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ORIGINAL ARTICLE

Characterisation of systemic reactions to subcutaneous immunotherapy with airborne allergens and classification according to WAO 2010

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KEYWORDS
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Abstract
Background: Systemic reactions (SR) to subcutaneous immunotherapy (SCIT) are rare but potentially severe. The use of different definitions and classifications hampered comparability between studies.
Aims: To determine the frequency of SR to SCIT with airborne allergens, and to characterise and classify them according to the WAO 2010 recommendations.
Methods: Cross-sectional, retrospective study. Data on patients, immunotherapy and SR to SCIT were collected from the SCIT record forms. During the study period, 22,332 SCIT injections were administered (3732 patients).
Results: A total of 26 SR (0.1% of administrations) were recorded in 16 (0.6%) patients (median age 22 years, nine males, all with rhinitis and nine with asthma). Twenty-one (81%) SR occurred during the induction phase; eight (31%) in the first hour after administration. According to the WAO 2010 classification, 12 (46%) were grade 1 and 14 (54%) were grade 2. Most grade 2 reactions occurred in asthmatics, presented as mild asthma symptoms and resolved without need for medical observation. Only two individuals without asthma presented grade 2 reactions, both with concurrent cutaneous and low respiratory symptoms; both required medical observation and treatment despite late onset; 82% ($n = 12$) of grade 2 reactions were late. No grade 3–5 reactions were registered and only one patient needed adrenaline treatment. No risk factors for SR to SCIT were identified in this study.
Conclusions: SCIT is a safe treatment when administered by trained staff. The WAO 2010 classification might be useful for retrospectively classifying the severity of reactions, although its usefulness in treatment decision needs further research.

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Background

Specific immunotherapy with airborne allergens has been used for more than a century with proven efficacy in both allergic rhinitis and asthma.[1,2]

Systemic reactions (SR) with subcutaneous immunotherapy (SCIT) are unusual but potentially severe, ranging from mild rhinitis to fatal reactions.[3] Poorly-controlled asthma, large local reactions, administration during pollen season and dosing error are the more frequently implicated risk factors,[4–6] although the evaluation of their relevance has been hampered by the use of different definitions and classifications of SR severity in previous studies.

The *European Academy of Allergy and Clinical Immunology* (EAACI) has proposed two different SCIT SR classifications, which have been widely used,[7,8] but not globally accepted. In 2010, the *World Allergy Organization* (WAO) published a new proposal for the classification of SCIT SR, suggesting that all these reactions should be promptly treated with adrenaline (Table 1).[5]

The aim of this study was to determine the frequency of SR to SCIT with airborne allergens, as well as to characterise and classify these reactions according to the WAO 2010 recommendations.

Methods

Study design and population

This was a cross-sectional, retrospective, descriptive study. Immunotherapy record forms from all patients with at least one administration of SCIT with airborne allergens in the Immunoallergology Division of a University Hospital in Porto, Portugal, from January 2008 to December 2010 were evaluated.

The immunotherapy record form was adapted to Portuguese in accordance to EAACI recommendations[8] and it was used to register patient and SCIT characteristics, administration date and dose, as well as local and systemic reactions. Immunotherapy record forms were analysed by at least two collaborators and data from patients with SR were collected. Moreover, emergency records of the Immunoallergology Division were also reviewed to guarantee that all the existing systemic reactions were included and accurately characterised.

During the study period, 22,332 SCIT injections were administered in 3732 patients.

Immunotherapy administration protocol

SCIT was administrated in the Immunoallergology Division by trained nurses or medical staff, always under supervision by an allergist. Adequate means for SR treatment were available at all time, including an emergency kit and rescue equipment. All patients under SCIT gave their written informed consent for the treatment.

Administered SCIT was of biologically standardised extracts in either depot (adsorbed in aluminium hydroxide or calcium phosphate) or polymerised formulations commercially available in Portugal. The administration schedules and dose adjustments were performed according to the producer's information and physician prescription. We defined immunotherapy schedules as conventional when maintenance dose was achieved in 3–6 months, ultra-rush when the maintenance dose was achieved in one day with two half-hour interval administrations, or rush when maintenance dose was achieved in 1–4 weeks. No cluster schedules were used.

Before administration, patients were systematically asked about late local and systemic reactions after the previous administration, as well as any current symptoms. All patients with asthma had their peak expiratory flow (PEF) measured before administration. The administration was postponed in patients with exacerbation of their allergic disease, uncontrolled asthma (PEF < 80% of their personal

Table 1 World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (WAO 2010).

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of ***1 organ system***: **Cutaneous** *or* **Upper respiratory** *or* **Conjunctival** *or* **Other** Nausea, metallic taste or headache	Symptom(s)/sign(s) of ***more than 1 organ system*** *or* **Lower respiratory** *or* **Gastrointestinal** *or* **Uterine cramps**	**Lower respiratory** ≥40% PEF or FEV1 drop *or* not responding to an inhaled bronchodilator *or* **Laryngeal, uvula or tongue oedema**	**Respiratory failure** *or* **Hypotension**	**Death**

Adapted from Cox et al.[5]
The final report should include the first symptom(s)/sign(s), the time of onset after the subcutaneous allergen immunotherapy injection and a suffix reflecting if and when adrenaline was or was not administered: a: ≤5 min; b: > 5 to ≤10 min; c: > 10 to ≤20 min; d: > 20 min; z: adrenaline not administered.

best), generalised cutaneous symptoms or recent infection. Pre-treatment with antihistamines or other drugs and dose adjustments in the pollen season are not routine practice in the Division. Pollen SCIT was started at least eight weeks before the pollen season.

SCIT was administered by deep subcutaneous injection in the outer aspect of the median third of the arm. After administration, patients were kept under observation for a minimum period of 30 min and all reactions were recorded.

Classification of adverse reactions

SR were categorised as immediate (when occurring during the first 30 min after administration) or late (when recorded in the following administration or requiring attendance of the immunoallergology emergency consultation/medical attention after the surveillance period). Manifestations and treatment were described based on the available information. The WAO 2010 severity classification was used to retrospectively assess severity.

Local reactions were described taking into account the local swelling (wheal) size; those with a mean diameter of $\geq$8 cm were considered as large local reactions.

Pollen counts

To account for the influence of SCIT administration during pollen season, we reviewed the data from pollen counts available in the Portuguese aerobiology network website for Porto.[9] Pollen was collected weekly with a Burkard Seven Day Volumetric Spore-trape® located on the rooftop of Hospital São João, at an altitude of 80 m above sea level. Results are shown as median pollen grain counts per cubic metre; counts between 1 and 30 pollen/m^3 are considered low, while >60 pollen/m^3 are considered high.

Statistical analysis

A descriptive analysis of the included variables was performed using frequencies and proportions for categorical variables and median with lower and upper limits for continuous variables.

Results

During the 3-year study period, 26 SCIT SR (0.1% of administrations) in 16 (0.6%) patients were recorded.

Characteristics of the patients, administered immunotherapy and SR are presented in Table 2. Patients with at least one SR had a median age of 22 years (11–50 years old), nine (56%) were male, all had rhinitis and nine (56%) also had asthma.

Ten (63%) patients were on mite immunotherapy. A polymerised extract with rush or ultra-rush schedule induction was used in 13 (81%) patients.

Twenty-one (81%) SR occurred during induction phase and all in the first seven months of immunotherapy. Eight (31%) were immediate and 12 (46%) were in the first 3 h after SCIT administration.

When grading reactions according to WAO 2010, 12 (46%) were grade 1 and 14 (54%, in nine patients) were grade 2, of which 12 (86%) were late (Table 2). Most of the grade 2 reactions occurred in individuals with asthma and presented as cough and/or dyspnoea and/or asthma exacerbation (79%). Only two (29%) patients without asthma diagnosis had grade 2 reactions, both with cutaneous manifestations associated with lower respiratory symptoms; both patients required medical care, despite the late onset. No grade 3–5 reactions were recorded. Only one patient needed treatment with intramuscular adrenaline and no biphasic reactions were registered.

One of the patients receiving pollen immunotherapy had a SR in March 2009, during a low pollen count week in Porto, while others had SR from September to November, outside the pollen season. Only two patients had a record of a local reaction in the previous administration, both with wheals $\leq$3 cm in diameter.

In six patients, a dose adjustment was made following the SR, with one patient only reaching the maintenance dose after five months. Two patients stopped immunotherapy.

Discussion

In this study, the frequency of SR to SCIT with airborne allergens (0.1% of administrations and 0.6% of patients) was similar to that reported by other recent studies in which mainly conventional induction schedules were used.[10–18] Considering that most (96%) of the extracts used in our Division are polymerised and administered in rush or ultra-rush schedules,[19] we may conclude that these formulations do not have an increased risk of SR, while allowing a faster achievement of the maintenance dose, as previously shown in immunotherapy using different rush or ultra-rush schedules.[20–22]

In the present study, none of the frequently implicated risk factors could explain the occurrence of SR. Uncontrolled asthma was identified by an unstructured symptom questionnaire and PEF measurement. Dosing errors were minimised by the registration of the administered dose in the immunotherapy record form. No patients presented with previous large local reactions, in contrast to what other authors have reported,[14,23] which may be related to the fact that these studies included hymenoptera venom immunotherapy and mostly conventional schedules with depot extracts. Also SCIT administration during pollen season has been reported as a risk factor for systemic reactions,[4,12] but during our three-year study only one patient had a SR during pollen season, and it was in a low pollen count week.

As shown by other authors,[12,24] most reactions occurred during induction or early maintenance phase. The large number of late onset reactions reported in our study, frequently with exacerbation of the patient's allergic disease on the day after the administration and most without seeking medical observation, was probably due to the fact that the patients were systematically inquired about these types of reactions before SCIT administration. These late reactions without medical confirmation may overestimate the frequency and severity of the described SR.

Table 2 Patients, immunotherapy and systemic reactions characterisation and classification according to WAO 2010 Grading System (grades 1–5).

Patient			Immunotherapy		Systemic reaction					
Age	Gender	Allergic disease	Extract	Administration	IN	Phase	Onset time	Grade	Description	Medical observation (treatment)
19	Male	Rhinitis	P. Pollen	Ultra-rush	2	Induction	Immediate	1z	Oropharyngeal pruritus, rhinorrhoea and sneezing	Yes (anti-histamine)
14	Male	Rhinitis	D. Mites	Conventional	1	Induction	Late (unknown)	1z	Sneezing	No
					2	Induction	Immediate	1z	Rhinorrhoea	Yes (anti-histamine)
29	Female	Rhinitis	D. Mites	Conventional	1	Induction	Immediate	1z	Nasal and facial pruritus and rhinorrhoea	Yes (anti-histamine)
46	Female	Asthma + Rhinitis	P. Mites	Rush	1	Induction	Late (6 h)	1z	Rhinosinusitis[a]	Yes – 1 week later
					2	Induction	Immediate	1z	Conjunctival and facial pruritus	Yes (unknown)
13	Male	Asthma + Rhinitis	D. Mites	Conventional	2	Induction	Late (2 h)	2z	Facial pruritus, nasal and conjunctival congestion	No
					3	Induction	Immediate	1z	Nasal congestion and rhinorrhoea	Yes (unknown)
					8	Induction	Late (1 day)	1z	Nasal pruritus and rhinorrhoea	No
					10	Induction	Late (1 day)	2z	Asthma exacerbation	No
22	Male	Rhinitis	P. Mites	Rush	1	Induction	Late (45 min)	1z	Oropharyngeal pruritus	No
16	Male	Rhinitis	P. Mites	Rush	4	Maintenance	Immediate	1z	Rhinorrhoea	Yes (anti-histamine)
					5	Maintenance	Late (1 day)	1z	Rhinorrhoea and sneezing[a]	No
11	Male	Asthma + rhinitis	P. Pollen	Ultra-rush	4	Maintenance	Late (unknown)	1z	Sneezing	No

Table 2 (*Continuación*)

Patient			Immunotherapy		Systemic reaction					
Age	Gender	Allergic disease	Extract	Administration	IN	Phase	Onset time	Grade	Description	Medical observation (treatment)
25	Female	Asthma + rhinitis	P. Pollen	Rush	2	Induction	Late (12 h)	2z	Cough and dyspnoea[a]	No
					3	Induction	Immediate	2z	Cough and dyspnoea	Yes (anti-histamine, IV corticosteroid)
27	Female	Asthma + rhinitis	P. Pollen	Ultra-rush	8	Maintenance	Immediate	2z	Cough	Yes (no need)
11	Male	Asthma + rhinitis	P. Pollen	Rush	3	Induction	Late (1 day)	2z	Dyspnoea	No
22	Male	Asthma + rhinitis	P. Mites	Ultra-rush	2	Induction	Late (2 days)	2z	Asthma exacerbation[a]	No
					3	Induction	Late (1 day)	2z	Asthma exacerbation[a]	No
					5	Induction	Late (1 day)	2z	Asthma exacerbation[a]	No
34	Female	Asthma + rhinitis	P. Mites	Rush	2	Induction	Late (unknown)	2z	Asthma exacerbation[a]	No
21	Female	Asthma + rhinitis	P. Mites	Ultra-rush	2	Induction	Late (8 h)	2z	Palpebral oedema, rhinorrhoea and dyspnoea[a]	No
					3	Induction	Late (1 day)	2z	Palpebral oedema, rhinorrhoea and dyspnoea[a]	No
50	Male	Rhinitis	P. Pollen	Ultra-rush	2	Induction	Late (1 h30)	2z	Generalised erythema → cough and wheezing[b]	Yes (anti-histamine, IV corticosteroid, nebulised β2-agonist)
28	Female	Rhinitis	P. Mites	Rush	7	Maintenance	Late (3 h)	2d	Generalised erythema → nasal congestion, conjunctival erythema and dyspnoea[b]	Yes (anti-histamine, IV corticosteroid, IM epinephrine)

IN: injection number; P: polymerised; D: depot; IV: intravenous; IM: intramuscular.
[a] Dose adjustment in the following administration.
[b] Stopped immunotherapy.

Table 3 Indications for immediate adrenaline administration in systemic reactions to airborne allergen subcutaneous immunotherapy.

Generalised pruritus, urticaria or flushing
Dyspnoea or wheezing with associated cutaneous or gastrointestinal symptoms, in non-asthmatic patients, or without improvement with inhaled β2-agonist
Laryngeal, uvula, or tongue oedema
Hypotension (systolic arterial pressure <90 mmHg)
Loss of consciousness

To our knowledge, this is the first European study to classify SCIT SR according to the WAO 2010 Grading System. In comparison with the American study by Phillips et al.,[24] a similar frequency of grade 1 (44%) reactions was found, although they have also reported grade 3 (6%) and grade 4 (9%) reactions.

We consider that the WAO 2010 classification has the added value of not being influenced by time of onset as, for example, the EAACI 2006 classification[8], since many of our reactions, including the most severe, were of late onset. However, we consider that this classification may not be adjusted to the subjective assessment of severity by both the patient and the physician, especially concerning SR classified as grade 2. In our population we report nine patients with grade 2 SR that can be clearly separated into two groups: first, the seven asthmatic patients with mild asthma exacerbations, most with no need for medical observation and/or treatment; and second, the two rhinitis patients who presented with generalised cutaneous symptoms and lower respiratory complaints and who, despite late presentation, required medical observation and were treated with systemic drugs. The importance of generalised cutaneous reactions, which may be the only initial symptom of anaphylaxis after specific immunotherapy, is emphasised by the 2010 Anaphylaxis Practice Parameter.[25] Also in the WAO 2010 document, it is stated that cutaneous manifestations may rapidly progress to more severe reactions,[5] despite being classified as grade 1.

In relation to the SR treatment, most were completely resolved with antihistamines and/or inhaled β2-agonists, without the need for adrenaline administration, which is not in accordance with WAO 2010 recommendations. Thus, we propose that SR presenting in the target organ implied in the patient's respiratory allergic disease can be treated with medication directed at the implied organ, while symptoms that are not usually present in that patient, such as lower respiratory complaints in a non-asthmatic or generalised cutaneous reactions in any patient, should evoke immediate medical observation and treatment with adrenaline (Table 3).

Despite only 31% of the presented SR were immediate, it is recommended to remain in observation for 30 min, especially during the induction phase, since most severe reactions, which would be classified as grades 3–5, are described in this time period.[13,15]

We reinforce the importance of informing the patients that, despite being rare, late reactions may occur. Patients should have an action plan and be advised to have their relief medication available after the 30 min observation period. They should also be advised to seek immediate medical observation in case of a more severe reaction.

We also propose that, before each SCIT administration, rhinitis and asthma control should be assessed using a validated and structured questionnaire (for example, CARAT[26]) in addition to PEF measurement; this can improve the identification of patients with uncontrolled allergic disease and may help to further minimise the risk of immunotherapy administration.

Lastly, an electronic and multicentre immunotherapy record form would be an important tool to improve the knowledge of immunotherapy administration, decrease the risk of undernotification and allow for analysis of risk factors for systemic reactions with subcutaneous immunotherapy.

In conclusion, subcutaneous immunotherapy is a safe treatment when administered by trained and equipped staff. The WAO 2010 classification of systemic reactions might be used to retrospectively classify the severity of reactions but it seems to have flaws as a tool for treatment decision. Most reactions were treated without the need for adrenaline administration; however, we emphasise the potential severity of generalised cutaneous reactions.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Disclosure

The results of this study have been partially and briefly presented at the 30th Congress of European Allergy and Clinical Immunology: Santos N, Pereira AM, Silva R, Torres da Costa J, Plácido JL. *Systemic reactions to subcutaneous immunotherapy with airborne allergens – a first characterization according to WAO's grading system*. Allergy. 2011;66(Suppl. 94):138.

Financial disclosure

None to declare.

Conflict of interest

None to declare.

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References

1. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev. 2007. CD001936.
2. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev. 2010. CD001186.
3. 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;113:1129–36.
4. Amin HS, Liss GM, Bernstein DI. Evaluation of near-fatal reactions to allergen immunotherapy injections. J Allergy Clin Immunol. 2006;117:169–75.
5. 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;125:569–74, 574.e1–7.
6. Cox L, Li J, Lockey R, Nelson H. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol. 2007;120:S25–85.
7. The European Academy of Allergology and Clinical Immunology (EAACI) Position paper: immunotherapy. Allergy. 1993;48 Suppl.:7–35.
8. 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.
9. Rede Portuguesa de Aerobiologia. Available from: http://www.rpaerobiologia.com [12.01.11].
10. Gastaminza G, Algorta J, Audicana M, Etxenagusia M, Fernandez E, Munoz D. Systemic reactions to immunotherapy: influence of composition and manufacturer. Clin Exp Allergy. 2003;33:470–4.
11. Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, Alvarez-Cuesta E. Immunotherapy safety: a prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. Clin Exp Allergy. 2004;34:527–31.
12. Dursun AB, Sin BA, Oner F, Misirligil Z. The safety of allergen immunotherapy (IT) in Turkey. J Investig Allergol Clin Immunol. 2006;16:123–8.
13. Winther L, Arnved J, Malling HJ, Nolte H, Mosbech H. Side-effects of allergen-specific immunotherapy: a prospective multi-centre study. Clin Exp Allergy. 2006;36:254–60.
14. 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;99:82–6.
15. DaVeiga SP, Caruso K, Golubski S, Lang DM. A retrospective survey of systemic reaction from allergen immunotherapy. J Allergy Clin Immunol. 2008;121 Suppl. 124.
16. Rank MA, Oslie CL, Krogman JL, Park MA, Li JT. Allergen immunotherapy safety: characterizing systemic reactions and identifying risk factors. Allergy Asthma Proc. 2008;29:400–5.
17. Serrano P, Justicia JL, Sanchez C, Cimarra M, Fernandez-Tavora L, Orovitg A, et al. Systemic tolerability of specific subcutaneous immunotherapy with index-of-reactivity-standardized allergen extracts administered using clustered regimens: a retrospective, observational, multicenter study. Ann Allergy Asthma Immunol. 2009;102:247–52.
18. Schiappoli M, Ridolo E, Senna G, Alesina R, Antonicelli L, Asero R, et al. A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. Clin Exp Allergy. 2009;39:1569–74.
19. Santos N, Pereira AM, Plácido JL, Castel-Branco MdG. Subcutaneous specific immunotherapy: local and systemic reactions. Allergy. 2010;65 Suppl.92:568.
20. Casanovas M, Martin R, Jimenez C, Caballero R, Fernandez-Caldas E. Safety of an ultra-rush immunotherapy build-up schedule with therapeutic vaccines containing depigmented and polymerized allergen extracts. Int Arch Allergy Immunol. 2006;139:153–8.
21. Smits WL, Giese JK, Letz KL, Inglefield JT, Schlie AR. Safety of rush immunotherapy using a modified schedule: a cumulative experience of 893 patients receiving multiple aeroallergens. Allergy Asthma Proc. 2007;28:305–12.
22. Brehler R, Klimek L, Pfaar O, Hauswald B, Worm M, Bieber T. Safety of a rush immunotherapy build-up schedule with depigmented polymerized allergen extracts. Allergy Asthma Proc. 2010;31:e31–8.
23. Calabria CW, Stolfi A, Tankersley MS. The REPEAT study: recognizing and evaluating periodic local reactions in allergen immunotherapy and associated systemic reactions. Ann Allergy Asthma Immunol. 2011;106:49–53.
24. Phillips JF, Lockey RF, Fox RW, Ledford DK, Glaum MC. Systemic reactions to subcutaneous allergen immunotherapy and the response to epinephrine. Allergy Asthma Proc. 2011;32:288–94.
25. Simons FE, Ardusso LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol. 2011;127, 587–93.e1–22.
26. Fonseca JA, Nogueira-Silva L, Morais-Almeida M, Azevedo L, Sa-Sousa A, Branco-Ferreira M, et al. Validation of a questionnaire (CARAT10) to assess rhinitis and asthma in patients with asthma. Allergy. 2010;65:1042–8.