantibodies was significantly higher in non-allergic patients than in control subjects. Hashimoto disease was the most common autoimmune disease observed. The results of this long-term observational study indicated a lack of a significant prevalence of new instances of autoimmune disease during 20 y of observation post-SIT and at a rate lower than that of non-allergic control subjects, suggesting that SIT is safe in this regard in the long term.

Introduction

Specific immunotherapy (SIT) involves the stimulation of immune tolerance with regard to a particular allergen. This method has become a recognized treatment for selected allergic diseases, such as allergic rhinitis and conjunctivitis, bronchial asthma or allergy to Hymenoptera venom, and, more recently, for food allergies and atopic dermatitis.¹

A major advantage of SIT is its ability to modify the natural history of allergic disease, as well as to reduce the frequency of the occurrence of multivalent allergies in an attempt to stop the so-called “allergic march” in children.^{2–3} A natural consequence of the widespread use of SIT is a continuous assessment of the short- and long-term safety of this type of therapy, with special observation of its interference with the immune system. Among the analyzed possible negative effects of SIT is the induction of autoimmune diseases. The application of SIT in patients with autoimmune disease is controversial. Pistis C et al. suggested that the coexistence of autoimmune disease is currently considered to be a relative contraindication. However, caution should be exercised when prescribing SIT to patients with autoimmune disease. Due to a lack of available data, the authors propose there is a relative contraindication in autoimmune disorders in remission and absolute contraindications in active forms.¹ A less

tolerant position for SIT and autoimmune disease was presented by Zuberbier T et al. They suggest that all serious autoimmune diseases (without specifying their nature) are contraindications for SIT.² However, Linneberg et al are inclined to the view of Pistosis et al. They consider that it seems reasonable to carefully evaluate the indication for SIT, that is, risks versus benefits, in patients with established autoimmune disease or a strong family history of autoimmune disease.³

Only a small amount of information on the effects of immunotherapy on the induction of autoimmune diseases has been published, mainly descriptions of individual cases. There was a single case description of systemic lupus erythematosus, which was activated in allergic patients during SIT. There were doubts whether the disease was not previously present prior to starting SIT. In addition, there was no immunological evidence for induction of immunological diseases by SIT.⁴ Similar individual cases of scleroderma, vasculitis and Sjögren's syndrome during SIT were described. However, there have been the same doubts about an association with autoimmune diseases as mentioned above.^{5–7}

The aim of this study was to assess the risks of such diseases over a 2 year follow-up of patients after the completion of SIT compared with patients with allergies but without SIT and with healthy subjects.

*Correspondence to: Andrzej Bozek; Email: andrzejbozek@o2.pl

Submitted: 06/25/2015; Revised: 08/10/2015; Accepted: 08/24/2015

<http://dx.doi.org/10.1080/21645515.2015.1087627>

Table 1. The incidence of new autoimmune diseases in patients after perennial or preseasonal SIT (group A or group B), in those with allergies but without SIT (group C) and in the healthy controls (group D)

Autoimmune disease	Group A N = 954	Group B N = 934	Group C N = 890	Group D N = 902	P
SLE	2	0	0	3	NS
Scleroderma	0	0	1	1	NS
Systemic vasculitis	0	0	0	1	NS
Rheumatoid arthritis	1	1	0	2	NS
Other arthritis	0	2	1	7*	0.04
Ankylosing spondylitis	0	1	0	1	NS
Psoriatic arthritis	0	0	1	2	NS
Hashimoto thyroiditis	3	2	2	11*	0.03
Graves' disease	0	0	1	2	NS
Ulcerative colitis	1	1	0	9*	0.03
Crohn disease	0	0	0	3	NS
Multiple sclerosis	0	0	1	1	NS
Psoriasis	1	0	1	8*	0.03
Vitiligo	0	1	0	2	NS
Pernicious anemia	0	0	1	1	NS
Others	1	1	0	9*	0.03
Total	9	9	9	63*	0.001

Legend: * significant differences between group D and group A, B, C in one-way analysis of variance ANOVA test, NS - not statistically significant, SLE - systemic lupus erythematosus

Results

New diagnosis of autoimmune disease

There were comparably low numbers of new incidences of autoimmune diseases in the group receiving immunotherapy and the group receiving only symptomatic treatment. The specific autoimmune diseases are significantly more prevalent in non allergic group of patients: 63 cases vs. 9 cases in every other analyzed groups ($p < 0.001$). These data are shown in **Table 1**.

Additionally, patients with allergies (group A, B, C) had a decreased risk of developing any of the analyzed autoimmune diseases, $HR = 0.76$ (95% CI: 0.62–0.88), compared with the other subjects (group D). There were no significant differences between groups A, B and C in this regard.

Autoantibody analyses

In patients after 3 y of immunotherapy, the detected autoantibodies were comparable with those of the control group without SIT but lower than those in the healthy subjects. These findings were independent of the type of immunotherapy (perennial or pre-seasonal) and from the cumulative doses of allergens administered during SIT. There were also no correlations between the types of allergies (house dust mites or pollen) and the presence of autoantibodies. Detailed data are shown in **Table 2**. The autoantibodies: dsDNA, Sm, ACA, Jo-1, RNA- polymerase, aTG, aTPO and anti-TRAB were significant more prevalent in non allergic patients vs. SIT groups.

The odds ratio for the appearance of any positive autoantibodies in patients after SIT was 0.91 (95% CI: 0.82, 0.98), and for any autoimmune disease, it was 0.92 (0.88, 1.04).

Ulcerative colitis, psoriasis, arthritis and Hashimoto disease were more prevalent in non allergic patients. In patients presenting with Hashimoto disease, the mean concentration of ATG

was 445.9 ± 119 IU/ml, and the mean concentration of ATPO was 361.7 ± 197.5 IU/ml.

Discussion

The safety and efficacy of SIT for IgE-mediated allergic diseases has been well documented.^{1,2,9,10} Although Linneberg et al reported several analyses of autoimmunity and other long-term consequences of SIT, corroboration of their findings is warranted given the evidence that the prevalence of autoimmunity is inversely associated with allergy and that the prevalence of autoimmunity varies in different regions.^{3,11} A similarity between groups A, B and C with respect to the occurrence of autoimmune diseases and autoantibodies show that in this study, the type of allergy and treatment has no effect on this phenomenon. There are no data in the literature on this issue.

The increased utilization of SIT with the introduction of sublingual immunotherapy increases the contemporary significance of the subject. The results obtained over a prolonged period indicated that SIT is safe in this regard. Moreover, all of the analyzed allergic patients, with or without SIT, had low predispositions to autoimmunity, as confirmed in other studies.^{9,11} It has been well documented that atopic patients with Th2 profiles have a lower autoimmune disease risk than those patients in which a Th1 profile is predominant.^{10,11} However, it appears that increasing IL-10 and TGF-B concentrations, as well as inducing lymphocyte tolerance and changes in the Th1/Th2 balance, could lead to autoimmune problems in patients after undergoing SIT. To assess the relationship between IgE-mediated allergies and autoimmune diseases from the perspective of a balanced profile of Th1/Th2 seems overly simplistic.^{12,13} According to some studies, the key cells that participate in both types of bonding are mast cells [13], the roles of which in allergic diseases are unequivocal; however, it was found that they were also important in autoimmune diseases, such as multiple

Table 2. The detected autoantibodies in the sera of patients (regardless of a diagnosis of autoimmune disease) after perennial or pre-seasonal SIT (group A or group B), in patients with allergies but without SIT (group C) and in the healthy controls (group D)

Type of antibodies	Number of positive results				NS
	Group A N = 954	Group B N = 934	Group C N = 890	Group D N = 902	P
dsDNA	5	5	4	16*	0.03
U1-nRNP	0	1	0	1	NS
RO	2	3	1	5	NS
Sm	2	2	4	7*	0.03
Scl 70	0	1	1	3	NS
ACA	1	4	4	19*	0.001
Jo-1	3	2	2	11*	0.04
U3-nRNP	0	0	1	1	NS
RNA-polymerase	1	1	3	23*	0.03
PM-Scl	0	1	0	1	NS
PCNA	0	0	1	1	NS
Ku	1	2	1	3	NS
Mi-1	0	0	0	1	NS
Mi-2	1	0	1	1	NS
Ribosomal-P	4	2	3	4	NS
AMA-M2	0	0	1	0	NS
pANCA	0	0	0	7	NS
cANCA	0	1	0	3	NS
aTG	7	6	9	48*	0.006
aTPO	9	11	4	54*	0.008
Anti-TRAB	6	6	7	21*	0.01

Legend: * significant differences between group D and group A, B, C in one-way analysis of variance ANOVA test, NS - not statistically significant

sclerosis, rheumatoid arthritis, Sjögren's syndrome, autoimmune thyroiditis and scleroderma. It was found that mast cells could be activated not only by allergens but also by contact with other active cells involved in the immune response, such as T cells and other low-molecular-weight substances. Activated mast cells in turn are a source of TNF- α , which is an important pro-inflammatory factor in several autoimmune diseases.¹³ The importance of Th17 cells that are involved in chronic inflammation, such as IL-17, which is present in both asthma and systemic diseases, including multiple sclerosis, systemic lupus erythematosus and others, has been discussed recently.^{14,15} Data indicating that SIT might trigger the development of some autoimmune diseases, such as scleroderma, systemic vasculitis, multiple sclerosis and others, have been based on only a few reports.^{4,7-11} In addition, these diseases are relative contraindications for SIT in many international guidelines; however, there are no recommendations to preclude active patients with these diseases before SIT if they do not have any clinical disease symptoms. As a result, the studied patients had not undergone antibody assays prior to treatment, which undoubtedly limited the observations because the authors could not evaluate the dynamics of the changes in the tested antibodies during treatment. It is also possible that some of the patients had autoimmune diseases before SIT but did not present with any clinical symptoms at that time. This possibility limited the precision of new diagnoses of autoimmune disease after SIT in the analyzed patients.

It is an important result that, regardless of the application of SIT, all allergic patients have a decreased risk of autoimmune disease. This finding is consistent with the literature.¹⁶ Lindelof et al performed a large epidemiological study with the following 2 groups: 68, 770 subjects were tested for total serum IgE, and 72,

228 were tested with Phadiatop for diagnosing allergic disease. Then, all of the subjects were linked with an inpatient registry for a follow-up with regard to the recorded discharges for 28 autoimmune diseases. Subjects with a positive Phadiatop test were at a statistically decreased risk of subsequent autoimmune disease in comparison with subjects with a negative test. However, there was no similar correlation between the total serum IgE and the risk of autoimmune diseases.

The limitations in the study were relatively short time of observation and the lack of opportunities for precise assessment of other rare antibodies. Evaluation of family history of autoimmune diseases and their impact on all of the patients could be of interest.

Our results indicated that allergic patients with or without SIT showed strong correlations between rare occurrences of autoantibodies and autoimmune diseases, independent of the type of allergy. However, further studies with double blind and placebo control regimen are required to precise evaluation the potentially risk of allergen, specific immunotherapy inducing autoimmune diseases. It is important to sufficiently long time for such observation.

In conclusion, in this prolonged observational study, SIT did not increase the prevalence of autoimmune disease or result in a significant presence of autoantibodies in serum.

Materials and Methods

Patients

A total of 2021 patients were pre-qualified for the study. The inclusion criteria included the following: allergies to house dust mites, fungi or pollen, with allergic rhinitis and/or asthma and

Table 3. The characteristics of the analyzed patients at the beginning of the observational period

Characteristics	Group A	Group B	Group C	Group D	P
number	954	934	890	902	NS
mean age at the start of the observation	32.4 ± 10.1	35.2 ± 7.6	32.7 ± 6.3	34.1 ± 5.0	NS
female (%)	473 (49.6)	429 (45.9)	421 (47.3)	445(49.3)	NS
allergic rhinitis (%)	822 (86.2)	837 (89.6)	786 (88.3)	-	NS
allergic rhinitis and asthma (%)	132 (13.8)	97(10.4)	104 (11.7)	-	NS
duration of disease (mean ± SD) at the start of SIT or symptomatic treatment	5.2 ± 3.6	4.2 ± 2.7	5.2 ± 3.6	-	NS
mean duration of SIT (± SD) in years	3.8 ± 0.4	3.6 ± 0.3	-	-	NS
mean cumulative dose of SIT (TU ± SD)	25931 ± 22340	12100 ± 9355	-	-	0.001

Legend: SIT - specific immunotherapy, SD - standard deviation, NS - not significant, TU - therapeutic units, * - the cumulative doses are not comparable due to different types of SIT (naturated HDM mixture and chemically modified allergen)

with the completion of at least a 3-year course of SIT to these allergens. The patients did not have a clinically active autoimmune or neoplastic disease or multi-organ failure at the start of SIT. One hundred three patients were excluded over the 20 y of prospective observation (dropouts, stopping of SIT due to the appearance of other contraindications). Finally, 1888 patients (902 women and 986 men) were analyzed in the study. The mean age of the patients in the group was 34.1 ± 12.4 y at the start of the prospective observation after finishing SIT. The mean age was 43.4 ± 10.2 y at the end of the study.

The patients were divided into the following subgroups:

1. after perennial immunotherapy: for patients with allergic rhinitis and/or bronchial asthma who received a minimum of a 3-year course of perennial immunotherapy to treat allergies to house dust mites using the Novo-Helisen Depot (composition: 708 *D. farinae* - 50%, 725 - *D. pteronyssinus* 50%; Allergopharma, Reinbek, Germany) and to pollen allergies using Allergovit (composition: 015 grass/cereals - 100% or composition: 108 Birch - 35%, 115 Alder - 30%, 129 Hazel - 35%, Allergopharma, Reinbek, Germany)
2. pre-seasonal immunotherapy: for patients with allergic rhinitis and/or bronchial asthma who received a minimum 3-year course of pre-seasonal immunotherapy to treat pollen allergies using Allergovit (composition: 015 grass/cereals - 100%; or composition: 108 Birch - 35%, 115 Alder - 30%, 129 Hazel - 35%, Allergopharma, Reinbek, Germany).
3. control group patients with allergies to house dust mites or to pollen with allergic rhinitis and/or bronchial asthma who received only symptomatic treatment and not SIT. The inclusion criteria for this group were a duration of allergy to house dust mites or pollen allergy comparable to that of the study group at the start of prospective observation and only 3–5 y of symptomatic therapy without SIT when immunotherapy was provided in the study group.
4. group patients without allergies. This control group consisted of healthy non-allergic subjects who were observed over the same period.

More detailed data are shown in Table 3.

Protocol

All of the patients were subjected to the following procedures:

1. analysis of diagnostic procedures (history of allergy, skin prick test and specific IgE) and assessment of the cumulative dose of Allergovit or Novo-Helisen Depot over the entire administration of SIT performed between 1985 and 1994.
2. The mean time of prospective observation after SIT was 20.2 ± 3.5 years, and the following procedures were performed between 2005 and 2014:
3. Monitoring of medical history of autoimmune and neoplastic diseases. We assessed the subjects for the following list of autoimmune diseases, according to the ICD-10 (International Classification of Disease, the 10th revision).⁸
4. of the patients underwent clinical examinations in addition to routine laboratory diagnostic tests, including antinuclear antibodies.

A. An automatic evaluation of test strips was performed using the EUROLinScan software (EUROIMMUNE, Medizinische Labordiagnostika, Germany). A positive result was indicated by the presence in serum of + to ++++. The following antibodies were evaluated via ELISA: dsDNA, histonic, U1-nRNP, Ro(SS-A/La (SS-B)), Sm, Scl⁻70, ACA, Jo-1, U3-nRNP, RNA-polymerase I, PM-Scl (PM-1), PCNA, Ku, Mi-1, Mi-2, Ribosomal-P-protein and AMA-M2.

B. In addition, some antibodies, including pANCA (normal range < 25.00 IU/ml), cANCA (normal range < 20.0 IU/ml), anti-thyroglobulin (aTG; normal range < 15.0 IU/ml), anti-peroxidase (aTPO; normal range < 34 IU/ml), and anti-TRAb (normal range < 1.8 IU/ml), were measured via electroluminescence (Roche, Katowice, Poland).

All of the visits, including routine laboratory tests as above, were conducted every 2 y over the entire observation period in the outpatient allergy clinic. All positive results for the presence of autoantibodies were recorded.

The study was approved by the Bioethical Committee of the District Medical Board of Silesia in Katowice, Poland (NN-3111/92).

Statistical analysis

The data that met the criteria for a normal distribution, such as age and disease duration, were analyzed using Student's t-test for independent variables. One-way analysis of variance (ANOVA) was used to compare the presence of autoimmune diseases or the type of autoantibodies among the groups. The odds ratio (OR) with a 95% confidence interval was used to assess the prevalence of autoimmune

diseases in the analyzed subjects. A hazard ratio (HR) was used to estimate the risk of autoimmune disease in the population. The Statistica computer program, version 8.1, was used (SoftPol, Cracow, Poland).

Disclosure of Potential Conflicts of Interest

There are no conflicts of interest.

References

1. Pistosis C, Demoly P, Bilo MB, Gerth van Wijk R, Pfaar O, Sturm GJ, Rodriguez Del Rio P, Tsoumani M, Gawlik R, Paraskevopoulos G, Rueff F, Valovirta E, Papadopoulos NG, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy* 2015; 70:897-909; PMID:25913519; <http://dx.doi.org/10.1111/all.12638>
2. Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Walter Canonica G, Merk H, Worm M, Wahn U, Bousquet J. GA²; LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy* 2010; 65(12):1525-30; PMID:21039596; <http://dx.doi.org/10.1111/j.1398-9995.2010.02474.x>
3. Linneberg A, Madsen F, Skaaby T. Allergen-specific immunotherapy and risk of autoimmune disease. *Curr Opin Allergy Clin Immunol* 2012; 12:635-9; PMID:22914311; <http://dx.doi.org/10.1097/ACI.0b013e3283588c8d>
4. Sequiera JF, Csic D, Keser G, Bukelica M, Karanagnostis S, Khamashta MA, Hughes GR. Allergic disorders in systemic lupus erythematosus. *Lupus* 1993; 2:187-99; PMID:8369810; <http://dx.doi.org/10.1177/096120339300200311>
5. Taylor RJ. Hypersensitivity vasculitis occurring in a patient receiving immunotherapy. *J Allergy Clin Immunol* 1991; 87:889-90; PMID:1826508; [http://dx.doi.org/10.1016/0091-6749\(91\)90139-F](http://dx.doi.org/10.1016/0091-6749(91)90139-F)
6. Maciel BM, Morfin BM. Specific immunotherapy-related scleroderma. *Case Report Rev Alerg Mex* 2009; 56:135-44
7. Turkcapar N, Kinikli G, Sak SD, Duman M. Specific immunotherapy-induced Sjogren's syndrome. *Rheumatol Int* 2005; 26:182-4; PMID:15965636; <http://dx.doi.org/10.1007/s00296-005-0606-x>
8. International Classification of Disease, the 10th revision. 2010. Available at <http://apps.who.int/classifications/icd10/browse/2010/en> (available 12.01.2010).
9. Bozek A, Kozłowska R, Jarzab J. The safety of specific immunotherapy for patients allergic to house-dust mites and pollen in relation to the development of neoplasia and autoimmune disease: a long-term, observational case-control study. *Int Arch Allergy Immunol* 2014; 163:307-12; PMID:24776522; <http://dx.doi.org/10.1159/000361022>
10. Calderon MA, Casale TB, Togias A, Bousquet J, Durham SR, Demoly P. Allergen-specific immunotherapy for respiratory allergies: from meta-analysis to registration and beyond. *J Allergy Clin Immunol* 2011; 127:30-8; PMID:20965551; <http://dx.doi.org/10.1016/j.jaci.2010.08.024>
11. Linnberg A, Jacobsen RK, Jespersen L, Abildstrom SZ. Association of subcutaneous allergen-specific immunotherapy with incidence of autoimmune disease, ischaemic heart disease, and morality. *J Allergy Clin Immunol* 2012; 129:413-9; PMID:22004944; <http://dx.doi.org/10.1016/j.jaci.2011.09.007>
12. Gołab J, Jakóbsiak M, Lasek W, Stokłosa T. *Immunologia*. Gołab J (Ed.), Warszawa: PWN, 2008.
13. Bachelet I, Levi-Schaffer F, Mekori YA. Mast cells: not only in allergy. *Immunol Allergol North Am* 2006; 26(3):407-25; PMID:NOT_FOUND; <http://dx.doi.org/10.1016/j.iac.2006.05.007>
14. Robinson DS. The role of the T-cell in asthma. *J Allergy Clin Immunol* 2010; 126(6):1081-91; PMID:20709383; <http://dx.doi.org/10.1016/j.jaci.2010.06.025>
15. Robinson KM, Manni ML, Biswas PS, Alcorn JF. Clinical consequences of targeting IL-17 and T_H17 in autoimmune and allergic disorders. *Curr Allergy Asthma Rep* 2013; 13(6):587-95; PMID:23760974; <http://dx.doi.org/10.1007/s11882-013-0361-0>
16. Lindelof B, Granath F, Tengvall-Linder M, Ekblom A. Allergy and autoimmune disease: a registry-based study. *Clin Exp Allergy* 2009; 39:110-5; PMID:19068101; <http://dx.doi.org/10.1111/j.1365-2222.2008.03115.x>