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Specific allergen immunotherapy – comparison between allergoids and allergen vaccines. A real-life study

Swoista immunoterapia alergenowa – porównanie szczepionek alergoidowych i alergenowych. Badanie typu *real-life*

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ABSTRACT

Introduction: Specific allergen immunotherapy (SIT) is a disease-modifying approach in allergic rhinitis treatment.

Aim: The aim of this study was to compare the efficacy and tolerance of the allergoids and allergen vaccines and pre-seasonal and perennial scheme of treatments. Secondly, we wanted to compare the influence of adverse events on the compliance and the patient's willingness to continue the therapy. Also we wanted to assess the relationship between the compliance, and the efficacy and tolerance of the treatment.

Material and methods: A retrospective observational study based on the original self-developed questionnaire was administered to 53 physicians, who use specific allergen immunotherapy in their daily practice. For this study a randomly selected group of patients, who had been treated with immunotherapy within the last 5 years, were selected.

Results: This study showed high effectiveness and tolerance of SIT in the first year, which increased up to the 3rd year after its administration, regardless of the approach used (allergoid/allergen extract), therapy scheme (perennial/pre-seasonal) and status (finished/unfinished), sex or the willingness to continue the therapy. Furthermore, sufficient patient-physician cooperation significantly ($p = 0.003$) increased SIT efficacy. There was a weak relationship ($r = 0.339$, $p < 0.05$) between the willingness to continue the therapy and the level of patient-physician cooperation. Finally, there was a strong relationship between SIT efficacy and tolerance after the 1st ($r = 0.591$, $p < 0.05$), 2nd ($r = 0.675$, $p < 0.05$) and 3rd ($r = 0.797$, $p < 0.05$) year after its first administration.

Conclusions: Specific immunotherapy is a highly effective and safe method that allows for a significant reduction of allergy symptoms and reduction/discontinuation of symptomatic treatment. The better the cooperation between the physician and the patient from the first year of its administration, the higher the effectiveness of immunotherapy and the greater the willingness to continue immunotherapy.

KEY WORDS

allergy, specific immunotherapy, allergoid, allergen extract.

STRESZCZENIE

Wprowadzenie: Swoista immunoterapia (SIT) alergenowa jest metodą modyfikującą przebieg choroby w leczeniu alergicznego nieżytu nosa.

Cel: Celem pracy było porównanie skuteczności i tolerancji alergoidów i szczepionek alergenowych oraz przedsezonowego i całorocznego schematu leczenia. Ponadto porównano wpływ zdarzeń niepożądanych na przestrzeganie zaleceń i chęć kontynuowania terapii przez pacjenta. Dokonano także oceny związku pomiędzy przestrzeganiem zaleceń a skutecznością i tolerancją immunoterapii.

Materiał i metody: W retrospektywnym badaniu obserwacyjnym przeprowadzonym z użyciem ankiety wzięło udział 53 lekarzy stosujących w codziennej praktyce swoistą immunoterapię alergenową. Do badania wybrano losową grupę pacjentów, którzy w ostatnich 5 latach byli leczeni immunoterapią.

Wyniki: Analiza danych wykazała wysoką skuteczność i tolerancję SIT w pierwszym roku, która wzrastała aż do trzeciego roku po jego zastosowaniu, niezależnie od zastosowanego podejścia (alergoid/ekstrakt alergenu), schematu terapii (całoroczna/przedsezonowa) i jej statusu (zakończona/niezakończona), płci oraz chęci kontynuowania terapii. Dobra współpraca pacjenta z lekarzem znacząco ($p = 0{,}003$) zwiększyła skuteczność immunoterapii. Stwierdzono również słaby związek ($r = 0{,}339$, $p < 0{,}05$) pomiędzy chęcią kontynuowania terapii a poziomem współpracy pacjent–lekarz. Ponadto występował silny związek między skutecznością immunoterapii a jej tolerancją po pierwszym ($r = 0{,}591$, $p < 0{,}05$), drugim ($r = 0{,}675$, $p < 0{,}05$) oraz trzecim ($r = 0{,}797$, $p < 0{,}05$) roku od pierwszego podania immunoterapii.

Wnioski: Immunoterapia swoista jest wysoce skuteczną oraz bezpieczną metodą umożliwiającą znaczną redukcję objawów alergii oraz zmniejszenia lub zaprzestania stosowania leczenia objawowego. Im lepsza jest współpraca pomiędzy lekarzem a pacjentem od pierwszego roku od jej podania, tym wyższa okazuje się skuteczność immunoterapii oraz większa chęć do kontynuacji immunoterapii.

SŁOWA KLUCZOWE

alergia, immunoterapia swoista, alergoid, ekstrakt alergenowy.

ADDRESS FOR CORRESPONDENCE

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INTRODUCTION

Allergic diseases are one of the most common chronic diseases and constitute a significant civilization problem. The World Allergy Organization (WAO) data show that the prevalence of allergies worldwide is 10–40% [1, 2]. In Europe, it is estimated that allergies affect over 150 million inhabitants, and after 2025 this number may exceed half of the European population [3]. Furthermore, the largest epidemiological study conducted in Poland in recent years – the ECAP study (Epidemiology of Allergic Diseases in Poland) showed that the incidence of atopy is 40%. The percentage of the population with atopy is higher in cities than in rural areas [4]. Allergic diseases have a huge impact on the entire population, not only by directly affecting the quality of life, but also indirectly through relatively large medical expenses, costs related to absence from work or school, or hospitalization costs. Insufficient allergy therapy generates annual indirect costs between 55 and 151 billion euros (approximately 2,405 euros for each patient/year) [5]. If an allergic disease is properly diagnosed in childhood and immunotherapy is used, we can reduce the risk of bronchial asthma and new allergies in the future [6].

Specific immunotherapy (SIT) involves the administration of gradually increasing doses of the allergen extract until immunological tolerance occurs [7, 8]. In the first stage of specific allergen immunotherapy (so-called build-up phase or induction phase), the patient is administered increasing doses of the allergen, starting with small doses administered 1–3 times a week. The allergen dose is gradually increased over a period of 3–6 months until immunological tolerance is achieved (maintenance dose is established). In the second phase of SIT (so-called

maintenance phase), the patient is given a maintenance dose every 4–6 weeks for a period of 3–5 years [9]. Many routes (subcutaneous (SCIT), sublingual (SLIT), epicutaneous (EPIT), local nasal (LNIT), intralymphatic (ILIT), oral (OIT) and intradermal (IDIT)) and approaches to SIT are utilized including allergoids and allergen vaccines [10, 11].

Specific allergen immunotherapy is so far the only disease-modifying approach in allergic rhinitis treatment. Clinical trial data indicated that the use of SIT results in a significant reduction of symptoms and no need to take symptomatic medications, compared to patients who had the same diagnosis and did not receive immunotherapy but only symptomatic treatment [12]. In the case of treatment of IgE-dependent allergy, which according to recommendations lasts 3–5 years, the final success depends on the patient's cooperation with the doctor and the willingness to continue the therapy for a long time (up to 10 injections per year) [13, 14]. So far many clinical trials have been published in this area but not many real-life studies have addressed the issue of tolerance and efficacy comparison between the perennial and pre-seasonal immunotherapy. Similarly not much data is available regarding the tolerance and efficacy comparison between the allergoids and allergen vaccines [15–17].

AIM

The aim of this study was to compare the efficacy and tolerance of the allergoids and allergen vaccines. The second aim of the study was to compare the pre-seasonal and perennial route of treatments in terms of efficacy and tolerance. We also wanted to compare the influence of adverse events on the compliance and the patient's willingness to continue the therapy. Also we wanted to assess the relationship between the compliance, and the efficacy and tolerance of the treatment. All these assessments were done in a real-life physician practices in Poland.

MATERIAL AND METHODS

STUDY DESIGN

This retrospective observational study based on the original self-developed questionnaire was administered to 53 physicians, who use specific allergen immunotherapy in their daily practice. We wanted to assess the effects of immunotherapy in real-life conditions in a typical allergy practice in Poland. The acceptance of the study protocol by the local ethical committee was not required (in accordance with Art. 2(c) of Directive 2001/20/EC of the European Parliament and the Council).

PATIENTS

For this study we qualified a randomly selected group of patients, selected by physicians who use SIT in their daily practice. Moreover, for this retrospective observational trial patients who had been treated with immunotherapy within the last 5 years were selected. The method of immunotherapy (subcutaneous or sublingual) as well as the product (brand, type) has not been determined. Therefore, the treatment was also allocated according to the random doctor's decision.

COLLECTED DATA

The questionnaires were completed by physicians based on the medical history of selected patients. The self-developed questionnaire included data on the physician (i.e. age, sex, specialization), patient characteristics (i.e. age, sex, disease), SIT product used (commercial name) and therapy scheme (i.e. perennial or pre-seasonal, allergen class, average number of injections administered per year, therapy status), possible resignation and reason for resignation.

Visual-analogue scale (VAS) was utilized as a measurement of the efficacy and tolerance (where 1 means excellent efficacy, whereas 10 was considered as completely ineffective) after 1, 2 and 3 years from the date of first SIT administration.

STATISTICAL ANALYSIS

The ANOVA test was utilized to compare SIT efficacy and tolerance for different SIT types, therapy schemes, therapy status and continuation, physician cooperation with patients and their sex. Spearman's correlation method was used to determine the relationship between efficacy and tolerance of SIT after 1, 2, and 3 years from the date of first administration and relationship between therapy continuation and cooperation with the patient. Results are expressed as mean ± SEM. The data with $p < 0.05$ were considered statistically significant. Statistical analysis was performed using Statistica 8.0 (StatSoft, Tulsa, OK).

RESULTS

CHARACTERISTICS OF THE PATIENTS

The questionnaire was administered to 63 physicians, who completed it based on the medical history of 688 patients, including 378 (54.9%) men and 310 (45.1%) women. Majority of patients (51.9%) were 31–60 years old, and the remaining patients were 0–30 years old (45.9%). The most common indicator for immunotherapy was rhinitis (in

TABLE 1. Patients' characteristic

Parameter	*N* (%)
Sex:	
Men	378 (54.9)
Women	310 (45.1)
Age:	
0–30 years	316 (45.9)
31–60 years	357 (51.9)
61–90 years	11 (1.6)
No data	4 (0.6)
Immunotherapy indicators:	
Rhinitis	607 (88.2)
Conjunctivitis	290 (42.2)
Asthma	240 (34.9)
Other	35 (5.1)
Allergens:	
Plant pollen	413 (60)
House dust mites	209 (30.4)
Alternaria fungi	6 (9.6)
Immunotherapy approach:	
Allergen extract from company A	217 (31.5)
Allergoid from company A	383 (55.7)
Allergoid from company B	56 (8.1)
Allergen extract from company C	24 (3.5)
Allergen extract from company D	1 (1.2)

607 (88.2%) patients). In more than one third of patients, the indication for immunotherapy was also conjunctivitis (in 290 (42.2%) patients) and asthma (in 240 (34.9%) patients). Immunotherapy was administered to patients with allergies to: grass pollen (in 413 (60%) patients), house dust mites (in 209 (30.4%) patients) and *Alternaria* fungi (in 6 (9.6%) patients). (shown in Table 1).

383 (55.7%) patients were treated with an allergoid vaccine from company A, 217 (31.5%) with an allergen extract from company A, 56 (8.1%) with an allergoid from company B, and 24 (3.5%) with an allergen extract from company C, and 1 (1.2%) with an allergen extract from company D. Perennial immunotherapy was administered to 584 (84.9%) patients (including 316 (54.1%) patients treated with an allergoid vaccine from company A, 215 (36.8%) patients treated with an allergen extract from company A, 31 (5.3%) patients treated with an allergoid vaccine from company B and 21 (3.6%) patients treated with an allergen extract from company C and 1 (0.2%) patient treated with an allergen extract from company D), pre-seasonal in 45 (15.1%) patients (including 40 (88.9%) patients treated with an allergoid vaccine from company A and 5 (11.1%) patients treated with an allergoid vaccine from company B). The majority of patients underwent SIT with preparations from company A (in 600/668 (89.8%) cases), therefore they were included in further analysis (shown in Table 1).

COMPARISON OF SIT EFFICACY AND TOLERANCE OF THE APPROACH AND THERAPY SCHEME

A continuous improvement in efficacy was observed from the first year through the third year of the treatment. The VAS score dropped from 3.15 ±0.13 to 2.47 ±0.1 and to 1.85 ±0.1 for the 1st, 2nd and 3rd year of observation, respectively, for the allergen extract and similarly from 3.3 ±0.1 to 2.38 ±0.1 and to 1.83 ±0.1 for allergoid treatment. The were no significant differences in efficacy of the allergoid and allergen extracts ($p = 0.707$). Furthermore, the efficacy of SIT was increasing with every year of its administration, both for perennial (3.14 ±0.08 for the 1st, 2.4 ±0.1 for the 2nd, 1.9 ±0.1 for the 3rd year of observation) and pre-seasonal (2.95 ±0.34 for the 1st, 2.4 ±0.3 for the 2nd, 1.2 ±0.1 for the 3rd year of observation) therapy scheme. Moreover, there were no significant differences in efficacy between the therapy schemes ($p = 0.827$) (shown in Figures 1 A, B).

There was an increase in tolerance of SIT, starting from the 1st year after its administration, both for the allergen extract and allergoid (VAS score for the allergen extract: 2.38 ±0.09 for the 1st, 1.9 ±0.1 for the 2nd, and 1.6 ±0.1 for the 3rd year of observation; VAS score for the allergoid: 2.35 ±0.008 for the 1st, 1.88 ±0.1 for the 2nd, and 1.61 ±0.1 for the 3rd year of observation). There were no significant differences in tolerance of the allergoid and allergen extracts ($p = 0.918$). Similar to efficacy, there was an increase in the tolerance of perennial and pre-seasonal SIT. The VAS score dropped from 2.4 ±0.006 for the 1st, 1.9 ±0.1 for the 2nd, and 1.6 ±0.1 for the 3rd year for perennial, and from 2.08 ±0.26 for the 1st, 1.8 ±0.3 for the 2nd, and 1.1 ±0.1 for the 3rd year for the pre-seasonal therapy regime. Such differences in SIT tolerance were not statistically significant ($p = 0.674$) (shown in Figures 1 C, D).

COMPARISON OF SIT EFFICACY AND TOLERANCE OF THE THERAPY STATUS AND WILLINGNESS TO CONTINUE THE THERAPY

In only 41.5% of therapies with SCIT from company A (in 249/600 cases, of which 157 (63.1%) used the allergoid vaccine and 92 (36.9%) used the allergen extract) have finished status, 42% have unfinished status

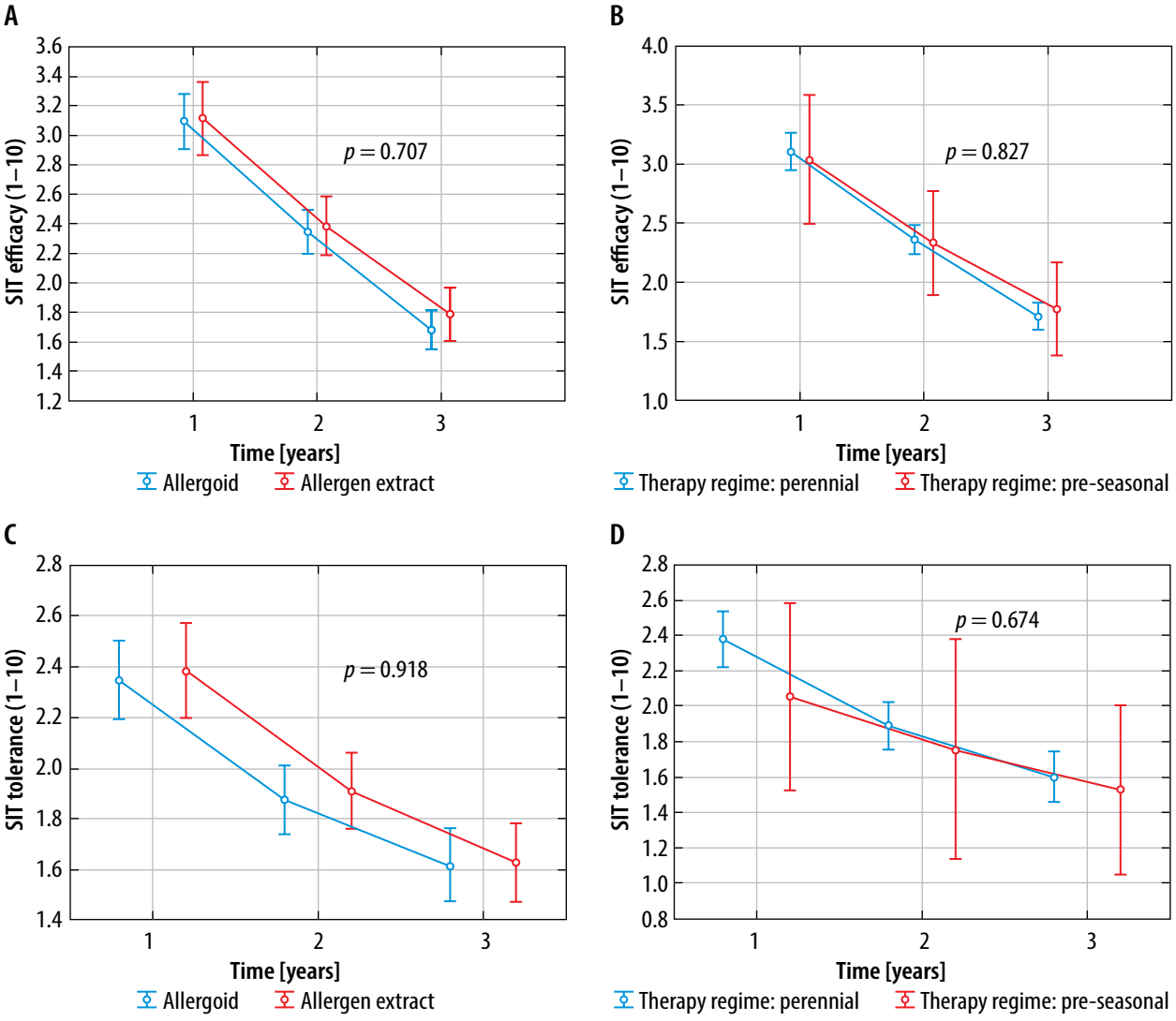

FIGURE 1. Comparison of SCIT efficacy (**A**, **B**) and tolerance (**C**, **D**) after 1, 2, 3 years from the first date of administration for different (**A**, **C**) immunotherapy approaches and (**B**, **D**) therapy regimes. Efficacy and tolerance after the 1st, 2nd and 3rd year after SIT administration were measured by visual-analogue scale (VAS) and then analyzed by ANOVA. VAS score 1 was considered as excellent efficacy, whereas 10 means completely ineffective. Results are expressed as mean ± SEM. Data with $p < 0.05$ were considered statistically significant

(in 252/600 cases, of which 166 (65.9%) used the allergoid vaccine and 86 (34.1%) used the allergen extract) and 16.5% (in 99/600 cases, of which 60 (60.6%) used the allergoid vaccine and 39 (39.4%) used the allergen extract) have unknown status. The number of patients who decided to continue the therapy with SCIT from company A (allergen extract/allergoid) for more than 3 years was 58% (in 348/600 cases, of which 217 (62.4%) used the allergoid vaccine and 131 (37.6%) used the allergen extract). 42% of patients withdrew from injectable immunotherapy before the age of 3 years (in 252/600 cases, of which 166 (65.9%) used the allergoid vaccine and 86 (34.1%) used the allergen extract).

SIT shows effectiveness after just one year of treatment. For patients with finished status of immunotherapy, VAS score for efficacy declined from 3.11 ±0.11 in the 1st, 2.5 ±0.1 in the 2nd to 1.9 ±0.1 in the 3rd year of immunotherapy. For patients with unfinished status of immunotherapy, efficacy VAS score dropped from 3.36 ±0.13 in the 1st, 2.5 ±0.1 in the 2nd, to 1.9 ±0.1 in the 3rd yead after first administration. Even in patients who did not complete the three-year treatment process, improvement was visible ($p = 0.489$). Furthermore, the efficacy of SIT was increasing starting from the 1st year, regardless of willingness to continue the therapy (VAS score dropped from 3.17 ±0.009 for the 1st, 2.4 ±0.1 for the 2nd, and 1.9 ±0.1 for the 3rd year after its administration, respectively in patients who would like to continue the therapy and from 3.53 ±0.19 for the 1st, 2.8 ±0.2 for the 2nd and 2.3 ±0.2 for the 3rd year after its administration in patients

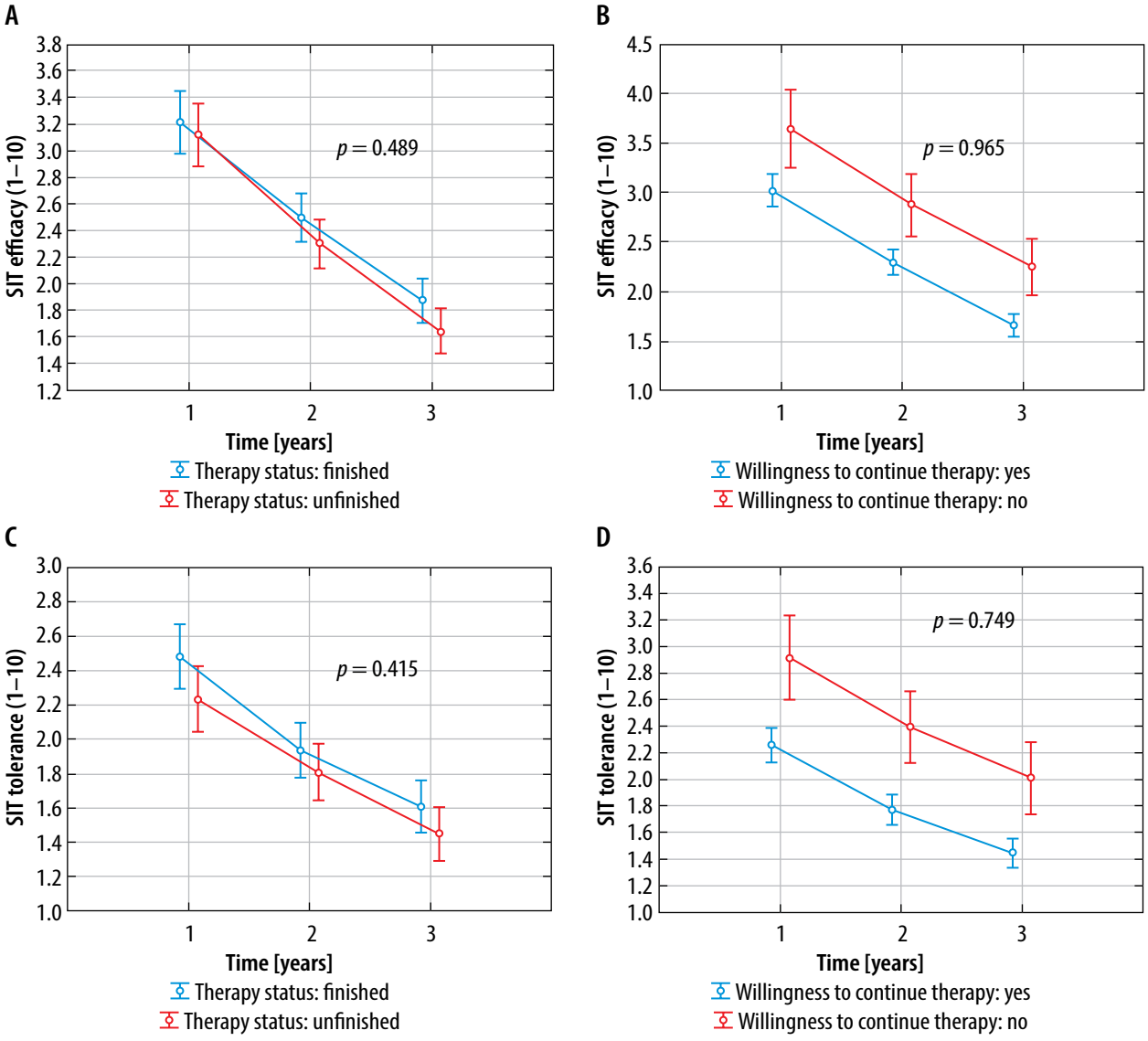

FIGURE 2. Comparison of SIT efficacy (**A**, **B**) and tolerance (**C**, **D**) after 1, 2, 3 years from the first date of administration for different therapy status (**A**, **C**) and willingness to continue the therapy (**B**, **D**). Efficacy and tolerance after the 1st, 2nd and 3rd year after SIT administration were measured by visual-analogue scale (VAS) and then analyzed by ANOVA. VAS score 1 was considered as excellent efficacy, whereas 10 means completely ineffective. Results are expressed as mean ± SEM. Data with $p < 0.05$ were considered statistically significant

who would not like to continue the therapy). There were no significant differences in VAS change over 3 years between patients willing and unwilling to continue SIT ($p = 0.965$) (shown in Figures 2 A, B).

Tolerance of specific allergen immunotherapy was high starting from the 1st year (2.4 ±0.09 and 2.5 ±0.09 for finished and unfinished therapy; 2.4 ±0.07 and 2.9 ±0.19 for willingness/lack of willingness to continue the therapy), and further increased at the 2nd (1.9 ±0.1 and 2.0 ±0.1 for finished and unfinished therapy; 1.9 ±0.1 and 2.4 ±0.2 for willingness/lack of willingness to continue the therapy) and the 3rd year (1.6 ±0.1 and 1.7 ±0.1 for finished and unfinished therapy; 1.7 ±0.1 and 2.1 ±0.2 for willingness/lack of willingness to continue the therapy) of its administration. There were no significant differences in the tolerance of SIT with respect to the therapy status (finished/unfinished; $p = 0.415$) or willingness to continue the treatment (willingness/not willing to continue the treatment; $p = 0.749$) (shown in Figures 2 C, D).

COMPARISON OF SIT EFFICACY AND TOLERANCE OF PATIENT-PHYSICIAN COOPERATION STATUS AND PATIENT SEX

SCIT from company A was administered to 56.5% of men (in 339/600 cases, of which 124 (36.6%) took the allergen extract and 215 (63.4%) took the allergoid) and 43.5% of women (in 261/600 cases, of which 93 (35.6%) took the

allergen extract and 168 (64.4%) took the allergoid). In 96% of therapies with SCIT products from company A (in 576/600 cases, of which 211 (36.6%) used the allergen extract and 365 (63.4%) used the allergoid vaccine) there was sufficient compliance. Only 4% of SCIT with products from company A (in 24/600 cases, of which 18 (75%) used the allergoid vaccine and 6 (25%) used the allergen extract) showed insufficient compliance. The main reasons for insufficient compliance included side effects/poor tolerance (in 4/24 (16.7%) patients), change of the patient's place of residence (in 5/24 (20.8%) patients), according to the patient, too time-consuming therapy (in 7/24 (29.2%) patients), feeling of insufficient effectiveness of treatment (in 2/24 (8.3%) patients), the patient is not aware of the stage of the disease/need for therapy (in 2/24 (8.3%) patients), the appearance of contraindications (in 4/24 (16.7%) patients), the symptoms disappeared during the therapy (in 2/24 (8.3%) patients), the patient did not appear at the next visit without giving a reason (in 11/24 (54.8%) patients).

With the continuation of therapy from the 1st year, through the 2nd year and the 3rd year, an increase in the effectiveness of SIT was observed both in patients with different cooperation with the physician during the therapy (VAS score changed from 3.16 ±0.07 and 4.52 ±0.4 in the 1st, 2.4 ±0.1 and 3.9 ±0.4 in the 2nd and 1.9 ±0.1 and 2.8 ±0.4 in the 3rd year after first administration, respectively for sufficient/insufficient compliance) and in both sexes (VAS score changed from 3.09 ±0.1 and 3.26 ±0.12 in the 1st, 2.4 ±0.1 and 2.5 ±0.1 in the 2nd, and 1.8 ±0.1 and 1.8 ±0.1 in the 3rd year after first administration, respectively for men and women). However, only in the case of sufficient cooperation between the patient and the physician, we observed a statistically significant increase in the effectiveness of SIT, compared to patients with insufficient cooperation ($p = 0.003$). Sex had no significant impact on differences in the effectiveness of the immunotherapy used ($p = 0.695$) (shown in Figures 3 A, B).

Continuation of SIT for a period of 3 years also increases the tolerance of therapy, both in patients with sufficient (VAS score dropped from 2.44 ±0.07, 2.0 ±0.1 to 1.7 ±0.1 in the 1st, 2nd and 3rd year of immunotherapy, respectively) and insufficient (VAS score dropped from 2.96 ±0.33, 2.6 ±0.3, to 2.3 ±0.3 in the 1st, 2nd and 3rd year of immunotherapy, respectively) cooperation with the physician, both in men (VAS score dropped from 2.22 ±0.007, 1.8 ±0.1, to 1.5 ±0.1 in the 1st, 2nd and 3rd year of immunotherapy, respectively) and women (VAS score dropped from 2.55 ±0.09, 2.0 ±0.1, to 1.7 ±0.1 in the 1st, 2nd and 3rd year of immunotherapy, respectively). Finally, the level of patient-physician cooperation and gender did not significantly affect the tolerance of immunotherapy ($p = 0.527$; $p = 0.153$, respectively) (shown in Figures 3 C, D).

CORRELATION BETWEEN SIT EFFICACY AND TOLERANCE AFTER THE 1ST, 2ND AND 3RD YEAR OF ITS ADMINISTRATION

A continuous improvement in efficacy and tolerance was observed from the first year through the third year of the treatment. The VAS score for efficacy dropped from 3.12 ±0.08 for the 1st, to 2.36 ±0.06 for the 2nd and to 1.72 ±0.05 for the 3rd year of observation, and similarly from 2.36 ±0.06 to 1.86 ±0.05 and to 1.51 ±0.05 for tolerance.

Spearman's correlation test showed that the effectiveness of immunotherapy depends on its high tolerance. In the 1st year of immunotherapy, a strong relationship between the effectiveness and tolerance of SIT was demonstrated ($r = 0.591$, $p < 0.05$). This relationship is also comparable after the 2nd year of desensitization ($r = 0.675$, $p < 0.05$). It increases significantly after the 2nd year of immunotherapy, up to the correlation coefficient value $r = 0.797$ after the 3rd year of treatment ($p < 0.05$) (shown in Figures 4 A–C).

CORRELATION BETWEEN WILLINGNESS TO CONTINUE SIT AND THE PATIENT-PHYSICIAN COOPERATION LEVEL

Spearman's correlation test showed a weak relationship ($r = 0.339$, $p < 0.05$) between the willingness to continue the therapy and the level of cooperation between the patient and the physician performing SIT. We can therefore conclude that the better the cooperation between the patient and the physician, the greater the willingness to continue immunotherapy (shown in Figure 4 D).

DISCUSSION

This study showed high effectiveness and tolerance of SIT in the first year, which increased up to 3rd year after its administration, regardless of the approach used (allergoid/allergen extract), therapy scheme (perennial/pre-seasonal) and status (finished/unfinished), sex or the willingness to continue the therapy. Furthermore, sufficient patient-physician cooperation significantly ($p = 0.003$) increased SIT efficacy. There was a weak relationship ($r = 0.339$, $p < 0.05$) between the willingness to continue the therapy and the level of patient-physician cooperation. Finally, there was a strong relationship between SIT efficacy and tolerance after the 1st ($r = 0.591$, $p < 0.05$), the 2nd ($r = 0.675$, $p < 0.05$) and the 3rd ($r = 0.797$, $p < 0.05$) year after its first administration.

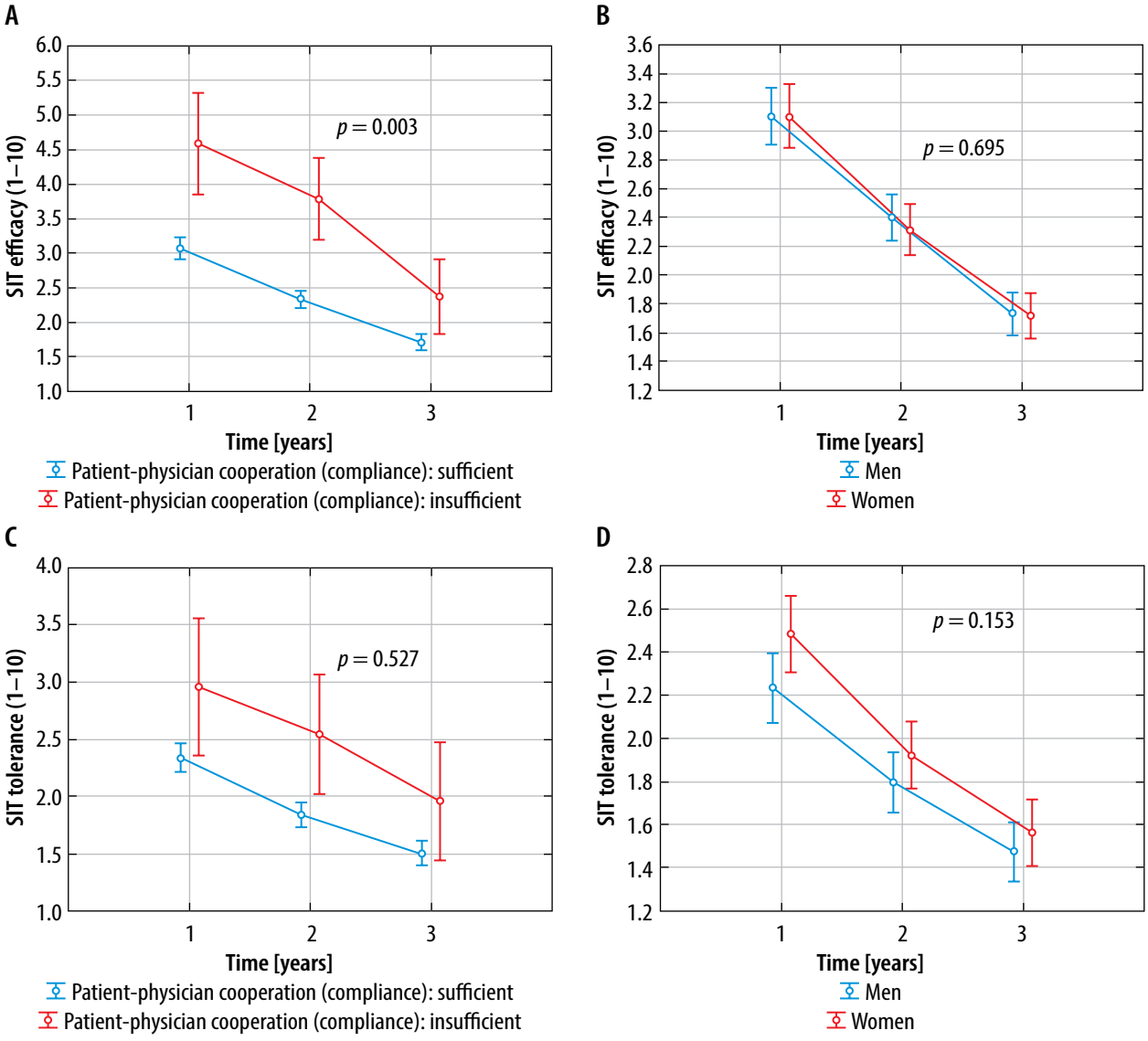

FIGURE 3. Comparison of SIT efficacy (**A**, **B**) and tolerance (**C**, **D**) after 1, 2, 3 years from the first date of administration for different level of patient-allergist cooperation (**A**, **C**) and sex (**B**, **D**). Efficacy and tolerance after the 1st, 2nd and 3rd year after SIT administration were measured by visual-analogue scale (VAS) and then analyzed by ANOVA. VAS score 1 was considered as excellent efficacy, whereas 10 means completely ineffective. Results are expressed as mean ± SEM. Data with $p < 0.05$ were considered statistically significant

The high effectiveness of specific immunotherapy is documented by many clinical studies. In meta-analysis by Calderon *et al.*, which compared the effectiveness of SIT in 15 clinical trials of patients allergic to seasonal allergens (i.e. grass pollen, birch), a statistically significant reduction in symptoms (SMD = –0.73; 95% CI: –0.97 to –0.50; $p < 0.00001$) and reduction in drug consumption (SMD = –0.57; 95% CI: –0.82 to –0.33; $p < 0.00001$) after the use of SCIT was found (in 13 out of 15 clinical trials) [18]. Another meta-analysis by Kiel *et al.* assessed the effectiveness of SCIT and SLIT in patients with seasonal rhinitis. Analysis of 17 clinical trials with SCIT showed a significant reduction in symptoms in all clinical trials (SMD = –0.65; 95% CI: –0.85 to –0.45; $p < 0.00001$), whereas in 16 clinical trials it showed a significant reduction in drug consumption (SMD = –0.55; 95% CI: –0.75 to 0.34; $p < 0.00001$). In 8 clinical trials it also showed a significant improvement in quality of life (SMD = –0.53; 95% CI: –0.66 to –0.39; $p < 0.00001$). Furthermore, the analysis of 42 clinical trials with SLIT showed a significant reduction in symptoms (SMD = –0.33; 95% CI: –0.42 to –0.25; $p < 0.00001$), and in 35 clinical trials it showed a significant decrease in medication consumption (SMD = –0.27; 95% CI: –0.37 to –0.17; $p < 0.00001$). In the case of 7 clinical trials, a significant improvement in quality of life was also noted (SMD = –0.37, 95% CI: –0.52 to –0.22; $p < 0.00001$) [19]. The Jansen *et al.* analysis of 23 clinical trials of patients with grass pollen allergy

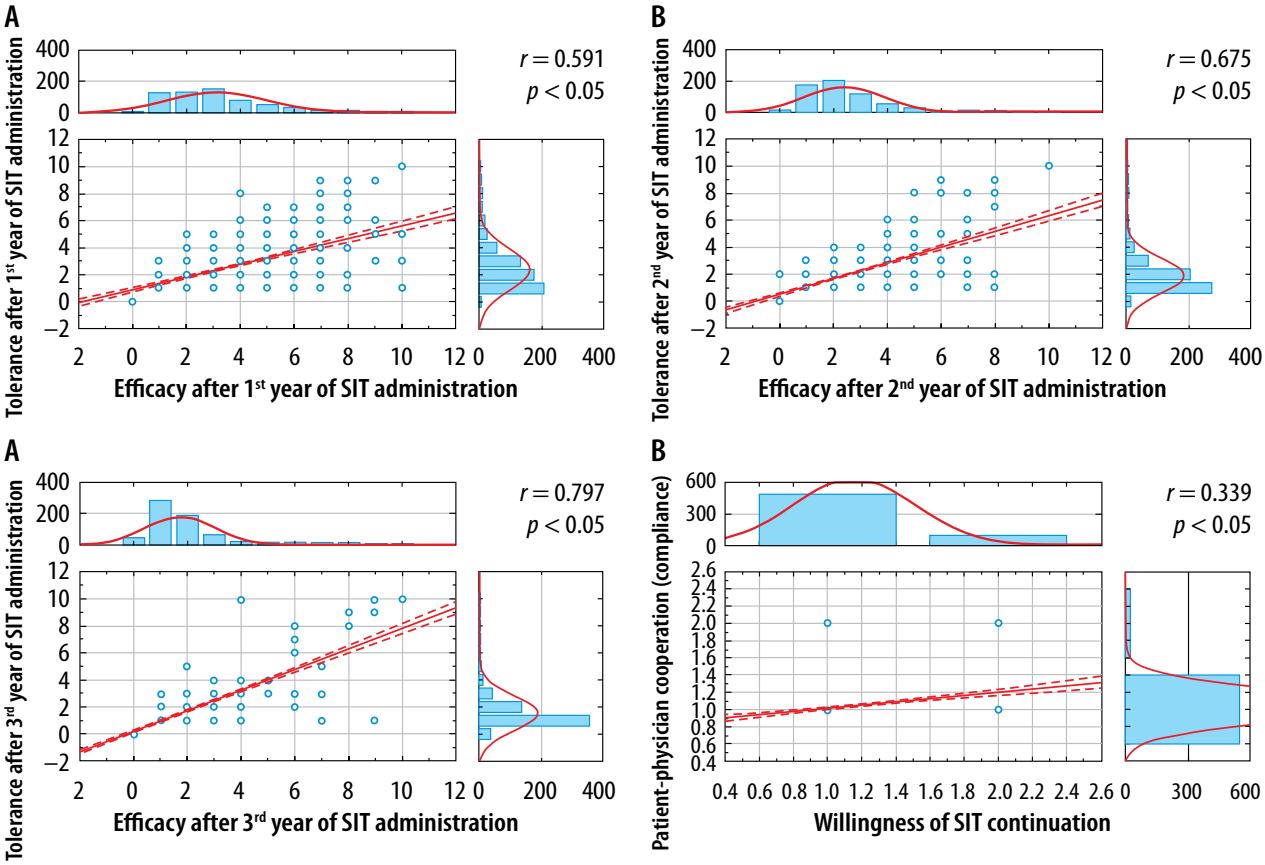

FIGURE 4. Spearman's correlation between efficacy and tolerance after 1, 2, 3 years from the first date of administration (**A**–**C**), patient-allergist cooperation and willingness to continue the therapy (**D**). Efficacy and tolerance after the 1st, 2nd and 3rd year after SIT administration were measured by visual-analogue scale (VAS) and then correlations were analyzed by Spearman's correlation test. VAS score 1 was considered as excellent efficacy, whereas 10 means completely ineffective. Results are expressed as mean ± SEM. Data with $p < 0.05$ were considered statistically significant

who underwent SLIT showed a significant reduction in the scale of symptoms (SMD = –0.35; 95% CI: –0.45 to –0.24; $p < 0.00001$). Similar results were obtained in 9 clinical trials in the treatment of patients allergic to tree pollen (SMD = –0.42; 95% CI: –0.77 to –0.06; $p = 0.02$) and 9 clinical trials in patients allergic to house dust mites (SMD = –0.97; 95% CI: –1.80 to –0.13; $p = 0.02$) [20].

Many studies show long-lasting clinical effects, even after SIT completion. Creating immunological tolerance to the allergen reduces allergy symptoms and the need for symptomatic treatment [21]. A perfect example is a clinical study by Eng *et al.* of patients with grass pollen allergy treated with SCIT, using the pre-seasonal method. During 3 years of immunotherapy use, the following were demonstrated: fewer symptoms of seasonal rhinitis ($p < 0.03$) and lower drug consumption ($p < 0.05$). In patients who received SCIT using the pre-seasonal method, there were also fewer new allergies (by 58%; $p < 0.05$) and a tendency to less frequent occurrence of seasonal asthma ($p = 0.008$) 6 years after the end of 3-year course of immunotherapy. Similar results persisted even 12 years after SCIT completion [22].

In our study, 58% (348 out of 600 of randomly selected patients from all over Poland) of patients decided to continue immunotherapy, of which 56.7% (217 out of 383 patients) with the allergoid, and 60.4% (131 out of 217 patients) with the allergen extract. Taking into account the fact that randomly selected allergy practices were analyzed throughout Poland, 58% is a high percentage. Comparing these data with data from many clinical trials, it turns out that the number of patients who completed the therapy in our analysis is really high. Sieber *et al.* compared the SIT continuation level for patients with allergoids and allergen extracts (based on the IN-SIGHT Health database) over the next 3 years of each patient's therapy. Analysis included data from 112 patients treated with the natural grass pollen extract administered sublingually (SLIT), 695 patients treated with the natural grass pollen extract administered by injection (SCIT) and 602 patients treated with the grass pollen allergoid administered by injection (SCIT) starting from 2005. After the 1st year of immunotherapy, half to two-thirds of patients were identified as continuing therapy. Then, after the 2nd year of immunotherapy, the number of patients

continuing immunotherapy decreased to one-third to one-half of patients.The study did not find any significant statistical differences in terms of SCIT, natural grass pollen extract and grass pollen allergoid. However, the use of SLIT compared to SCIT showed a significant increase in the number of people who continued therapy after the 1st (vs. SCIT allergen extract $p = 0.0015$; vs. SCIT allergoid $p = 0.0152$) and 2nd (vs. SCIT allergen extract $p = 0.0003$; vs. SCIT allergoid $p = 0.0111$) year of immunotherapy. Additionally, women continued therapy significantly longer than men ($p = 0.001$). A similar relationship was obtained for continuation of treatment in older people ($p = 0.001$) compared to young people [23]. One clinical trial by Lemberg *et al.* from a German allergy center comparing SCIT and SLIT showed that the percentage of all patients who discontinued treatment was 34.8%. A higher rate of withdrawal from continuation of immunotherapy was noted among patients treated with SLIT (39.0%) compared to SCIT patients (32.4%). The largest percentage of patients dropped out in the first year of therapy, which is crucial for completing the entire immunotherapy course. Patients who finished the first year of therapy are much more willing to continue immunotherapy, and the probability that they will complete the entire course is very high [24]. The Kiel *et al.* study analyzed data from 6,486 patients treated with immunotherapy, including 2,796 patients treated with SCIT and 3,690 patients treated with SLIT. Only 18% (1,167 of 6,486 patients) of patients completed a 3-year course of immunotherapy (for SCIT – 23%, and for SLIT – 7%). The average length of treatment for SCIT was 1.7 years, for SLIT only 0.6 years [19]. In a retrospective study by Egert-Schmidt *et al.* conducted in Germany, data from SCIT and SLIT used in inhalant allergies were analyzed. 42% and 45% of patients, respectively, completed 3 years of SCIT therapy for grass pollen allergens and household allergens. In the case of SLIT, only 16% of patients completed 3 years of treatment [25].

Musa *et al.* in his retrospective study assessed the level of patient cooperation in immunotherapy and also analyzed the factors that are associated with interruption of cooperation and, consequently, reduced therapy effectiveness. The analysis included 236 patients (150 patients treated with SCIT and 86 patients treated with SLIT) with allergic rhinitis with/without coexistence of asthma. The mean duration of therapy was 31.0 ±18.3 months for SCIT and 15.9 ±14.7 months for SLIT ($p < 0.001$). 88 patients continued therapy for 3 years with SCIT (58%). Only 10 patients continued SLIT therapy for 3 years (11.6%). The most common reasons for not continuing SCIT included injection frequency (82.2%), treatment duration (70.9%) and the need to travel to the doctor (67.7%). However, in the case of SLIT, patients most often indicated: inconvenience (43.4%), visible improvement without treatment (30.2%), poor efficacy perception (25%). Patient cooperation is influenced by many different factors, including factors related to the treatment protocol, depending on the patient, depending on the doctor, the doctor-patient relationship and on the nature of the disease [26].

CONCLUSIONS

Specific immunotherapy is a highly effective and safe method that allows for a significant reduction of allergy symptoms and reduction/discontinuation of symptomatic treatment. High effectiveness and tolerance of specific immunotherapy are observed both with the use of allergoids and allergen extracts, with pre-seasonal and perennial therapy, as well as with finished and unfinished therapy. Specific immunotherapy is effective and safe regardless of gender or differences in willingness to continue the therapy. The better the cooperation between the physician and the patient from the first year after its administration, the higher the effectiveness of immunotherapy and the greater the willingness to continue immunotherapy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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