Efficacy and tolerability of house dust mites subcutaneous immunotherapy with monomeric allergoid: an Italian multicenter study

Enrico Compalati[1], Isabella Atzeni[2], Sergio Cabras[3], Paolo Fancello[4], Rocco Longo[5], Franco Frati[1]

[1]Lofarma S.p.A., Scientific Medical Department, Milan, Italy

[2]Allergy Office, "Nostra Signora di Bonaria" Hospital, San Gavino Monreale, Italy

[3]Allergy and Clinical Immunology Privat Practice, Oristano, Italy

[4]Allergy Office, Sanluri Health Center, ASL Mediocampidano, Sanluri, Italy

[5]Territorial Allergy Service, ASP Vibo Valenzia, Tropea, Italy

Summary

Background. Subcutaneous immunotherapy is an effective treatment of respiratory allergy and allergoids offer a treatment option characterized by reduced IgE-binding properties to improve the safety profile. Purpose of this study was to investigate the efficacy and the safety of an injective monomeric allergoid in patients with moderate to severe persistent allergic rhinitis due to house dust mites. **Methods.** in a perspective, controlled, observational study a suspension of 0.70 mL at 10 BU/mL containing a mixture of carbamylated extract of *Dermatophagoides* was injected monthly for 12 months, following a 5-weeks build-up phase (0.10-0.20-0.30-0.50-0.70 mL weekly), to 58 patients (mean age 25.1 ± 12.7). A matching group of 60 patients (mean age 34.0 ± 14.2) was observed as control, and both groups were allowed to assume standard pharmacotherapy. After one year, changes from baseline in visual analogue scale for symptoms and drugs intake were compared; satisfaction rate was based on patients' and physicians' judgements. **Results.** In respect to baseline both groups showed an improvement in symptoms with a significant difference in favor of immunotherapy. Drugs intake was significantly lower in patients receiving injections. High level of agreement was found between doctors and patients on their rate of satisfaction. No serious reactions occurred, and at least a mild episodic local or systemic reaction was reported by a limited number of patients. **Conclusions.** In routine practice injective monomeric allergoid of house dust mites was safe and associated with a perceived significant clinical benefit in persistent rhinitis shown by objective and subjective outcomes.

Key words

Subcutaneous immunotherapy; SCIT; monomeric allergoid; house dust mites; efficacy.

IMPACT STATEMENT

A 5-weeks up-dosing of SCIT with HDM monomeric allergoid is safe and one year of treatment appears effective in improving persistent allergic rhinitis in real life conditions.

Introduction

Subcutaneous allergen immunotherapy (SCIT) is regarded as an effective treatment of respiratory allergy based on the progressive inoculation of increasing amounts of allergen extracts with the purpose of modulating a protective immune response (1). From the clinical point of view, the short-term outcome of a SCIT course is the perceived relief of allergy symptoms and the gradual reduction of antiallergic medications (2, 3). This therapeutic approach has been used in clinical practice for decades and its efficacy has been remarked by systematic reviews of several clinical studies (4, 5). The safety of SCIT has been investigated in numerous surveillance studies and the risk factors for the occurrence of severe adverse reactions have been partially identified (6-8). When proper safety measures and precautions are implemented, SCIT results generally safe; however, for each preparation the benefits must be weighed also against the real risks of rare life-threatening allergic reactions and fatal anaphylaxis (9).

Different research lines have been directed to promote the tolerability and patients' acceptance of this medical intervention. All of them share the basic principle of using hypoallergenic variants to reduce the allergic response against the cure itself (10). Chemically modified allergen extracts, known as allergoids, have been used for a long time to treat allergic patients with the advantage of their reduced allergenicity but preserved immunogenicity (11, 12). Different methods of generating allergoids have been developed in the past years and the polymerization of native allergens was the most common (13). Subsequently, the carbamylation of lysine residues to generate monomeric allergoids was introduced, maintaining the same molecular weight and conformational structure of the native counterpart, but with reduced IgE-binding properties (14). The selective loss of ionic charge of the ε-lysil-residues modified into ureido groups alters the hydrophilic nature of the molecule important in the expression of IgE reactivity, eluding the risk of generating new epitopes through the molecular rearrangement. Conversely, the polymerization process, which results from cross-linking protein with aldehydes to form high molecular weight polymers with fewer exposed IgE-reacting determinants, can potentially synthesize allergen chains with new epitopes, which may result in the induction of specific antibodies that are not related to the native protein (15, 16). The immunological pathways of this active principle have been partially investigated when administered sublingually, even if further aspects still need to be elucidated (17-19).

Monomeric allergoids have been successfully adsorbed on calcium phosphate (CaP) in depot suspensions for SCIT. CaP, developed 40 years ago as an adjuvant approved by the World Health Organization and historically included in vaccines against various infectious diseases, can contribute to redirect the T-helper 2 immune response toward T-helper 1 and IgG production, like aluminum salts (20-21).

The purpose of this study was to collect information on perceived efficacy and tolerability of injective monomeric allergoid with 5-weeks induction scheme in patients with allergic rhinitis (AR) caused by house dust mites (HDM).

Materials and methods

Patients and study design

This study was performed with a perspective, open-label, controlled design in 5 centers of three different Italian regions from autumn 2009 to autumn 2010. All participants or their parents were informed of the nature and objectives of the study and provided their consent. Ethics Committees were simply notified given the observational nature of the study.

To eligible outpatients, between 12 and 64 years, with a diagnosis of moderate to severe (according to ARIA classification) HDM-induced persistent AR for at least 1 year, with or without concomitant, clinically controlled, mild asthma (according to GINA criteria) immunotherapy was prescribed (22, 23). Clinically relevant HDM allergy had to be confirmed by skin prick testing (HDM ≥3 mm) and/or HDM-specific serum IgE (>0.7 kU/L). Subjects with sensitization to other seasonal allergens or animal dander, with respiratory tract infections, pregnancy or lactation, suspected drug or alcohol abuse, previous immunotherapy with HDM extracts within the last 5 years, continuous or frequent treatment with systemic corticosteroids, b-blockers and other contraindications for immunotherapy were excluded from the selection. Lung function was measured at baseline in participants with history of concomitant asthma, and before injections in case of suspicious loss of asthma control. A matching group with similar characteristics but unwilling to start immunotherapy and receiving only standard pharmacotherapy on demand, was used as control (**figure 1**). No additional diagnostic procedures to routine standard care were applied, in compliance with the observational nature of the study. The efficacy assessment was conducted through the evaluation of the improvement in the health condition related to allergy symptoms at the end of the treatment, and the calculation of the mean usage of anti-allergic drugs on demand during the study.

Study medication and treatment schedule

Immunotherapy consisted in progressive injections of a suspension of carbamylated monomeric allergoid mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (1: 1) extracts, adsorbed on CaP (Lais-in®, Lofarma Spa, Milan), standardized at 10 BU/mL, equivalent to 4 µg Eq./ml of major allergens Group 1 (Der p 1 and Der f 1) (determined on the purified extract before chemical modification). The biological unit (BU) is equivalent to 1/100 of the concentration of extract which, before being chemically modified, induces a mean wheal equivalent to that induced by 10 mg/mL histamine during skin allergy testing.

The treatment schedule was administered according to doctors' decisions based on the recommendations of the manufacturer. Subjects were enrolled and treated for 12 months following a 5-weeks up-titration (0.10–0.20–0.30–0.50–0.70 mL, at weekly step-up). The monthly maintenance dose was 0.70 mL. After injections, patients remained under medical supervision for at least 30 minutes and if needed, based on local and systemic reactions, dose adjustments were admitted, with prompt availability of resuscitation tools. All patients were allowed to assume as needed antiallergic drugs. A diary was given to all participants to register the intake of antiallergic medications and report the late side effects of SCIT.

Efficacy and satisfaction assessment

Subjects were instructed to rate at study beginning and after one year a Visual Analog Scale (VAS) for the level of impairment due to the symptoms of AR (itching, sneezing, rhinorrhea, obstruction)

to analyze changes over time; the average VAS score was calculated (24). Patients graded the severity of their disease related to mite exposure by putting a vertical line on a 100-mm bar representing severity from 0: “highest level of symptoms” to 100: “no symptoms”. The question translated from Italian language on allergic symptoms was “how much is your wellbeing related to the severity of allergy symptoms in the last 4 weeks?”.

The VAS on allergy symptoms severity represents a simple, reliable, and fully validated subjective psychometric response scale in adults. ARIA 2008 guidelines include a rank classification with "mild" AR = 0–30 mm, "moderate" AR = 31–70 mm and "severe" AR = 71–100 mm, when the scale reflects the following rating: 0=Not troublesome, 100=Worst thinkable troublesome (25, 26). In this case the direction of the scale was simply reversed.

The average weekly intake of anti-allergic medications, registered on a diary during the study period, was calculated by the sum of individual daily score attributed to each drug used, based on the assumed clinical effects on symptom reduction (0 = no rescue medication taken; 1 = use of topical antihistamine; 2 = use of oral antihistamine; or 3 = use of nasal corticosteroids). A baseline value was estimated at study beginning with the same criteria on the ongoing medication intake.

Patients and physicians were additionally asked to express a self-judgment of clinical satisfaction at the end of the study following a predefined scale (unsatisfactory, discreet, good, optimal).

Safety and tolerability assessment

The frequency was calculated for the occurring local (which can manifest as erythema, pruritus and swelling at the injection site) and systemic reactions (rhinitis, itching, flushing, erythema, localized urticaria, generalized urticaria, angioedema, cough, itchy throat, difficult swallowing, mild-moderate-severe asthma, abdominal pain, nausea, vomiting, hypotension, shock). Large local reactions (LLRs) were defined as pruritus and/or erythema (>2.5 cm) at the site of injection (8, 27). The severity of systemic reactions was evaluated according to the EAACI Grading of Severity of Systemic Side effects (28), which distinguishes among no symptoms (0), mild (I), moderate (II), severe reactions (III) and anaphylaxis (IV). Local and systemic reactions occurring within 30 min after injection were recorded by the investigator onsite. Late reactions were recorded by patients in a diary and reported to the investigator at the subsequent control visit, or by rapid direct contact if needed.

Patients and physicians were asked to express a self-judgment of satisfaction for tolerability at the end of the study following a predefined scale (unsatisfactory, discreet, good, optimal).

Statistical analysis

No formal statistical sample size and power computations were performed given the explorative and observational nature of the investigation. Based on the safety outcome, it was estimated that at least 36 patients with HDM-induced AR had to be treated with SCIT. In fact, in case no specific event (e.g. anaphylaxis) is observed, the target number of 36 evaluable patients allow to exclude proportions of 10% or greater of this event (i.e. 95% confidence interval 0-11.4%, Wilson’s method). The safety evaluation set was composed of enrolled subjects, who have been exposed to the study medication at least once. The frequency of treatment emergent adverse events (TEAEs) and overall subjective self-judgments were calculated with descriptive statistics. Average scores for patients’ wellbeing from VAS and use of antiallergic medications were compared between groups with non-

parametric Mann-Whitney U Test and intragroup changes with Wilcoxon signed rank test. Differences were considered statistically significant at the 5% level of significance using two-sided tests. The statistical analyses were carried out using SPSS Statistics software, version 17.7.

Results

In total, 118 patients (57 males and 61 females) participated, 58 undergoing a SCIT course (mean age 25.1 ±12.7 years) and 60 receiving pharmacotherapy alone (mean age 34.0 ±14.2), with similar baseline clinical characteristics. A history of asthma in their life was documented in 15 subjects of the first and in 14 subjects of the second group. All subjects had been suffering from respiratory allergy for years (10.9 ±8.5 and 6.8 ±5.3, respectively), and concluded the study after 12 maintenance doses (total injections given 986).

Clinical efficacy and satisfaction

At the end of the treatment a significant improvement compared to baseline was observed in both groups for the VAS score of AR symptoms ($p<0.001$), with a statistically significant difference in favor of the SCIT group (mean 81.6, SE 1.25 vs mean 50.1, SE 1.90; $p<0.05$). The average change from baseline was respectively 58.6 ($p<0.001$) and 15.5 ($p<0.001$) (**figure 2a**).

The average weekly score for anti-allergic medication intake was largely inferior in the group receiving SCIT during the 12 months (from mean 22.4, SE 3.60 to mean 6.7, SE 1.30; $p<0.001$). Conversely, in the control group patients continued as expected to use medications to control their allergic disease (from mean 21.8, SE 2.10 to mean 21.6, SE 2.21; ns). The difference between arms was significant ($p<0.05$) (**figure 2b**).

Patients' subjective overall judgement of clinical satisfaction was optimal in 31 cases, good in 23, discreet in 3 cases and unsatisfactory in 1 case. In controls, it was optimal in 5 cases, good in 14 cases, discreet in 13 cases and unsatisfactory in 4 cases. Physicians rated as optimal in 31 cases, good in 24 and discreet in 2 cases. In controls, the rating was optimal in 5 cases, good in 14 cases, discreet in 7 cases but unsatisfactory in 10 cases (**figure 3**).

Safety and tolerability

During the study, no serious adverse events were reported, epinephrine was never used, and no hospitalization was needed. Overall, episodic TEAEs of mild intensity were reported by 16 patients (27.58 %) out of 58 treated with SCIT, corresponding to a rate of 0.016 of all administered doses. Of these TEAEs, 3 were reported as treatment-related: local itching by 8 patients, local pain by 5 patients, diffuse itching by 1 patient; episode of fever and asthma symptoms were judged as possibly related for 2 patients. None of the reported reactions determined treatment interruption or dose-adjustment. Overall, the number of allergic local reactions (none was LLR) was 13 (3 at dose 0.1 mL, 2 at doses of 0.2 mL; 2 at 0.3 mL; 4 at 0.5 mL, 2 at 0.7 mL) and that of systemic reactions was 2 (at doses of 0.7 mL). Diffuse itching and asthma symptoms, occurring in medical office and at home in the maintenance phase respectively, were classified as a systemic reaction of Grade 1.

Patients' subjective overall judgement of SCIT tolerability was optimal in 38 cases, good in 18 and discrete in 2 cases. Physicians' subjective judgment was optimal in 37 cases, good in 19 and discrete in 2 cases. Nobody rated the treatment as unsatisfactory (**figure 4**).

Discussion and conclusions

The safety of injective HDM monomeric allergoid was early investigated in a previous dose-escalation study involving 45 adult subjects affected by AR with or without asthma (29). During a cautious slow up-dosing of 12 weeks, including the administration of 0.1, 0.3, 0.5, 0.8 mL of three concentrations (0.1 BU/mL, 1 BU/mL, 10 BU/mL respectively), and a maintenance of 4 months, 12 cases of TEAEs were attributed to the treatment. Mild related allergic reactions (dyspnea, asthma episodes, pain at the arm, diffuse itching, headache, localized urticaria), not requiring treatment interruption or hospitalization, occurred in 17.7% of patients. Another previous explorative study evaluated the clinical efficacy perceived by 15 patients aged 15-45 years, who reported a VAS improvement after 7 months with 0.8 mL of 10 BU/mL monthly; during the 5-weeks short up-dosing (0.1, 0.2, 0.4, 0.6 mL) no adverse reactions were observed in 7 patients (46.6%), while two patients reported pain at the arm, three local itching, two LLR and fever (30).
In current perspective, controlled study, the previous findings were confirmed by the low rate of TEAEs and by the subjective tolerability referred by patients and physicians with high rate of concordance. The absence of serious and severe reactions, whose occurrence might be expected with accelerated build-up regimens, is of major importance (31-33). The adopted schedule can thus be regarded as a valid proposal for the use of injective HDM monomeric allergoid.

The overall rate of TEAEs was low and involved a limited number of treated subjects (27.58%). Local reactions at injection site with native extracts are rather common, generally being experienced by 26–86% of patients (33, 34). In this study 13 subjects (22.4%) reacted with transient mild local itching and pain during the build-up phase.
Two patients (3.44%) reported a systemic reaction, one very likely to be treatment related (diffuse itching), but without further progression and self-resolving. An asthmatic patient reported during the study period an episodic worsening of bronchial symptoms easily managed by a short course of bronchodilator and low dose inhaled corticosteroid. This event was prudently considered possibly treatment-related, anyway asthma is known to be a complex disease with different triggers and underlying mechanisms.
Even if related to the product and the dose used, the risk of systemic reactions of various severity in conventional build-up protocols is usually low (1.8-7.4% of patients), and even lower in HDM-sensitized patients compared with pollen-allergic patients. In cluster and rush up-dosing the risk seems to increase up to 38% (35, 36). On the other hand, the specific characteristics of the monomeric allergoid extract can explain the observed level of tolerability. The low IgE-binding properties, demonstrated by EAST-inhibition experiments, justify the limited activation of the allergic cascade after the extract administration, resulting in lower local and systemic side effects (14). This principle suggests that when similar results are confirmed by large scale studies or post-marketing surveillance, accelerated build-up phases can be safely introduced to rapidly reach the effective maintenance dose (37). This was the case in another clinical pilot experience on 30 subjects receiving a rush schedule (0.20 mL plus 0.50 mL after half an hour in a single induction day), where no reactions occurred in 70% of them, and 30% referred local mild reaction (38).

The total absence of severe, near fatal and delayed systemic reactions also limits the perspective of prescribing self-injectable epinephrine at physician's discretion as stated by some guidelines (8, 39). A further element favoring the safety in respect to aqueous solution, is represented by the slow

release of active principle by the formulation adsorbed on CaP microcrystals, which further facilitates the uptake by phagocytic cells, thereby enhancing the protein immunogenicity (20). In respect to aluminum salts, CaP is a compound naturally present in the organism and has been shown to induce lower local inflammation and a more balanced immune response (21).

All subjects were admitted to taking rescue medication on demand and in the main group a consumption of less than one third in respect to controls was evident. Nevertheless, SCIT with HDM carbamylated allergoid was associated with a better significant clinical benefit observed through subjective outcomes. VAS related to patients' severity of allergic symptoms was significantly improved at the end of the study. VAS provides a psychometric continuous scale for subjective magnitude estimation of the AR discomfort and correlates well with the severity of ARIA levels of disease (24). According to Bousquet et al., a difference of greater than 1 cm is significant to separate patients without improvement from those with improvement (25, 26). Despite that the non-randomized placebo-controlled design represents a clear limitation for the quality of the evidence, in this study patients receiving SCIT and those receiving pharmacotherapy increased the mean VAS score of 5,9 cm and 1,5 cm, respectively. The average score at the end of the study was 8,2 cm corresponding to a mild level of AR severity, whereas pharmacotherapy alone improved to a moderate level (5 cm). Net of possible recall bias on baseline evaluation, the improvement of some extent in control group despite a comparable intake of medications could be the result of the progressive anti-allergic treatment and of the perspective expectations of patients aware of being part of a clinical study.
Without interim evaluations of the VAS, it was not possible to establish the time of treatment effect onset. On the other hand, this kind of evaluation may be affected by seasonal variations in HDM environmental levels and only day-by-day data collection of exposure levels and efficacy outcome may provide robust information.
Being an observational study, environmental sanitation measures (such as encase mattress, permeable bed covers, acaricides, carpet and curtain removal, vacuum cleaner with integral HEPA filter) could not be discouraged before the start of the study, to minimize variations in the levels of indoor allergens. Therefore, an impact on the outcomes of other interventions as part of the standard of care cannot be excluded. Finally, since patients were not characterized for their IgE-reactivity to individual allergenic determinants of HDM, no extrapolation can be made on the effect of SCIT regarding their molecular allergenic profile patterns.

In conclusion, the safety profile with 5-weeks induction up to a maintenance dose of 0.7mL of 10 BU/mL, and the efficacy of SCIT with carbamylated monomeric allergoid, observed in a real practice study design, are promising and consistent in the overall subjective assessment of both patients and physicians, who mainly expressed optimal or good level of satisfaction, important to document a treatment acceptance that is pivotal for an expected long-term treatment compliance.

Fundings

The study was independent and did not receive any funding.

Contribution

IA, SC, PF, RL participated in study Conceptualization, Investigation.

EC participated in manuscript Writing – original draft. FF participated in manuscript Writing – review & editing.

Conflicts of interest

IA, SC, PF, RL have no conflicts of interest regarding this manuscript.

EC, FF are employees of Lofarma S.p.A, Milano, Italy.

References

1. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy. 2018; 73(4): 765-798. DOI: 10.1111/all.13317
2. Bousquet J, Lockey RF and Malling HJ. WHO Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Allergy 1998; 53 (Suppl. 44): 1-42. DOI: 10.1016/s0091-6749(98)70271-4
3. European Medicines Agency; Committee for medicinal products for human use (CHMP). Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. London, 20 November 2008 Doc. Ref. CHMP/EWP/18504/2006.
4. Passalacqua G, Bagnasco D, Canonica GW. 30 years of sublingual immunotherapy Allergy. 2020; 75:1107–1120. DOI: 10.1111/all.14113
5. Dhami S, Nurmatov U, Arasi S, Khan T, Asaria M, Zaman H, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. Allergy. 2017; 72(11): 1597-1631. DOI: 10.1111/all.13201
6. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: national surveillance study on allergen immunotherapy (2008–2013). Ann Allergy Asthma Immunol. 2016; 116(4):354-359. DOI: 10.1016/j.anai.2016.02.001
7. Bernstein DI, Wanner M, Borish L, Liss GM. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990–2001. J Allergy Clin Immunol. 2004; 113(6):1129-36. DOI: 10.1016/j.jaci.2004.02.006
8. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011; 127(1 Suppl): S1–S55. DOI: 10.1016/j.jaci.2010.09.034
9. Cox L, Aaronson D, Casale TB, Honsinger R, Weber R. Allergy immunotherapy safety: location matters! J Allergy Clin Immunol Pract. 2013; 1(5): 455-7. DOI: 10.1016/j.jaip.2013.08.001
10. Grammer LC, Shaughnessy MA, Patterson R. Modified forms of allergen immunotherapy. J Allergy Clin Immunol 1985; 76(2Pt2): 397-401. DOI: 10.1016/0091-6749(85)90661-x
11. Maasch HJ, Marsh DG. Standardized extracts modified allergens-allergoids. Clin Rev Allergy. 1987; 5(1): 89-106. DOI: 10.1007/BF02802259
12. Satitsuksanoa P, Głobińska A, Jansen K, van de Veen W, Akdis M. Modified Allergens for Immunotherapy. Curr Allergy Asthma Rep. 2018; 18(2): 9. DOI: 10.1007/s11882-018-0766-x
13. Carnes J, Gallego MT, Moya R, Iraola V. Allergoids for Allergy Treatment. Recent Pat Inflamm Allergy Drug Discov. 2018; 12(2): 110-119. DOI: 10.2174/1872213X12666180221155908
14. Mistrello G, Brenna O, Roncarolo D, Zanoni D, Gentili M, Falagiani P. Monomeric chemically modified allergens: immunologic and physicochemical characterization. Allergy. 1996; 51(1): 8-15. DOI: 10.1111/j.1398-9995.1996.tb04543.x
15. Ibarrola I, Sanz ML, Gamboa PM, Mir A, Benahmed D, Ferrer A, et al. Clin Exp Allergy. 2004; 34(2): 303-9. doi: 10.1111/j.1365-2222.2004.01859.x.

16. López-Matas MA, Gallego M, Iraola V, Robinson D, Carnés J. Depigmented allergoids reveal new epitopes with capacity to induce IgG blocking antibodies. Biomed Res Int. 2013:2013:284615. doi: 10.1155/2013/284615
17. Di Gioacchino M, Perrone A, Petrarca C, Di Claudio F, Mistrello G, Falagiani P et al. Early cytokine modulation after the rapid induction phase of sublingual immunotherapy with mite monomeric allergoids. Int J Immunopathol Pharmacol. 2008; 21(4): 969-76. DOI: 10.1111/j.1398-9995.1996.tb04543.x
18. Burastero SE, Mistrello G, Falagiani P, Paolucci C, Breda D, Roncarolo D et al. Effect of sublingual immunotherapy with grass monomeric allergoid on allergen-specific T-cell proliferation and interleukin 10 production. Ann Allergy Asthma Immunol. 2008; 100(4): 343-50. DOI: 10.1016/S1081-1206(10)60597-2
19. Cosmi L, Santarlasci V, Angeli R, Liotta F, Maggi L, Frosali F et al. Sublingual immunotherapy with Dermatophagoides monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon-gamma- and interleukin-10-production. Clin Exp Allergy. 2006; 36(3): 261-72. DOI: 10.1111/j.1365-2222.2006.02429.x
20. Gupta RK, Siber GR. Adjuvants for human vaccines-current status, problems and future prospects. Vaccine. 1995; 13(14): 1263-1276. DOI: 10.1016/0264-410x(95)00011-o
21. Masson JD, Thibaudon M, Belec L, Crepeaux G. Calcium phosphate: a substitute for aluminum adjuvants? Expert Rev Vaccines. 2017; 16(3): 289-299. DOI: 10.1080/14760584.2017.1244484
22. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001; 108(5 Suppl): S147-334. DOI: 10.1067/mai.2001.118891
23. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2010 (update). Available from: https://ginasthma.org/wp-content/uploads/2019/01/2010-GINA.pdf (last access: 25/06/2024).
24. Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Méchin H, Daures JP, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. Allergy. 2007; 62(4): 367-72. DOI: 10.1111/j.1398-9995.2006.01276.x
25. Bousquet PJ, Combescure C, KlossekJM, Daure` s, JP, BousquetJ. Change in visual analog scale score in a pragmatic randomized cluster trial of allergic rhinitis. J Allergy Clin Immunol 2009; 123(6): 1349-54. DOI: 10.1016/j.jaci.2009.02.033
26. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update. Allergy.2008; 63(Suppl 86): 8-160. DOI: 10.1111/j.1398-9995.2007.01620.x
27. Roy SR, Sigmon JR, Olivier J, Moffitt JE, Brown DA, Marshall GD. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. Ann Allergy Asthma Immunol 2007; 99(1): 82-6. DOI: 10.1016/S1081-1206(10)60626-6
28. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. Allergy 2006; 61(suppl 82): 1-20. DOI: 10.1111/j.1398-9995.2006.01219_1.x
29. Fancello P, Atzeni I, Bruno M, Cantone R, Galimberti M. Carbamylated monomeric dermatophagoides allergoid: a tolerability study with a depot formulation given by subcutaneous route. Allergy 2009; 64 (Suppl. 90):179-538. DOI: 10.1111/j.1398-9995.2009.02076.x

30. Fancello P, Atzeni I, Bruno M, Falagiani P. Safety and efficacy of carbamylated monomeric dermatophagoides allergoid depot formulation given by subcutaneous route. Allergy 2010. 65 (Suppl. 92): 209-682. DOI: 10.1111/j.1398-9995.2010.02393.x
31. Copenhaver CC, Parker A, Patch S. Systemic reactions with aeroallergen cluster immunotherapy in a clinical practice. Ann Allergy Asthma Immunol. 2011; 107(5): 441-447. DOI: 10.1016/j.anai.2011.06.026
32. James C, Bernstein DI. Allergen immunotherapy: an updated review of safety. Curr Opin Allergy Clin Immunol. 2017; 17(1): 55-59. DOI: 10.1097/ACI.0000000000000335
33. Prigal SJ. A ten-year study of repository injections of allergens: local reactions and their management. Ann Allergy. 1972; 30(9): 529-535. PMID: 5056915
34. Tankersley MS, Butler KK, Butler WK, Goetz DW. Local reactions during allergen immunotherapy do not require dose adjustment. J Allergy Clin Immunol. 2000; 106(5): 840-843. DOI: 10.1067/mai.2000.110468
35. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol. 2010; 125(3): 569-74. DOI: 10.1016/j.jaci.2009.10.060
36. Rodríguez Del Río P, Vidal C, Just J, Tabar AI, Sanchez-Machin I, Eberle P, et al. The European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): A paediatric assessment. Pediatr Allergy Immunol 2017; 28(1): 60-70. DOI: 10.1111/pai.12660
37. Frati F, Incorvaia C, Silvestri F S, Pisani A, Marastoni L, Cavalieri C, et al. Safety of subcutaneous immunotherapy with carbamylated allergoids based on data from a pharmacovigilance database. Immunotherapy. 2022; 14(15): 1219-1224. DOI: 10.2217/imt-2021-0302
38. Brivio G, Boscolo MA, Compalati E. Tolerability and efficacy of house dust mite injective rush immunotherapy with monomeric allergoid compared to sublingual administration in patients with allergic rhinitis. Allergy. 2013; 68 (Suppl. 97), 337-497. DOI: 10.1111/all.12251
39. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Immediate and delayed-onset systemic reactions after subcutaneous immunotherapy injections: ACAAI/AAAAI surveillance study of subcutaneous immunotherapy year 2. Ann Allergy Asthma Immunol. 2011; 107: 426-431. DOI: 10.1016/j.anai.2011.05.020

Figures

Figure 1. Study design

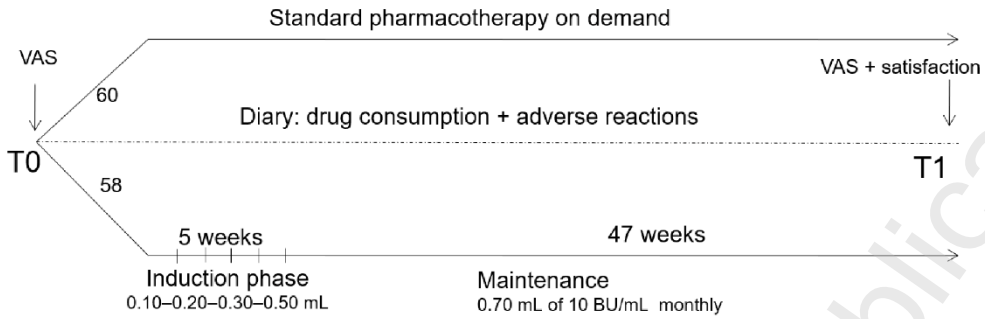

Figure 2. VAS score (mm) of the six individual symptoms of allergic rhino conjunctivitis (a) and weekly anti allergic medication score (b) at baseline (T0) and at the end of treatment (T1) in SCIT group (case) and pharmacotherapy group (control).

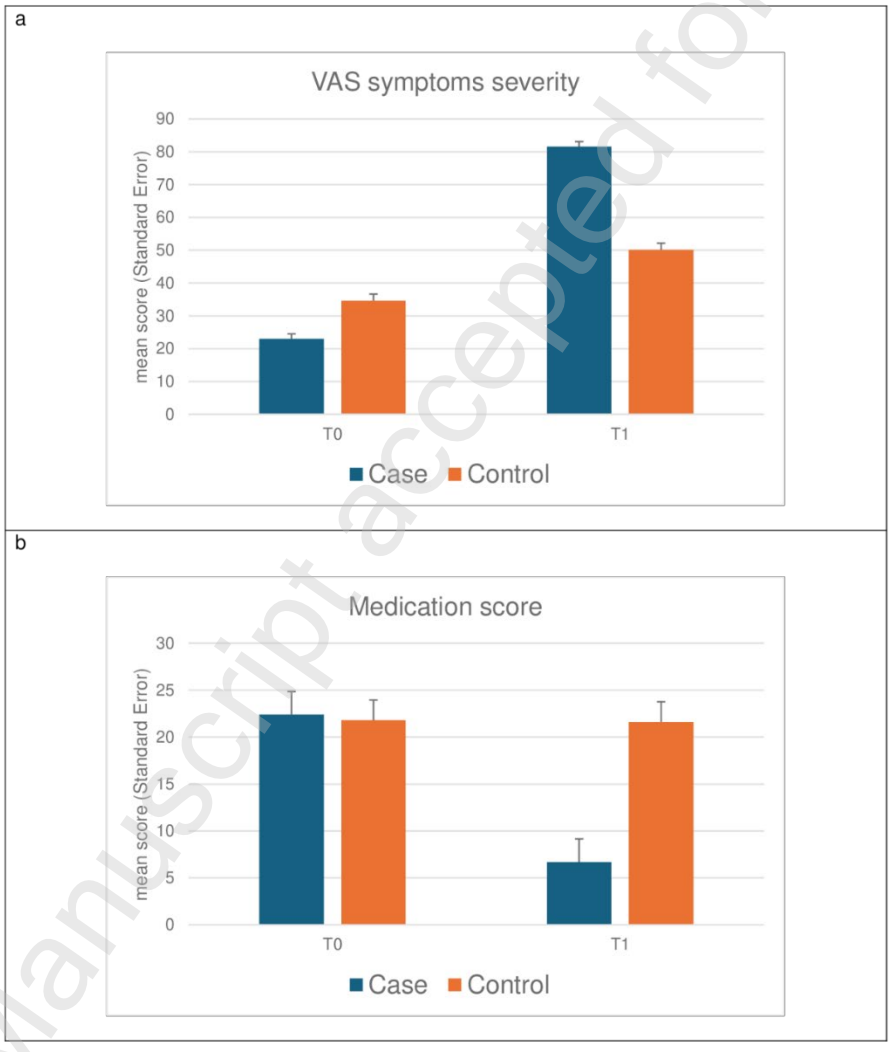

Figure 3. End of study clinical satisfaction through subjective overall judgement by patients (a) and physicians (b) in SCIT group (case) and pharmacotherapy group (control).

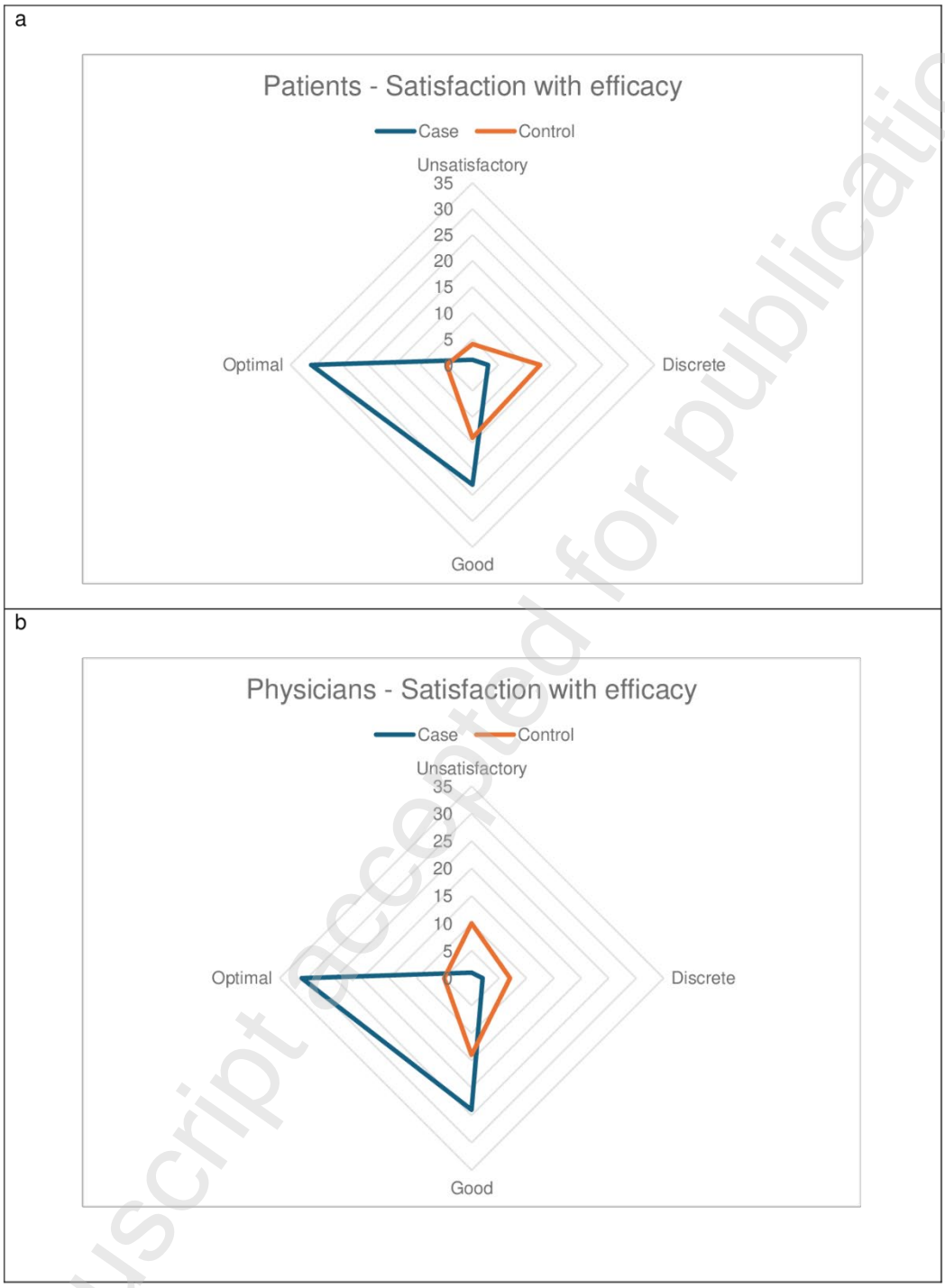

Figure 4. End of study satisfaction through subjective overall judgement by patients (a) and physicians (b) on the perceived tolerability of the treatment in SCIT group (case) and pharmacotherapy group (control).