edra | Issn 1764-1489 | Volume 55 N. 3/2023 – May 2023

European Annals of Allergy and Clinical Immunology

THE OFFICIAL JOURNAL OF AAIITO | ASSOCIAZIONE ALLERGOLOGI IMMUNOLOGI ITALIANI TERRITORIALI E OSPEDALIERI
THE OFFICIAL JOURNAL OF SPAIC | SOCIEDADE PORTUGUESA DE ALERGOLOGIA E IMUNOLOGIA CLINICA

3/2023

www.eurannallergyimm.com

European Annals of Allergy and Clinical Immunology

The online submission system

European Annals of Allergy and Clinical Immunology uses an online submission and review system for all papers evaluation.
Electronic submission allows a more efficient processing of manuscripts and offers Authors the option to track the progress of the review process whenever they need to. The link to the editorial system is http://eaaci.edmgr.com, it is also available on the Journal website: ***www.eurannallergyimm.com***.

The Authors are invited to submit their manuscripts through the online editorial system; manuscripts sent by e-mail, post or fax are not considered for publication.
All the Authors should read carefully the Guide for Authors before starting their submissions. Full information about the manuscript preparation are available on the Journal website. During submission, Authors will be first asked to select the article type, enter the manuscript title and provide Author information. Through a menu, a general topic area should be selected: these will help to match manuscripts to the best available editors and reviewers.Reviewers will access papers via the editorial system platform and will be invited and sent to it by email.

Full Authors Guidelines and the online Submission System link, are available on the Journal website:

www.eurannallergyimm.com

European Annals of Allergy and Clinical Immunology

www.eurannallergyimm.com

THE OFFICIAL JOURNAL OF AAIITO
ASSOCIAZIONE ALLERGOLOGI IMMUNOLOGI ITALIANI TERRITORIALI E OSPEDALIERI

THE OFFICIAL JOURNAL OF SPAIC
SOCIEDADE PORTUGUESA DE ALERGOLOGIA E IMUNOLOGIA CLINICA

edra

Editors in Chief and Managing Directors

Maria Beatrice Bilò
P. Carreiro-Martins

Chief Executive Officer

Ludovico Baldessin

Editorial Coordinator

Barbara Moret

Publishing Editor

Jessica Guenzi
j.guenzi@lswr.it
Ph. 039 (0)2-89293.926

Production Manager

Paolo Ficicchia
p.ficicchia@lswr.it
Ph. 0039 (0)2-88184.222

Sales

dircom@lswr.it

Subscription

abbonamentiedra@lswr.it
Ph. 0039 (0)2-88184.317
Italy subscription: 60 euro
World subscription: 85 euro

Printing

Rotomail Italia S.p.A., Strada Rivoltana (SP 14), 12/AB 20060 Vignate (MI), Italy

EDRA SpA

Via G. Spadolini, 7
20141 Milano - Italy
Tel. 0039 (0)2-88184.1
Fax 0039 (0)2-88184.301
www.edizioniedra.it

"European Annals of Allergy and Clinical Immunology" registered at Tribunale di Milano - n. 336 on 22.10.2014

We are Crossref Sponsored Member

The contents of this Journal are indexed in PubMed, Scopus, Embase and Web of Science®

Table of Contents

Eur Ann Allergy Clin Immunol Vol 55, N.3, 101-114, 2023

Edward Balai[1], Keshav Kumar Gupta[2], Karan Jolly[2], Adnan Darr[3]

Posterior nasal nerve neurectomy for the treatment of rhinitis: a systematic review and meta-analysis

[1]University Hospitals Coventry & Warwickshire, NHS Trust, U.K.
[2]University Hospitals Birmingham, NHS Foundation Trust, U.K.
[3]The Royal Wolverhampton Hospitals, NHS Trust, U.K.

Key words

Allergy; rhinology; chronic rhinitis; posterior nasal nerve; neurectomy.

Corresponding author
Edward Balai
University Hospitals Coventry & Warwickshire NHS Trust
Clifford Bridge Road
Coventry, CV2 2DX, U.K.
ORCID: 0000-0003-1086-1552
E-mail: edward.balai@nhs.net

Doi
10.23822/EurAnnACI.1764-1489.268

Impact statement

This systematic review shows there is some limited evidence to suggest posterior nasal nerve neurectomy can improve rhinitis symptoms in adult patients, and the incidence of serious adverse events associated with posterior nasal nerve ablation appears to be low.

Summary

Background. *Posterior nasal nerve neurectomy (PNNN) is a surgical option for the treatment of refractory chronic rhinitis. It can be performed by surgical dissection, cryotherapy, or laser ablation. This systematic review aimed to assess the effect of PNNN on Total Nasal Symptom Score (TNSS) in adults with chronic rhinitis.* ***Methods.*** *A systematic review of EMBASE, MEDLINE, PubMed and ClinicalKey databases was conducted in November 2021. Studies reporting PNNN performed as a single procedure in adult patients with allergic, non-allergic or mixed chronic rhinitis, and TNSS as the outcome measure, were included.* ***Results.*** *Database search identified 39 articles, of which 8 (463 patients) were included in the review. Two were randomized sham-controlled trials and six were prospective single-arm, unblinded and uncontrolled studies. Pooled analysis of data from the two randomized controlled trials found active treatment was associated with a significantly greater response ≥ (30% reduction in TNSS from baseline) rate (OR 3.85, 95%CI 2.23-6.64, $p < 0.00001$).* ***Conclusions.*** *This systematic review identified there is some limited evidence to suggest cryotherapy or radiofrequency ablation of the posterior nasal nerve can improve TNSS in adult patients. However, this is from a limited number of trials with short follow-up. Future research should focus on prospective randomized controlled trials with larger numbers of participants and medium to long term follow up in order to help draw more valid conclusions regarding the true effectiveness of PNNN in this patient cohort.* ***Study registration.*** *The systematic review was registered prospectively on the PROSPERO database in July 2021 (ID: CRD42021270486).*

Introduction

Rhinitis is chronic condition characterized by inflammation of the nasal mucosa, associated with symptoms of congestion, rhinorrhea, sneezing, pruritis that are present for at least 12 weeks per year. It has a global prevalence of 30% (1), affecting 10-20% of adults in the United Kingdom (UK) and United States of America (USA) (2, 3), and can lead to a significant reduction in quality of life and high health-care utilization. Whilst medical therapy remains the mainstay of management, approximately 10-22% of patients will be refractory to such intervention (4). Surgical options include inferior turbinate surgery in combination with vidian neurectomy (VN) or posterior nasal nerve neurectomy (PNNN), of which the latter two aim to eliminate the parasympathetic autonomic supply to the nasal mucosa (5). PNNN differs from VN by targeting only the post-ganglionic posterior nasal branches as they exit the sphenopalatine foramen. This modification is thought to be a safer technique with a lower incidence of complications such as cheek and palatal numbness, and dry eyes (6).

PNNN can be performed either by surgical dissection and nerve resection, cryotherapy, radiofrequency, and laser ablation. These

ablative techniques were first described in 2017 and are primarily performed endoscopically under local anesthesia. The lateral nasal wall at the posterior middle meatus is targeted with either liquid nitrogen, radiofrequency energy, or a diode laser to produce local neural tissue ablation (7, 8).

Total Nasal Symptom Score (TNSS) is a patient-assessed symptom questionnaire which evaluates the severity of the main symptoms of rhinitis: rhinorrhea, nasal congestion, nasal itching, and sneezing. The patient retrospectively reflects on the severity of each symptom over the preceding 12 hours and evaluates it using a scale of 0 − No symptoms, 1 − Mild, 2 − Moderate, or 3 − Severe. The TNSS is calculated as the sum of the individual scores. When considering changes in TNSS, a reduction from baseline of ≥ 1 is considered the minimal clinically important difference (MCID) (9).

We aimed to evaluate the existing literature through a systematic review to assess the effect of PNNN on the TNSS in adult patients with chronic rhinitis, and the safety profile of this treatment when performed as a single procedure.

Methods

Study design

A systematic review and descriptive analysis were performed of all published data related to the management of rhinitis with PNNN as a single procedure. The protocol for the systematic review was registered prospectively on the PROSPERO database in July 2021 (ID: CRD42021270486). We report our findings in accordance with PRISMA reporting guidelines (10).

Search strategy

Electronic searches of the following databases: EMBASE (1974-January 2021), MEDLINE (1946-January 2021), PubMed, Cochrane Library, ClinicalTrials.gov (via Cochrane) and ClinicalKey (1946-January 2021), were systematically conducted for articles written in English in November 2021. Databases were accessed through the University of Hospitals Birmingham NHS Trust library with the assistance of an Information Specialist Librarian. The full search terms can be found in **table I**.

Table I *- Full electronic database search strategy.*

Database	Search term	Results
Medline	(posterior nasal nerve).ti,ab	364
	(endoscopic).ti,ab	159,366
	Endoscopy/	53,772
	(2 OR 3)	183,613
	(section).ti,ab	164,990
	(ablation).ti,ab	97,334
	(division).ti,ab	102,612
	(5 OR 6 OR 7)	363,030
	(1 AND 4 AND 8)	4
	(1 AND 4)	56
	(posterior nasal nerve).ti,ab [Humans]	238
	(posterior nasal neurectomy).ti,ab	22
	(endoscopic posterior nasal neurectomy).ti,ab	8
EMBASE	(posterior nasal nerve).ti,ab	29
	(endoscopic).ti,ab	257,229
	ENDOSCOPY/	110,560
	(section).ti,ab	220,230
	(ablation).ti,ab	149,430
	(division).ti,ab	122,705
	(13 OR 14)	319,841
	(15 OR 16 OR 17)	489,353
	(12 AND 18 AND 19)	4
	(posterior nasal neurectomy).ti,ab	20
	(endoscopic posterior nasal neurectomy).ti,ab	7
PubMed	(posterior nasal nerve).ti,ab	31
	(section).ti,ab	509,387
	(ablation).ti,ab	108,215
	(division).ti,ab	199,6906
	(endoscopic).ti,ab	470,758
	(posterior nasal neurectomy).ti,ab	17
	(endoscopic posterior nasal neurectomy).ti,ab	5

Study selection

Following the initial search, duplicated articles were excluded. All subsequent articles were independently screened by two authors (EB/AD) according to their titles and abstracts for eligibility against the inclusion and exclusion criteria. Discrepancies were reviewed by a third author (KKG). All studies that reported data from any single modality of PNNN for adult patients with allergic, non-allergic or mixed rhinitis were included. Studies were included if they reported on procedure efficacy (comparison of pre- and post-operative TNSS) and safety (reported adverse events). Articles unavailable in English or as a full text, conference abstracts, combination procedures and articles reporting data in a pediatric population (< 18 years) were excluded.

Data extraction

Data extraction was performed independently by two authors (EB/KKG), with any discrepancies resolved by a third author (AD). Primary outcome measures were 1) a change in post-procedure TNSS (efficacy endpoint) and 2) reported adverse events

(safety endpoint). Any other efficacy endpoints reported in the data were also extracted. Data was also extracted pertaining to study design, patient demographics, and procedure details.

Statistical analysis

A descriptive report with summary data tables was produced to summarize the literature. For the randomized controlled trials, a weighted estimate of the treatment effects across trials as odds ratios (OR) and respective 95% confidence intervals using a Mantel-Haenzel random-effects model for all outcome events was calculated. Results were deemed statistically significant at $p < 0.05$. Heterogeneity was tested for using the I^2 statistic to quantify the percentage of total variation across studies. The amount of heterogeneity as "low", "moderate" or "high" for I^2 values of 25%, 50% and 75% respectively. Statistical analysis and meta-analysis were performed using Review Manager 5.4.

Risk of bias scoring

Two reviewers (EB/KKG) independently assessed the non-randomized studies for risk of bias using the ROBINS-I tool (11) and the randomized studies for risk of bias using the RoB 2 tool (12). Discrepancies were resolved with arbitration by a third reviewer (AD).

Results

Study selection

The study selection process is detailed in **figure 1**. Our electronic database search identified 39 articles, with no duplicates. After primary screening based on the title and abstract, 12 articles remained for eligibility screening based on the full text. A further four articles were excluded based on the exclusion criteria. Eight full texts were subsequently included in our qualitative and quantitative analysis.

Study characteristics

Study design and baseline characteristics are summarized in **table II**. Six included studies were prospective, pre-post, single-arm studies and two were randomized, sham-controlled, single-blinded trials. Except for the single-center study by Krespi *et al.* (13), all were multi-center studies. Del Signore *et al*. used variable block size distribution by site with a 1:1 allocation (15). Stolovitzky *et al*. used a 2:1 site-stratified block randomization (16). In both RCTs the patients were blinded to their assignment and blindfolded during the treatment. All were carried out in the USA and six out of the eight had industry sponsorship. Follow up periods varied between 3 months (13-16), 9 months (17), 12 months (18, 19), and 24 months (20).

Participants

The included studies represented 463 participants. In the seven studies that reported on patient demographics, the average age ranged from 53.3 years (18) to 60 years (14). Gender split ranged from 35% male (16) to 50% male (19). Chang *et al*. (17) and Ow *et al*. (20) reported results from the same patient cohort (pilot data and longer term follow up respectively).

All eight studies included patients with allergic, non-allergic or mixed sub-types of rhinitis, although. Stolovitzky *et al*. included patients with chronic rhinitis > 6 months, moderate-to-severe symptoms of rhinorrhea, mild-to-severe nasal congestion and a total TNSS ≥ 6, and did not perform allergy testing (16). Patients who had prior procedures or surgery for chronic rhinitis were excluded. Del Signore *et al*. included patients with moderate-to-severe symptoms of chronic rhinitis and a total TNSS ≥ 4 (15). They also excluded patients who had prior procedures or surgery for chronic rhinitis. Chang *et al*. (17) and Ow *et al*. (20) specified that symptoms must have been present for a minimum of 6-months, with a total TNSS ≥ 4. Yen *et al*. included patients with moderate-to-severe rhinorrhea and mild-to-severe nasal congestion symptoms for at least 3 months (14). Krespi *et al*. included patients with chronic rhinitis and nasal congestion but did not detail a minimum required symptom duration (13). Gerka Stuyt *et al.* specified that patients must have had failure of trial of medical therapy for at least 3 months (19). Four studies required patients to discontinue ipratropium bromide at least 3-days pre-procedure and throughout the follow up period (14, 15, 17, 20).

Intervention

Bilateral PNNN was performed as a single procedure in all studies, using a single surgical modality of either cryotherapy (14, 15, 17-20), radiofrequency (16), or continuous wave laser (13) (**table III**). Five studies used ClariFix (Stryker ENT, Plymouth MN, USA) to perform the cryoablation endoscopically in line with the manufacturer's guidance (14, 15, 17, 18, 20). In the sham control arm of the study by Del Signore *et al*. the cryoprobe was held in place while a separate device with a canister loaded was held near the participant and activated to provide the sound of gas release (15). Gerka Stuyt *et al*. did not report details of the specific device they used for cryoablation (19). Krespi *et al*. used a 940 nm diode laser (Epic-S, Biolase, Irvine CA) with a 400-micron malleable fiber tip, with continuous wave laser (5W, non-contact mode for 10-15 seconds) (13). Stolovitsky *et al*. used the RhinAer System (Aerin Medical, Sunnyvale CA, USA) to perform radiofrequency neurolysis in patients in the active arm. For the patients in the sham arm the stylus was identically applied to the tissue and sounds mimicking the treatment were played but no radiofrequency energy was delivered (16). Procedures were performed primarily under local anesthesia (13-20), however in the study by Krespi *et al*., a small cohort required sedation (13). All studies involved bilateral treatment, either at single (posterior middle meatus) (13, 15, 17-20) or multiple sites (middle and inferior meatus) (14, 16).

Figure 1 *- Study selection process of included articles.*

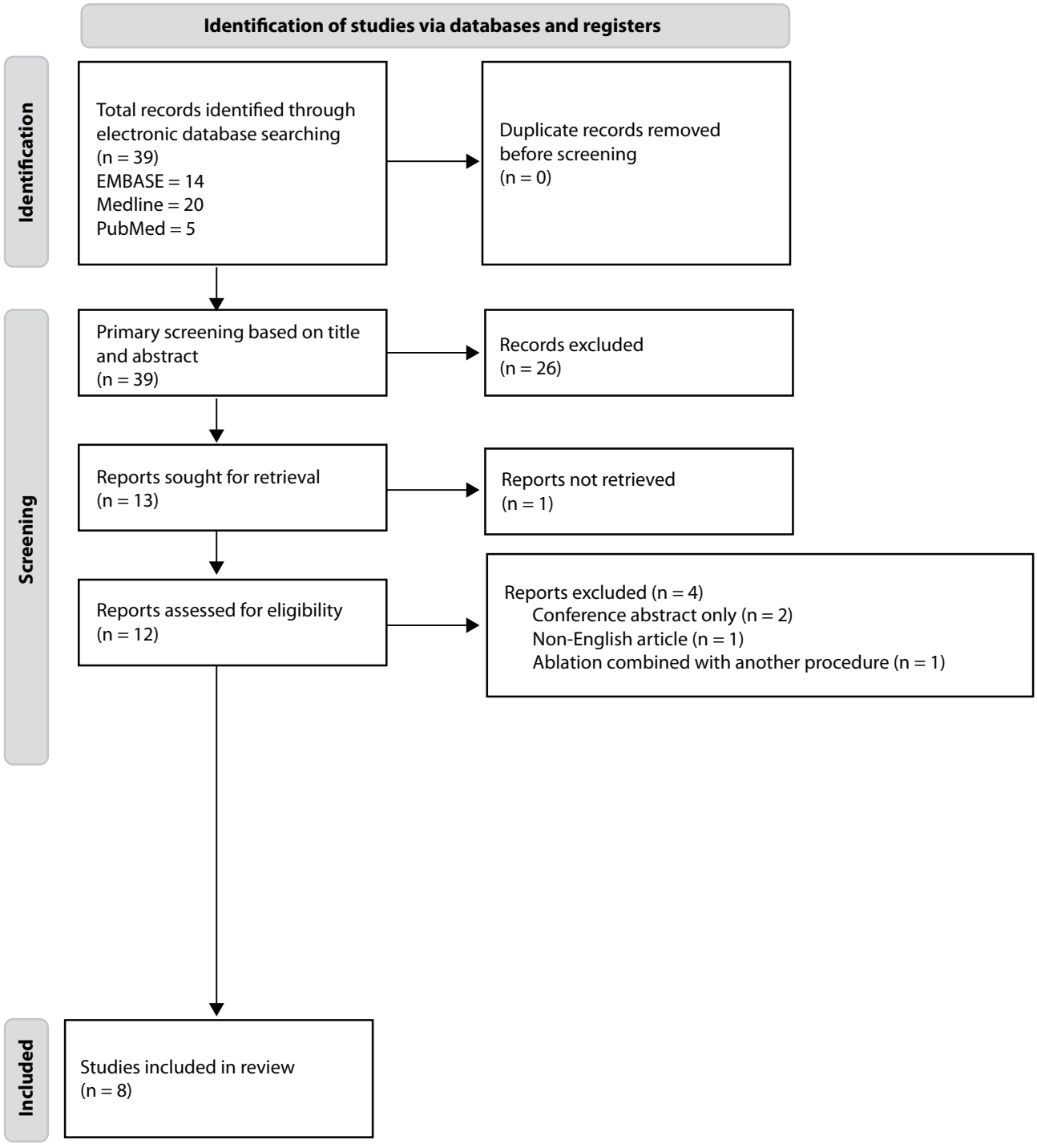


Table II *- Study design and baseline characteristics of all included studies and participants.*

Study	Design	Funding/ sponsorship	n	Age (years)	Gender (M:F)	Inclusion criteria	Allergic/non-allergic	Pre-procedure medical therapy (n, %)
Hwang, 2017	Pre-post study, prospective, single-arm	Arrinex Inc. (Stryker ENT)	27	53.3 ± 3.3	10 : 17	Adult patients only TNSS rhinorrhea score ≥ 2 TNSS nasal congestion score ≥2	Allergic: 13 Non-allergic: 13 Unknown: 1	Not reported
Chang, 2020	Pre-post study, prospective, single-arm	Stryker Corp.	100	58.6 ± 16.2	35 : 63	Adult patients only Symptoms for > 6 months Symptoms not controlled with ≥ 4 weeks INCS TNSS rhinorrhea score 2 or 3 TNSS nasal congestion score 1, 2 or 3 Total TNSS ≥ 4	Allergic: 28 Non-allergic: 70	Oral steroid: 5 INCS: 40 Oral antihistamines: 33 Intra-nasal antihistamine: 8 Saline rinse: 39 Oral alpha-agonist: 8 Intra-nasal alpha-agonist: 6 Oral antileukotriene: 15 Ipratropium bromide discontinued 3 days before procedure and throughout follow up
Yen, 2020	Pre-post study, prospective, single-arm	Arrinex Inc. (Stryker ENT)	30	60 ± 15.8	14 : 16	Adult patients only Moderate-to-severe rhinorrhea Mild-to-severe nasal congestion Symptoms for > 3 months	Allergic: 11 Non-allergic: 17	Not reported Ipratropium bromide discontinued 3 days before procedure and throughout follow up
Krespi, 2020	Pre-post study, prospective, single-arm	No financial support	32	Not reported	Not reported	Adult patients only Chronic rhinitis and nasal congestion	Allergic and non-allergic included Specific numbers not reported	Not reported

Study	Design	Funding/ sponsorship	n	Age (years)	Gender (M:F)	Inclusion criteria	Allergic/non-allergic	Pre-procedure medical therapy (n, %)
Ow, 2021	Pre-post study, prospective, single-arm	Stryker ENT	100	57.1 ± 13.4	36 : 64	Adult patients only Chronic rhinitis for > 6 months Failure of trial of medical therapy for > 1 month	Allergic: 19 Non-allergic: 43	Not reported Ipratropium bromide discontinued 3 days before procedure and throughout follow up
Stuyt, 2021	Pre-post study, prospective, single-arm	No financial support	24	60 (25-91)	12 : 12	Adult patients only Failure of trial of medical therapy for > 3 months	Allergic: 3 Non-allergic: 16 Mixed: 5	Anti-cholinergic: 13 Steroid: 14 Antihistamines: 9 Saline rinse: 5
Stolovitzky, 2021	Randomized, sham-controlled trial, multicentre, prospective, single-blinded	Aerin Medical	117 Active (78) Control (39)	Active treatment: 57.3 ± 14.8 Sham control: 57.8 ± 14.4	Active treatment: 28 : 49 Sham control: 13 : 26	Patients aged 18-85 years Chronic rhinitis for > 6 months TNSS rhinorrhea score 2 or 3 TNSS nasal congestion score 1, 2 or 3 Total TNSS ≥6 Excluded patients with prior procedures or surgery for chronic rhinitis	Allergy testing not performed. Seasonal allergic rhinitis excluded.	Active treatment arm Antihistamines: 56 (72.7) Decongestants: 22 (28.6) Oral leukotriene inhibitors: 4 (5.2) Intra-nasal steroid sprays: 34 (44.2) Intra-nasal anticholinergic sprays: 19 (24.7) Sham control arm Antihistamines: 28 (71.8) Decongestants: 10 (25.6) Oral leukotriene inhibitors: 3 (7.7) Intra-nasal steroid sprays: 26 (66.7) Intra-nasal anticholinergic sprays: 8 (20.5)
Del Signore, 2021	Randomized, sham-controlled trial, multicentre, prospective, single-blinded	Stryker ENT	133 Active (68) Control (65)	Active treatment: 52.3 ± 15.8 Sham control: 58.3 ± 16.4	Active treatment: 23 : 45 Sham control: 33 : 32	Patients aged ≥ 21 years Moderate-to-severe symptoms of chronic allergic or non-allergic rhinitis TNSS rhinorrhoea score ≥ 2 TNSS nasal congestion score ≥1 Total TNSS ≥ 4 Excluded patients with prior procedures or surgery for chronic rhinitis	Allergy test within 12 months of baseline Active treatment: Allergic 29 Non-allergic 39 Sham control: Allergic 28 Non-allergic 37	Active treatment arm Antihistamines: 20 (29.4) Antihistamine/steroid: 2 (2.9) Decongestant: 2 (2.9) Immunotherapy: 0 Intra-nasal steroid sprays: 16 (23.5) Ipratropium bromide: 0 Leukotriene inhibitors: 5 (7.4) Saline lavage: 5 (7.4) Sham control arm Antihistamines: 26 (40) Antihistamine/steroid: 0 Decongestant: 2 (3.1) Immunotherapy: 2 (3.1) Intra-nasal steroid sprays: 13 (20) Ipratropium bromide: 0 Leukotriene inhibitors: 3 (4.6) Saline lavage: 1 (1.5)

*TNSS: Total Nasal Symptom Score; INCS: intra-nasal corticosteroid.

Table III *- Summary of results from individual studies.*

Study	Surgical Modality	Site	Anesthetic	Pre-operative TNSS	Post-operative TNSS	Follow up
Hwang, 2017	Cryotherapy	Posterior middle meatus Bilateral	LA	All patients: 6.2 ± 0.5 (n = 27)	7 d: 4.3 ± 0.4* (n = 27) 30 d: 2.6 ± 0.3* (n = 27) 90 d: 2.7 ± 0.4* (n = 27) 180 d: 2.3 ± 0.5* (n = 21) 365 d: 1.9 ± 0.3* (n = 15)	365 days
				Allergic: not reported (n = 13)	30 d: 2.5 ± 0.6* (n = 13) 90 d: 3.1 ± 0.6* (n = 13) 180 d: 2.7 ± 0.9 (n = 10) 365 d: 2.5 ± 0.6* (n = 6)	
				Non-allergic: 6.5 ± 0.7 (n = 13)	30 d: 2.6 ± 0.3* (n = 13) 90 d: 2.4 ± 0.4* (n = 13) 180 d: 1.7 ± 0.4* (n = 10) 365 d: 1.6 ± 0.4* (n = 9)	
Chang, 2020	Cryotherapy	Posterior middle meatus Bilateral	LA	All patients: 6.1 ± 1.9 (n = 98)	30 d: 2.9 ± 1.9* (n = 97) 90 d: 3.0 ± 2.3* (n = 96) 180 d: 3.0 ± 2.1* (n = 95) 270 d: 3.0 ± 2.4* (n = 92)	270 days
Yen, 2020	Cryotherapy	Middle meatus Inferior meatus Bilateral	LA	All patients: 7.0 (5.0-9.0) (n = 30)	1 month: 3.5 (2.0-6.0)* (n = 30) 3 months: 2.5 (2.0-5.0)* (n = 30)	3 months
Krespi, 2020	Laser	Posterior middle meatus Bilateral	LA (n = 21) Sedation (n=11)	All patients: 6.0 ± 0.7 (n = 32)	30 d: "60% improvement in TNSS" (n = 32) 90 d: 2.3 ± 0.4* (n = 32)	90 days
Ow, 2021	Cryotherapy	Posterior middle meatus Bilateral	LA	All patients: 6.0 (5.0-7.0) (n = 91)	12 months: 3.0 (1.0-4.0)* (n = 91) 18 months: 2.0 (1.0-4.0)* (n = 57) 24 months: 2.0 (1.0-4.0)* (n = 57)	24 months

Study	Surgical Modality	Site	Anesthetic	Pre-operative TNSS	Post-operative TNSS	Follow up
Stuyt, 2021	Cryotherapy	Posterior middle meatus Bilateral	LA	All patients: 12 hr: 6.92 ± 2.8 2 wk: 7.75 ± 3.1 (n = 24)	12 hr TNSS 30 d: 3.17 ± 2.4* (n = 24) 90 d: 2.92 ± 1.4* (n = 24) 1 yr: 3.08 ± 2.6* (n = 18) 2 wk TNSS 30 d: 3.79 ± 2.1* (n = 24) 90 d: 3.88 ±1.8* (n = 24) 1 yr: 3.76 ± 2.1* (n = 18)	12 months
				Allergic: 12 hr: 6.67 ± 3.2 2 wk: 8.67 ± 2.5 (n = 3)	12 hr TNSS 30 d: 2.67 ± 2.5 (n = 3) 90 d: 1.33 ± 1.5 (n = 3) 1 yr: 2.6 ± 0.6 (n = 1) 2 wk TNSS 30 d: 2.33 ± 2.5 (n = 3) 90 d: 1.67 ± 2.0 (n = 3) 1 yr: 3.3 ± 1.1* (n = 1)	
				Non-allergic: 12 hr: 7.1 ± 3.1 2 wk: 7.75 ± 3.6 (n = 16)	12 hr TNSS 30 d: 3.0 ± 2.0* (n = 16) 90 d: 3.5 ± 1.0* (n= 16) 1yr: 3.13 ± 3.0* (n=12) 2 wk TNSS 30 d: 4.21 ± 1.7* (n = 16) 90 d: 4.56 ± 1.7* (n = 16) 1 yr: 3.94 ± 2.4* (n = 12)	
				Mixed: 12 hr: 6.4 ± 2.1 2 wk: 7.2 ± 1.6 (n = 5)	12 hr TNSS 30 d: 4.0 ± 3.6 (n = 5) 90 d: 2.0 ± 1.2* (n = 5) 1 yr: 3.2 ± 2.2 (n=5) 2 wk TNSS 30 d: 3.4 ± 3.0* (n = 5) 90 d: 3.3 ± 0.8* (n = 5) 1 yr: 4.0 ± 1.4* (n = 5)	

Study	Surgical Modality	Site	Anesthetic	Pre-operative TNSS	Post-operative TNSS	Follow up
Stolovitzky, 2021	Radiofrequency	Posterior middle meatus Superior portion of posterior inferior turbinate Bilateral	LA	Active treatment arm: (n = 77) Mean TNSS 8.3 ± 1.9 Rhinorrhea 3 (IQR 2-3) Congestion 3 (IQR 2-3) Itching 2 (IQR 1-2) Sneezing 2 (IQR 1-2) Sham control arm: (n = 39) Mean TNSS 8.2 ± 1.8 Rhinorrhoea 3 (IQR 2-3) Congestion 3 (IQR 2-3) Itching 1 (IQR 1-2) Sneezing 2 (IQR 1-3)	Responder rate: Active arm 67.5% (95%CI 55.9%-77.8%)* Sham control 41.0% (95%CI 25.6%-57.9%)* Reduction in total TNSS: Active arm -3.6 (95%CI -4.2 to -3.0)* Sham control -2.2 (95%CI -3.2 to -1.3)* Rhinorrhea scores change at 3 months: Active arm -1 (IQR -2 to 0)* Sham control 0 (IQR -2 to 0)* Congestion scores change at 3 months: Active arm -1 (IQR -2 to 0)* Sham control 0 (IQR -1 to 0)* Itching scores change at 3 months: Active arm -1 (IQR -1 to 0) Sham control 0 (IQR -1 to 0) Sneezing scores change at 3 months: Active arm -1 (IQR -1 to 0) Sham control -1 (IQR -1 to 0)	3 months
Del Signore, 2021	Cryotherapy	Posterior middle meatus Bilateral	LA	Active treatment arm: (n = 68) Mean rTNSS 8.0 ± 1.8 Rhinorrhea 2.6 ± 0.5 Congestion 2.3 ± 0.8 Itching 1.5 ± 0.8 Sneezing 1.8 ± 0.7 Sham control arm: (n = 65) Mean rTNSS 8.1 ± 1.9 Rhinorrhea 2.4 ± 0.5 Congestion 2.4 ± 0.7 Itching 1.5 ± 0.9 Sneezing 1.8 ± 0.8 Use of allergy/rhinitis medications: Active arm 32 (47.1%) Sham arm 32 (49.2%)	Responder rate: Active arm 47/64 (73.4%)* Sham control 23/63 (36.5%)* Reduction in total TNSS: Active arm -3.7 (95%CI -4.3 to -3.1)* Sham control -1.8 (95%CI -2.5 to -1.1)* Rhinorrhea scores change at 90 d: Active arm -1.2 (95%CI -1.4 to -1.0)* Sham control -0.4 (95% CI -0.6 to -0.2)* Congestion scores change at 90d: Active arm -1.2 (95%CI -1.4 to -1.0)* Sham control -0.6 (95%CI -0.8 to -0.4)* Itching scores change at 90 d: Active arm -0.7 (95%CI -0.9 to -0.5) Sham control -0.4 (-0.7 to -0.1) Sneezing scores change at 90d: Active arm -0.6 (95%CI -0.8 to -0.4) Sham control -0.5 (95%CI -0.7 to -0.2) Use of allergy/rhinitis medication: Active arm 26 (40.0%) Sham arm 22 (34.4%)	90 days

*TNSS: Total Nasal Symptom Score; LA: local anesthetic; *p < 0.05.

Primary outcomes

In the pre-post single-arm studies the primary outcome was a change in TNSS from pre-operative baseline, to varying intervals of post-operative follow-up. Whereas in the two randomized sham-controlled trials the primary outcome was responder rate at follow-up, where a response was defined as a ≥ 30% improvement (decrease) in TNSS from baseline.

Gerka Stuyt *et al*. adopted a 5-item TNSS, with an additional sub-domain focused on the effect on sleep, at each measure of TNSS they asked participants for one score based on a 12-hour period of retrospective reflection and one based on a 2-week period (19). All other studies used a standard 4-item TNSS and did not specify the exact time frame patients were asked to reflect upon to calculate this (13-18, 20). All studies reported the occurrence of any adverse events (**table IV**).

Change in the use of medication was measured at 12-months by Gerka Stuyt *et al*. (19), at 90 days by Del Signore *et al*. (15) and Stolovitzky *et al*. (16), 60 days by Krespi *et al*. (13), and at all follow up visits by Chang *et al*. (17). Timing of outcome measures ranged from 7 days to 2 years post-procedure.

Results of individual studies

Hwang *et al*. reported the results of cryotherapy ablation at the posterior middle meatus in 27 patients (18). Six patients were lost to follow up at 180 days and twelve patients at 365 days. Baseline mean TNSS was 6.2 (SD 0.5). They reported a statistically significant decrease between pre-operative and post-operative mean TNSS of -3.6 (SE 0.11) at 30 days, -3.5 (SE 0.12) at 90 days, -3.9 (SE 0.15) at 180 days, and -4.3 (SE 0.14) at 365 days. Baseline pre-operative TNSS for patients in the allergic rhinitis sub-group was not reported. In the non-allergic rhinitis sub-group (n = 13) there was a statistically significant decrease between pre-operative and post-operative mean TNSS of -3.9 (SE 0.21) at 30 days, -4.1 (SE 0.22) at 90 days, -4.8 (SE 0.25) at 180 days, and -4.9 (SE 0.26) at 365 days. There were a total of 17 adverse events (**table IV**).

Chang *et al.* reported the results of cryotherapy ablation at the posterior middle meatus in 100 patients, with longer term follow up of these patients reported by Ow *et al.* (17, 20). Five patients were excluded and only 62 patients consented to long-term follow up, with a further 3 lost to follow up at 18 months and 24 months. Baseline mean TNSS was 6.1 (SD 1.9). Chang *et al*. reported statistically significant reduction between pre-operative and post-operative mean TNSS of -3.2 (SE 0.27) at 30 days, -3.1 (SE 0.30) at 90 days, -3.1 (SE 0.29) at 180 days, and -3.1 (SE 0.31) at 270 days. Specific data for allergic and non-allergic rhinitis sub-groups was not included in the paper. In the post-operative period 21.4% (n = 33) pre-operative medical therapies were discontinued. However, 59 medications were also newly initiated in the follow up period. Ow *et al.* reported a statistically significant reduction in median TNSS of -3.0 (IQR 1.0-4.0) at 365 days, and of -4.0 (IQR 1.0-4.0) at 548 and 730 days. There was a statistically significant difference in median change between participants with pre-operative TNSS values of > 7 compared to those with values < 7, with higher pre-operative scores associated with increased reduction in median TNSS at all follow up time points except 365 days and 730 days. There was a total of 31 treatment-related adverse events reported (**table IV**).

Yen *et al*. reported the results of cryotherapy ablation at the middle and inferior meatus in 30 patients (14). Baseline median TNSS was 7.0 (IQR 5.0- 9.0). They reported a statistically significant reduction between pre-operative and post-operative median TNSS of -3.5 (IQR 2.0-6.0) at 30 days, and of -4.5 (IQR 2.0-5.0) at 90 days. They reported a total of 30 non-serious adverse events (**table IV**).

Krespi *et al*. reported the results of continuous wave laser ablation at the posterior middle meatus in 30 patients (13). Baseline mean TNSS was 6.0 (SD 0.7). At 30 days follow-up they reported that there had been a 60% improvement in the TNSS but did not include the full data in their paper. They reported a statistically significant reduction between pre-operative and post-operative mean TNSS of -3.7 (SE 0.14) at 90 days. The authors reported that at 60 days follow up there had been a 60% reduction in medication use. There were no reported adverse events.

Gerka Stuyt *et al*. reported the results of cryotherapy ablation at the posterior middle meatus in 24 patients (19). Six patients were lost to follow up at 365 days. Baseline mean 12-hour TNSS was 6.92 (SD 2.8) and mean 2-week TNSS was 7.75 (SD 3.1). They reported a statistically significant reduction between pre-operative and post-operative mean 12-hour TNSS of -3.75 (SE 0.75) at 30 days, -4.0 (SE 0.64) at 90 days, and -3.84 (SE 0.85) at 365 days. There was also a statistically significant reduction between pre-operative and post-operative mean 2-week TNSS of -3.96 (SE 0.76) at 30 days, -3.87 (SE 0.72) at 90 days, and -3.99 (SE 0.85) at 365 days. In the allergic rhinitis sub-group (n = 3), there was a statistically significant reduction between pre-operative and post-operative mean 2-week TNSS of -5.37 (SD 1.1) at 365 days. In the non-allergic rhinitis sub-group (n = 16), they reported a statistically significant reduction between pre-operative and post-operative mean 12-hour TNSS of -4.1 (SE 0.92) at 30 days, -3.6 (SE 0.81) at 90 days, and -3.97 (SE 1.17) at 365 days. There was also a statistically significant reduction between pre-operative and post-operative mean 2-week TNSS of -3.54 (SE 0.99) at 30 days, -3.19 (SE 0.99) at 90 days, and -3.81 (SE 1.20) at 365 days. There were no reported adverse events.

Stolovitzky *et al*. reported the results of radiofrequency neurolysis in 78 patients randomly assigned to the active treatment arm and a sham procedure in 39 patients assigned to the control arm. One patient was lost to follow up in the active treatment arm. At 3-months follow-up they reported a significantly higher percentage of responders in the active treatment arm *versus* the sham control: 67.5% (95%CI 55.9%-77.8%) *vs* 41.0% (95%CI 25.6%-57.9%), p = 0.009. Baseline TNSS was similar between active (8.3, 95%CI 7.9-8.7) and sham (8.2, 95%CI 7.6-8.8) arms, but

Table IV *- Summary of all reported adverse events.*

Adverse event	Number of patients		
Hwang, 2017	Ear blockage (n = 13) Nasal dryness (n = 3) Epistaxis* (n = 1) Total events: 17		
Chang, 2020 & Ow, 2021	Bloody nasal discharge (n = 1) Burning sensation in nose (n = 1) Epistaxis (n = 2) Hyperemia (n = 1) Middle turbinate hematoma (n = 1) Increased mucous secretion (n = 1) Newly noted ostia (n = 2) Facial pain (n = 1) Retained pledget (n = 1) Synechiae (n = 1) Facial pain (n = 2) Headache (n = 4) Dizziness (n = 1) Dry eyes (n = 2) Watery eyes (n = 1) Altered taste (n = 3) Teeth sensitivity (n = 1) Dry mouth (n = 1) Sinusitis (n = 4) Total events: 31		
Yen, 2020	Headache (n = 12) Pain (n = 10) Palatal numbness (n = 8) Total events: 30		
Krespi, 2020	No adverse events reported		
Stuyt, 2021	No adverse events reported		
Stolovitzky, 2021		Active arm	Sham control
	Pain	n = 1	
	Sinusitis	n = 1	
	Epistaxis		n = 1**
	Dry eyes	n = 1	
	Total events:	3	1
Del Signore, 2021		Active arm	Sham control
	Pain	n = 25	n = 1
	Headache	n = 4	
	Nasal congestion	n = 2	
	Palatal numbness	n = 2	
	Vasovagal	n = 1	n = 1
	Epiphora	n = 2	
	Anxiety	n = 1	
	Dizziness	n = 1	
	Drug reaction	n = 1	
	Sinusitis	n = 1	
	Vomiting		n = 1
	Total events:	40	3

*Required electrocautery in the operating theatre; **required nasal packing.

there was a significantly greater decrease in mean TNSS in the active treatment arm: -3.6 (95%CI -4.2 to -3.0) *vs* -2.2 (95%CI -3.2 to -1.3), p = 0.013. The decrease in rhinorrhea and congestion sub-scores at 3-months was significantly greater in the active treatment arm, while the decrease in nasal itching sub-score did not reach statistical significance. A total of 12 patients increased medication use during follow-up, 7 were in the active treatment arm and 5 in the sham control arm. Assigning these patients as non-responders did not change the outcome of the primary endpoint analysis. Four adverse events were recorded (**table IV**).

Del Signore *et al*. reported the results of cryotherapy ablation in 68 patients randomly assigned to the active treatment arm and 65 assigned to the sham control. Six patients were excluded prior to follow-up. At 90-day follow-up there was a significantly higher percentage of responders in the active arm compared to the sham arm: 73.4% *vs* 36.5%, p < 0.001. Baseline TNSS was similar between active (8.0 ± 1.6) and sham (8.1 ± 1.9) arms, but there was a significantly greater decrease in mean TNSS in the active treatment arm at 90-days: -3.7 (95%CI -4.3 to -3.1) *vs* -1.8 (95%CI -2.5 to -1.1), p < 0.001. Repeated-measures multivariate analysis showed that only the treatment arm (OR for treatment *vs* sham: 3.43 (95%CI 1.827-6.43, p = 0.0001)) and the TNSS value at baseline (OR 1.321 (95%CI 1.095-1.593, p = 0.0036)) were associated with the primary outcome of ≥ 30% improvement in TNSS. There was no association with rhinitis sub-type. Evaluation of individual TNSS items showed significantly greater improvement in rhinorrhea and nasal congestion scores in the active arm, but no significant difference between arms for nasal itching and sneezing scores. At 90-day follow-up, there was a decrease in the percentage of patients using medications in both the active (47.1% to 40%) and sham (49.2% to 34.4%) arms.

In the pooled analysis of data from these two randomized controlled trials (**figure 2**), active treatment was associated with significantly greater responder rate (OR 3.85, 95%CI 2.23-6.64, p < 0.00001). There was no evidence of heterogeneity (I^2 = 0%).

Risk of bias within studies

All six of the included non-randomized studies were deemed to be at an overall moderate risk of bias (**figure 3**). The studies were unblinded, uncontrolled and non-randomized and thus considered to have a serious risk of bias regarding the subjective outcome measures (13, 14, 17-20).

Hwang *et al.* and Gerka Stuyt *et al.* were deemed to be at serious risk of bias due to confounding factors as they made no attempt at reporting or controlling concurrent medical treatment pre and post-intervention (18, 19). The remaining four studies required patients to have discontinued Ipratropium Bromide prior to and throughout the study period but did not control other medications (13, 14, 17, 20).

Hwang *et al*. and Gerka Stuyt *et al*. were deemed to have moderate risk of bias due to missing data as both had significant numbers of patients lost to follow-up (18, 19). The study by Ow *et al*. was deemed to have serious risk of bias, with 44% of patients from the original cohort lost to follow up at the 548-day and 730-day time-points. The two randomized sham-controlled trials were both deemed to be at an overall low risk of bias (15, 16) (**figure 3**).

Discussion

This systematic review identified some evidence to suggest cryotherapy or radiofrequency ablation of the posterior nasal nerve can lead to a higher patient response rate and greater improvement in TNSS when compared to a sham control procedure. Observed improvements appeared to be greater for symptoms of rhinorrhea and nasal congestion, as opposed to itching or sneezing. Medication use was not controlled for in any of the included studies and there were differing reports of both increased and decreased use across active treatment and control groups at follow-up. However, evidence for these conclusions on the effect of PNN ablation was limited to just two randomized controlled trials, both of which had a short duration of follow-up and relatively high baseline TNSS suggesting a patient group with severe and refractory symptoms.

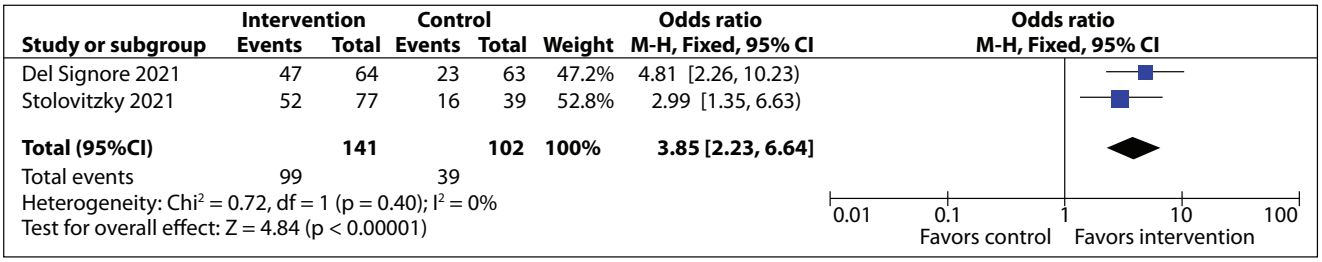
While the remaining six non-randomized studies included within this review reported a reduction in the average post-operative TNSS sustained over longer periods of follow-up, these studies were deemed to have moderate-to-severe risk of bias across multiple domains that limits the ability to draw reliable conclusions from the data.

We found that while there was a reasonably high total number of reported adverse events (125 reported from 461 procedures), these were predominantly non-serious and transient (13-20). The most commonly reported were ear blockage, headache, pain, palatal numbness, altered taste, and sinusitis, all of which had resolved at 90-day follow-up. There were three serious adverse events reported: one episode of epistaxis requiring electrocautery under general anesthesia (18), one episode that required nasal packing (16), and one anxiety attack that required patient transfer to the emergency department (15). The highest proportion of adverse events was reported by Yen *et al.*, where there were 30 events reported in a cohort of 30 patients (14). This was the only study to use cryotherapy ablation of multiple sites within the nasal cavity, increasing the number of sites and thus the area of mucosal damage in the nasal cavity may somewhat explain the higher relative numbers of adverse events reported.

Limitations

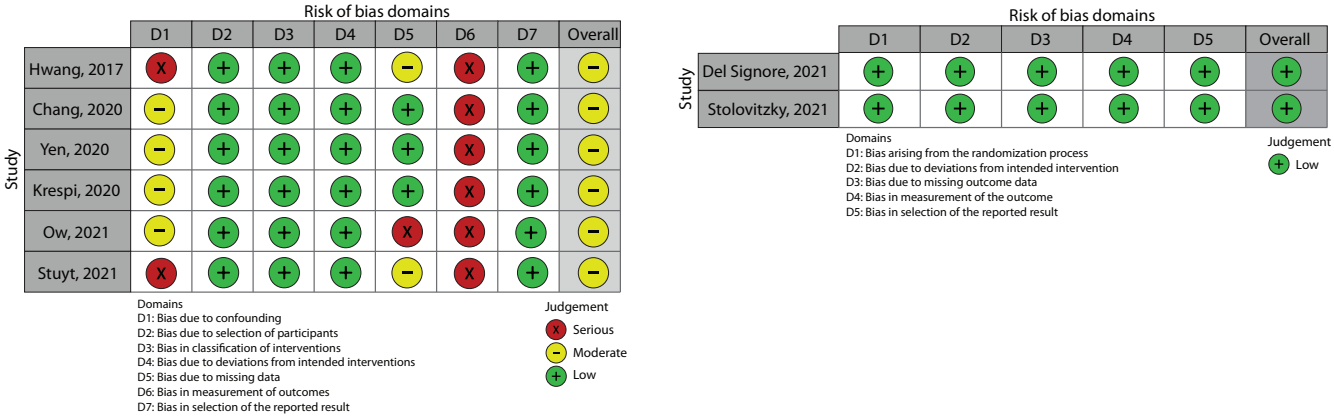
There are several limitations at a study, outcome, and review level that must be taken into consideration when interpreting these results. Six of the included studies had a similar broad design of a prospective, pre-post, single-arm trial and thus were all un-blinded, non-randomized and un-controlled. The risks

Figure 2 *- Association between posterior nasal nerve ablation and Total Nasal Symptom Score.*



Comparison: posterior nasal nerve ablation *versus* sham control procedure; outcome: patient responder rate (≥ 30% improvement in TNSS from baseline) at 3-months follow-up.

Figure 3 *- Assessment of risk of bias within included studies using ROBINS-I tool and RoB-2 tool (22).*



of bias introduced by this design have been discussed in the relevant section above.

Both of the randomized sham-controlled trials cohorts were predominantly Caucasian patients with a selection criteria that required more severe symptoms at baseline. The reported baseline mean TNSS's in these two trials were higher than seen in the previous six single-arm studies. This may limit the external validity of these studies findings. TNSS was used as a standard pre-operative and post-operative measurement of severity of rhinitis symptoms in each of the studies. However, there was variation in whether a 12-hour, 24-hour or 2-week retrospective reflective period was used, with some studies not giving any specific details. There may also be significant variation in a patient's score depending on the time of day they complete the TNSS, it was unclear whether this was accounted for in any of the studies.

It should also be noted that the six studies reporting outcomes after the use of the ClariFix (Stryker ENT, Plymouth MN, USA) cryoablation device or the RhinAer System (Aerin Medical, Sunnyvale CA, USA) were industry sponsored (14-18, 20). At a review level, we were limited in terms of incomplete retrieval of identified research as the translated full text of one report was unavailable at our institution (21).

Conclusions

This is the first systematic review and meta-analysis of the current literature in this area of rhinology. It shows there is some limited evidence to suggest cryotherapy or radiofrequency ablation of the posterior nasal nerve can improve TNSS in adult patients. However, this is from a limited number of trials with short follow-up. The incidence of serious adverse events associated with posterior nasal nerve ablation appears to be low. Future research should focus on higher quality prospective randomized controlled trials with larger numbers of participants and medium to long term follow up in order to help draw more valid conclusions regarding the true effectiveness of PNNN in this patient cohort.

Fundings

None

Contributions

EB: conceptualization, investigation, formal analysis, methodology, writing - original draft, writing - review & editing. KG: investigation, formal analysis, writing - review & editing. KJ: conceptualization, investigation, formal analysis, writing - review & editing. AD: conceptualization, methodology, supervision, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;86:8-160. doi: 10.1067/mai.2001.118891.
2. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern P, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600.
3. Settipane RA, Charnock DR. Epidemiology of rhinitis: allergic and nonallergic. Clin Allergy Immunol. 2007;19:23-34. Available at: https://pubmed.ncbi.nlm.nih.gov/17153005/.
4. Lieberman P, Kaliner MA, Wheeler WJ. Open-label evaluation of azelastine nasal spray in patients with seasonal allergic rhinitis and nonallergic vasomotor rhinitis. Curr Med Res Opin. 2005;21(4):611-8. doi: 10.1185/030079905X41408.
5. Bleier BS, Schlosser RJ. Endoscopic anatomy of the postganglionic pterygopalatine innervation of the posterolateral nasal mucosa. Int Forum Allergy Rhinol. 2011;1(2):113-7. doi: 10.1002/alr.20011.
6. Halderman A, Sindwani R. Surgical management of vasomotor rhinitis: a systematic review. Am J Rhinol Allergy. 2015;29(2):128-34. doi: 10.2500/ajra.2015.29.4141.
7. Disselhoff BC, Rem AI, Verdaasdonk RM, Kinderen DJ, Moll FL. Endovenous laser ablation: an experimental study on the mechanism of action. Phlebology. 2008;23(2):69-76. doi: 10.1258/phleb.2007.007038.
8. Kompelli AR, Janz TA, Rowan NR, Nguyen SA, Soler ZM. Cryotherapy for the Treatment of Chronic Rhinitis: A Qualitative Systematic Review. Am J Rhinol Allergy. 2018;32(6):491-501. doi: 10.1177/1945892418800087.
9. Downie SR, Andersson M, Rimmer J, Leuppi JD, Xuan W, Akerlund A, et al. Symptoms of persistent allergic rhinitis during a full calendar year in house dust mite-sensitive subjects. Allergy. 2004;59(4):406-14. doi: 10.1111/j.1398-9995.2003.00420.x.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71.
11. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. doi: 10.1136/bmj.i4919.
12. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available at: www.training.cochrane.org/handbook.
13. Krespi YP, Wilson KA, Kizhner V. Laser ablation of posterior nasal nerves for rhinitis. Am J Otolaryngol. 2020;41(3):102396. doi: 10.1016/j.amjoto.2020.102396.
14. M Yen D, B Conley D, O'Malley EM, Byerly TA, Johnson J. Multiple Site Cryoablation Treatment of the Posterior Nasal Nerve for Treatment of Chronic Rhinitis: An Observational Feasibility Study. Allergy Rhinol (Providence). 2020;11:2152656720946996. doi: 10.1177/2152656720946996.
15. Del Signore AG, Greene JB, Russell JL, Yen DM, O'Malley EM, Schlosser RJ. Cryotherapy for treatment of chronic rhinitis: 3-month outcomes of a randomized, sham-controlled trial. Int Forum Allergy Rhinol. 2022;12(1):51-61. doi: 10.1002/alr.22868.
16. Stolovitzky JP, Ow RA, Silvers SL, Bikhazi NB, Johnson CD, Takashima M. Effect of Radiofrequency Neurolysis on the Symptoms of Chronic Rhinitis: A Randomized Controlled Trial. OTO Open. 2021;5(3):2473974X211041124. doi: 10.1177/2473974X211041124.
17. Chang MT, Song S, Hwang PH. Cryosurgical ablation for treatment of rhinitis: A prospective multicenter study. Laryngoscope. 2020;130(8):1877-84. doi: 10.1002/lary.28301.
18. Hwang PH, Lin B, Weiss R, Atkins J, Johnson J. Cryosurgical posterior nasal tissue ablation for the treatment of rhinitis. Int Forum Allergy Rhinol. 2017;7(10):952-6. doi: 10.1002/alr.21991.
19. Gerka Stuyt JA, Luk L, Keschner D, Garg R. Evaluation of In-Office Cryoablation of Posterior Nasal Nerves for the Treatment of Rhinitis. Allergy Rhinol (Providence). 2021;12:2152656720988565. doi: 10.1177/2152656720988565.
20. Ow RA, O'Malley EM, Han JK, Lam KK, Yen DM. Cryosurgical Ablation for Treatment of Rhinitis: Two-Year Results of a Prospective Multicenter Study. Laryngoscope. 2021;131(9):1952-7. doi: 10.1002/lary.29453.
21. Huang B, Li P, Meng QX, He L, Gao XH, Xie JH. [A study of the curative effect of endoscopic-assisted posterior nasal neurotomy on patients with moderate severe persistent allergic rhinitis]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2017;31(19):1501-3. Chinese. doi: 10.13201/j.issn.1001-1781.2017.19.009.
22. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021;12(1):55-61. doi: 10.1002/jrsm.1411.

ORIGINAL ARTICLE | Eur Ann Allergy Clin Immunol | Vol 55, N.3, 115-121, 2023

Cristiana Ferreira[1], Eva R. Gomes[2], Joana Lopes[3], Susana Cadinha[3]

Portuguese version of Parent-reported Drug Hypersensitivity Quality of Life Questionnaire (P-DrHy-Q): assessment of reliability and validity

[1]Centro Hospitalar Tamega e Sousa, Penafiel, Guilhufe, Portugal
[2]Department of Allergy and Clinical Immunology, Centro Hospitalar e Universitário do Porto, Porto, Portugal
[3]Department of Allergy and Clinical Immunology, Centro Hospitalar Vila Nova de Gaia/Espinho, EPE, Vila Nova de Gaia, Portugal

Key words

Drug hypersensitivity; quality-of-life questionnaire for caregivers; validity and reliability; P-DrHy-Q.

Corresponding author
Cristiana Ferreira
Centro Hospitalar Tamega e Sousa
Penafiel
Avenida do Padre Americo 210
4564-007 Guilhufe, Portugal
ORCID: 0000-0003-1676-1595
E-mail: cristianascferreira@gmail.com

Doi
10.23822/EurAnnACI.1764-1489.221

Summary

Background. *Drug hypersensitivity in children impacts the quality of life of the patients and their caregivers. The parent-reported drug hypersensitivity quality of life questionnaire (P-DrHy-Q), the first disease-specific quality-of-life questionnaire for caregivers who have children with drug hypersensitivity, was recently developed. The aim of this study was to assess the validity and reliability of the Portuguese version of the P-DrHy-Q.* ***Methods.*** *A translation of the Parent-reported Drug Hypersensitivity Quality of Life Questionnaire (P-DrHy-Q) to the Portuguese population was performed, assessing its applicability in 74 caregivers from two allergy departments. The analyses included internal consistency (Cronbach's alpha) and test–retest reliability: 14 caregivers completed the P-DrHy-Q without any intervention one week after answering the first questionnaire.* ***Results.*** *The 12-item scale assessed the mental health and social activity. The internal consistency of the scale was good (Cronbach's alpha = 0.884), and the test-retest associations were excellent (intra-class correlation coefficient = 0.985; $p < 0.001$). The mean value of the questionnaire was 37.01 (SD 18.57), with Mental Health being more affected than Social Activity. Employed caregivers had a significant higher score ($p < 0.001$). No other factor was statistically significant.* ***Conclusions.*** *The Portuguese version of the P-DrHy-Q is valid for evaluating quality of life impairment in Portuguese caregivers of children with drug hypersensitivity. Its application might be relevant for future research and provide clinicians and researchers with a tool to define which psychosocial support is required to provide more comprehensive care in drug hypersensitivity.*

Impact statement

Portuguese version of the P-DrHy-Q has been developed and culturally adapted for use in Portuguese speaking population. The questionnaire may be used both in research and in routine practice in Portugal.

Introduction

Measurement of health-related quality of life (HRQoL) is critical in the global evaluation of the impacts of the diseases and their therapies (1, 2). HRQoL scales are widely used in allergic diseases as well as other chronic illnesses as an endpoint in clinical trials and in routine clinical practice (3).

These assessment measures, increasingly used, are most of the times formulated in English, targeted for its use only in the English-speaking population. Translation and cultural adaptation of health questionnaires published and applied in other cultures is important in the international setting, as they provide the use of the tool in clinical practice and in research, provide greater accuracy in measuring health aspects related to the population in question, comparison of results between different samples, as well as the cross-cultural studies.

Hypersensitivity reactions to drugs in children have a parent-reported prevalence of around 10%, with a much lower real prevalence, and a lower prevalence of confirmed DH as compared to adults (4). DHRs are considered a public health problem due to associated morbidity and socioeconomic costs.

Drug hypersensitivity may also affect the mental health and quality of life of patients and family members. The Drug Hypersensitivity Quality of Life Questionnaire was initially created by Baiardini *et al.*, and the results showed good validity, internal consistency, and reliability (5). However, measuring the quality of life in children is different from adults. Later, Yuenyongviwat *et al.* developed and validated a questionnaire for the assessment of the specific burden of drug hypersensitivity from the caregiver's perspective, using a multi-dimensional concept to examine the impact of the health status on the quality of life of caregivers who have children with a history of drug hypersensitivity: the Parent-reported Drug Hypersensitivity Quality of Life Questionnaire (P-DrHy-Q) (6).

Given the absence of specific assessment tools designed for evaluating the quality of life in caregivers who have children with drug hypersensitivity in Portugal, the main objective of this study was to develop and assess the validity and reliability of a Portuguese version of Parent-reported Drug Hypersensitivity Quality of Life Questionnaire (P-DrHy-Q). The secondary objectives were to evaluate P-DrHy-Q in different caregivers and patients' subgroups (drug hypersensitivity, type of reaction, age, single or multiple drug hypersensitivity reactions and sociodemographic of the caregivers).

Materials and methods

Ethics

The research project was approved by the Ethics Committee and carried out in accordance with the Declaration of Helsinki. All participants gave their oral informed consent to participate.

Study design and subject

Study participants were prospectively recruited from two different Allergy and Clinical Immunology Department located in tertiary healthcare centers in North of Portugal between June to July 2020. The inclusion criteria were an age under 18 years and having objective symptoms compatible with drug hypersensitivity suspicion. Medical records were scrutinized by the investigators, to determine eligibility. Parents of eligible children were invited to participate. Parents were asked to fulfill the questionnaire, and instructions were given by the investigators on how to proceed. Sociodemographic and clinical characteristics of the children and caregivers were recorded.

Parent-reported Drug Hypersensitivity Quality of Life Questionnaire (P-DrHy-Q)

P-DrHy-Q which was originally developed in Thailand includes 12 items evaluated on a ten-point Likert scale (from 1 (not at all) to 10 (many)), investigating two different domains: Mental Health and Social Activity (6). It was designed to be completed by the caregiver, it is easy to administer and to score and requires a few minutes to complete. Questions and scores were formulated so that higher scores reflected worse HRQoL.

Translation and cross-cultural adaptation methods

The process of linguistic equivalence was initiated by contacting the authors of the original questionnaire to ask for authorization to use it in the present study. Cross-cultural translation was performed according to guidelines (7). Linguistic validation consisted in 3 steps: forward translation, backward translation and comprehensibility testing. Forward translation was performed by two independent translators that had no previous knowledge of the questionnaire. Both were native speakers in the target language. Supported by an experienced specialist in drug allergy diagnosis and treatment, a combined version was obtained. Agreement was achieved through unanimity on a single reconciled version with all elements (translators and physician). The consensual version was tested in caregivers of children with a history of drug hypersensitivity. No comments, doubts or suggestions were posed, showed that the questions were easily understandable and do not require explanation.

Reliability

Reliability measures were of two types: 1) Internal consistency was evaluated using Cronbach's alpha calculated for each scale, and 2) Test-retest reliability (reproducibility). P-DrHy-Q was administered twice to 14 caregivers separated by 7 days interval in the absence of any significant clinical or personal change; intraclass correlation coefficients quantified reproducibility of scores over 7 days.

Statistical analysis

SPSS version 22 (SPSS-Inc, Chicago, IL) was used for statistical analysis. Quantitative variables were expressed as means ±

standard deviations, with 95% confidence intervals. Qualitative variables were compared using χ^2 test and Fisher's exact test. The normality was verified using the Shapiro-Wilk test. For all variables, significance was set at $p < 0.05$ for two tails. The internal consistency of the scale was evaluated using Cronbach's alpha coefficient. It is accepted crossways that alpha > 0.7 is acceptable, > 0.8 is good, and > 0.9 is excellent. Intra-class correlation coefficient was performed to assess the discriminative reliability of the test-retest associations.

Results

In the cognitive debriefing no comments, doubts or suggestions were done.

Characteristics of the participants

There were no refusals to participate in the study. A total of 74 caregivers with a child with a reliable history of drug hypersensitivity were included in this study.

Demographic characteristics of the patients were shown in **table I**: 48.6% (n = 36) of the children were females and 51.4% (n = 38) were males. Ages ranged from 1-15 years with an average of 5.08 ± 3.64 years. Mild reactions in 85.1% (n = 63) of cases, moderate 9.5% (n = 7) and severe 5.4% (n = 4) were observed. The most common implicated drugs to hypersensitivity reactions were antibiotics (65/74 patients, 87.8%) and non-steroidal anti-inflammatory drugs (5/74 patients, 6.8%) and 2 (2.7%) had a history of drug hypersensitivity reaction to more than one drug.

Demographic characteristics of the caregivers were shown in **table II**: 86.5% (n = 64) were female and 13.5% (n = 10) were male. Their ages were ranged from 30-45 years in 74.3% (n = 55), 20-30 years in 16.2% (n = 12) and over 45 years in 9.5% (n = 7). 47.3% (n = 35) had basic education, 27.0% (n = 20) university graduation. 78.4% (n = 58) were employed and 21.7% (n =16) unemployed. 89.2% (n = 66) were married and 98.6% were the main caregiver. Most of the family income was above 600 euros (€)/month. None of them have previous experienced in care of children with drug hipersensitivity.

The average global score was 37.01 (0-120), mean Mental Health 27.92 ± 13.66 (0-50; questions 1-5) and Social Activity 9.09 ± 6.34 (0-70; questions 6-12) (**table III**). The Mental Health presented higher scores than social that indicate that is the domain more affected in the caregivers.

There were no statistically significant differences in the scores between the clinical characteristics of the patients (sex, age, severity of the reaction or number of drugs involved). However, in regard to sociodemographic characteristics of the caregivers, it was found that when the caregiver is employed, the Social Activity Score is higher compared to unemployed cases (**table IV**).

Table I *- Demographic and clinical characteristics of the children.*

	n (%)	Mean ± SD
Gender		
Female	36 (48.6%)	
Male	38 (51.4%)	
Age		5.08 ± 3.64
Reaction severity		
Mild (urticaria, maculopapular exanthema, eczema)	63 (85.1%)	
Moderate (angioedema, serum-like disease, dyspnea, vomits)	7 (9.5%)	
Severe (generalized exfoliative dermatitis, erythroderma, cutaneous vasculitis, bullous eruptions, DRESS, NET/SJS)	4 (5.4%)	
Drug class		
Antibiotic	65 (87.8%)	
B-Lactamic	61 (82.4%)	
Others	4 (5.4%)	
NSAIDs	5 (6.8%)	
Anticonvulsants	1 (1.4%)	
Psychotropic drugs	3 (4.1%)	
Number of drugs		
1	72 (97.3%)	
> 1	2 (2.7%)	

Reliability

The P-DrHy-Q showed adequate internal consistency, as demonstrated by the very strong Cronbach's alpha coefficient (C = 0.884). In **table V**, the values represented are the Cronbach's alpha coefficient of the scale if that question were excluded. Mental Health and Social Activity subscales were also adequate: C = 0.988, $p < 0.001$; and C = 0.997, $p < 0.001$, respectively (**table VI**).

Test-retest reliability was assessed on 14 caregivers and was excellent: ICC = 0.985, $p < 0.001$ (**table VI**) for scales, but also in Mental Health and Social Activity subscales: ICC = 0.978, $p < 0.001$ and ICC = 0.992; $p < 0.001$ respectively (**table VI**).

Discussion

Evaluation of patient-reported outcomes by validated tools, either disease-specific when available or generic ones, in clinical trials for allergic diseases are very important. An original questionnaire allowing the assessment of impact of biopsychosocial

Table II *- Sociodemographic characteristics of the caregivers.*

	n (%)
Sex	
Female	64 (86.5%)
Male	10 (13.5%)
Current age	
20-30 y	12 (16.2%)
30-45 y	55 (74.3%)
> 45 y	7 (9.5%)
Main caregiver	
No	2 (1.4%)
Yes	72 (98.6%)
Marital status	
Married	66 (89.2%)
Divorced	2 (2.7%)
Single	6 (8.1%)
Occupation	
No	16 (21.7%)
Yes	58 (78.4%)
Education	
Basic	35 (47.3%)
Technological	7 (9.5%)
University graduation	20 (27%)
Master's	10 (13.5%)
Doctorate	2 (2.7%)
Number of children within family	
1-2	65 (87.6%)
2-4	9 (12.2%)
Family income, euros (€)/month	
< 600	3 (4.1%)
600-1,500	35 (47.3%)
1,500-3,000	18 (24.3%)
> 3,000	18 (24.3%)
Previous experience in care of children with drug hypersensitivity	
No	74 (100%)
Yes	0 (0%)

Table III *- Total scores for the P-DrHy-Q and subscales.*

Scores	Total (n = 74) Mean ± SD
Total	37.01 ± 18.57 [0-120; questions 1-12]
Mental Health	27.92 ± 13.66 [0-50; questions 1-5]
Social Activity	9.09 ± 6.34 [0-70; questions 6-12]

factors on drug allergy in caregivers of drug hypersensitivity pediatric patients entitled P-DrHy-Q has recently been developed and validated (6). The original version was primarily developed in English language. In the present study this tool was translated and culturally adapted to Portuguese speaking population. To our best knowledge, our study is the first that validates P-DrHy-Q for another language and culture after development of the original questionnaire. Cross-cultural adaptation is relevant because, currently, there is no other measure for quality of life of caregivers with drug hypersensitivity children in Portugal. The decision to culturally adapt the P-DrHy-Q, rather than to develop a new measure, was based on the fact that the adaptation of a previously described and validated measure, which has been translated and validated to other languages, makes it possible to compare results across studies conducted in different countries. This present study contributes to attain this gap, both in clinical trials and in routine practice.

The results of the study showed that the P-DrHy-Q is a self-applied psychosocial impact scale in drug allergy. Furthermore, it is a brief and low-cost way to assemble data that may guide the clinician to decide which factors should be included in a multidisciplinary approach to the caregivers. The factor analysis demonstrated that the scale may be used to measure two types of parental burden: mental health and social activity. Both of these domains had excellent internal reliability in both versions of the scale. The statistical analyses provided evidence that Portuguese version of the P-DrHy-Q met the standards for good internal consistency reliability with a Cronbach's alpha of $R = 0.884$, $p < 0.001$ along with excellent test-retest reliability, ICC = 0.985 (Thailand version: Cronbach's alpha = 0.897 and the test–retest reliability, ICC = 0.9439, $p < 0.001$). Therefore, it may be possible to adapt the scale to incorporate two sub-scale scores as well as an overall score to provide more information on the type of parental burden that is most salient.

The average score of P-DrHy-Q in our 74 for caregivers of patients who had suffered an allergic reaction with a drug were 37.01 ± 18.57. Its application demonstrated negative impact on mental health and social activity in the caregivers of affected children. In our study we found higher score in the mental score than the social.

We believe that our study had some strengths. The study was performed in two different Allergy and Clinical Immunology Department and includes patients with different types of drug allergy.

Table IV *- Item-scale correlations on the P-DrHy-Q.*

	Score Total	Mental Health	Social Activity
	Patients		
Gender			
Female	0.828	0.894	0.727
Male			
Age		0.691	0.930
Severity of the reaction			
Mild	0.232	0.401	0.077
Moderate			
Severe			
Number of drugs			
1	0.788	0.802	0.806
> 1			
	Caregivers		
Sex			
Female	0.492	0.493	0.593
Male			
Current age			
20-30 y	0.201	0.222	0.259
30-45 y			
> 45 y			
Main caregiver			
No	0.677	0.996	0.217
Yes			
Marital status			
Married	0.632	0.828	0.263
Divorced			
Single			
Occupation			
No	0.182	0.370	**0.001***
Yes			
Education			
Basic	0.515	0.302	0.981
Technological			
University graduation			
Master's			
Doctorate			
Number of children within family			
1-2	0.571	0.523	0.775
2-4			
Family income, euros (€)/month			
< 600	0.605	0.604	0.608
600-1,500			
1,500-3,000			
> 3,000			

Table V *- Mean score, squared, minimum and maximum value, multiple correlations, and Alpha Cronbach if item deleted, for each question of the P-DrHy-Q.*

	Mean	Standard deviation	Min; max	Multiple correlation	α Cronbach if excluded
Mental Health					
1. O seu sono alterou devido à alergia aos medicamentos do seu filho? [Did you have sleep disorder problem due to your child's drug allergy?]	2.86	2.6	1; 10	0.758	0.871
2. A alergia aos medicamentos do seu filho afetou seu humor? [Did your child's drug allergy affect your mood?]	2.78	2.63	1; 10	0.740	0.871
3. Esteve preocupado/a que a possibilidade do seu filho vir a ter outra reação alérgica aos medicamentos? [Were you worried that your child will be allergic to drug again?]	6.97	2.83	1; 10	0.569	0.873
4. A preocupação do seu filho ter outra reação alérgica aos medicamentos afetou-o/a? [Would the worry of your child allergic to drug again affected you?]	4.49	2.80	1; 10	0.704	0.867
5. O medo do seu filho ter outra reação alérgica a medicamentos afetou-o/a? [Would the fear of your child allergic to drug again affected you?]	5.22	2.95	1; 10	0.760	0.867
6. Receia que o seu filho venha a ter dificuldades de aprendizagem devido à sua alergia aos medicamentos? [Did you worry that your child would have a learning problem due to drug allergy?]	1.95	1.92	1; 10	0.531	0.877
7. A alergia aos medicamentos do seu filho deixou-o/a frustrado/a? [Did your child's drug allergy make you frustrated?]	3.65	2.85	1; 10	0.338	0.884
Social Activity					
8. Precisou de cuidar do seu filho mais do que o habitual nas saídas com ele? [Did you needed to take care of your child more than usual when you go out?]	2.62	2.62	1; 10	0.842	0.861
9. A alergia aos medicamentos do seu filho fez com que não tivesse tempo para as suas atividades de lazer (desporto, ler um livro, ver um filme, refeições fora)? [Did you have time for leisure activities (exercise, movie, eating out) although your child's drug allergy?]	1.74	1.63	1; 10	0.653	0.877
10. A alergia aos medicamentos de seu filho fez com que ele se sentisse diferente das outras crianças? [Did your child's drug allergy make him/her feel discriminated?]	1.5	1.21	1; 7	0.417	0.886
11. A alergia aos medicamentos do seu filho afetou o orçamento da sua família? [Did your child's drug allergy affect your family budget?]	1.74	1.54	1; 8	0.284	0.882
12. A alergia aos medicamentos do seu filho afetou as suas interações sociais? [Did your child's drug allergy affect your social interactions?]	1.49	1.35	1; 8	0.522	0.880

Square brackets: translation of the questions for Journal's readers.

Table VI *- Internal consistency and test-retest reliabilities of the P-DrHy-Q Scale and subscales.*

	Number of items	Cronbach´s alphas	ICC
Total scale P-DrHy-Q	12	0.884	0.975
Subscales			
Mental Health	7	0.988	0.978
Social Activity	5	0.997	0.992

Second, we had opportunity to observe relationship of the P-DrHy-Q scores to other clinical factors of the patients and sociodemographic characteristics of the caregivers. In the process of validating the DrHy-Q questionnaire, Baiardini *et al*. found that the highest score (and therefore worse QoL) occurred in patients who had suffered anaphylaxis (5). Results of our study showed that the group of caregivers employed had significantly higher P-DrHy-Q scores, in particular Social Activity Score, indicating a worse HRQoL compared to unemployed individuals, which can be explained due to a more stressful life in the employed caregivers and less time available to control situation to less control in child diary activity. No other statistically significances were found.

This study has also several limitations. Our study has a small sample size; the analysis of a greater number of cases may reveal more robust results.

Other limitation of the study was that it does not takes into account the influence of a drug allergy evaluation and does not analyze if the quality of life improved significantly after completing a drug allergy evaluation. Gatamintza *et al.* conducted a prospective multicenter study in Spain to evaluate the quality of life of patients who suffered a possible allergic drug reaction, and analyzed the effect of a drug allergy evaluation (8). A total of 346 adult's patients answered the specific questionnaire twice: before the drug allergy evaluation, and 1 month after it was completed. The quality of life was found to be significantly improved after completing a drug allergy evaluation.

The Portuguese version of the P-DrHy-Q has been developed and culturally adapted for use in Portuguese speaking population. This is the first parent-reported health-related quality of life instrument for drug allergy. This study demonstrated that the Portuguese version of the P-DrHy-Q can be a tool to evaluate interaction of biopsychosocial factors in caregivers of drug hypersensitivity patients. It shows good internal consistency and reliability. The questionnaire may be used both in research and in routine practice in Portugal. Gaining information on which type of parental burden is more salient provide more comprehensive care in drug hypersensitivity and may be useful in determining appropriate support for the caregivers.

Fundings

None.

Contributions

CF, EG, JL, SC: study design, writing – original draft, writing - review & editing. CF: results interpretation.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Baiardini I, Pasquali M, Giardini A, Specchia C, Passalacqua G, Venturi S, et al. Rhinasthma: a new specific QoL questionnaire for patients with rhinitis and asthma. Allergy. 2003;58(4):289-94. doi: 10.1034/j.1398-9995.2003.00079.x.
2. World Health Organisation. Measurement of quality of life in children: Report of a WHO/IACAPAP Working Party. Division of Mental Health, Geneva; 1993.
3. Leplège A, Hunt S. The problem of quality of life in medicine. JAMA. 1997;278(1):47-50. doi: 10.1001/jama.1997.03550010061041.
4. Gomes ER, Brockow K, Kuyucu S, Saretta F, Mori F, Blanca-Lopez N, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. Allergy. 2016;71(2):149-61. doi: 10.1111/all.12774.
5. Baiardini I, Braido F, Fassio O, Calia R, Giorgio WC, Romano A, et al. Development and validation of the Drug Hypersensitivity Quality of Life Questionnaire. Ann Allergy Asthma Immunol. 2011;106(4):330-5. doi: 10.1016/j.anai.2010.12.014.
6. Yuenyongviwat A, Wirodwanich T, Jessadapakorn W, Sangsupawanich P. Development and validation of the parent-reported Drug Hypersensitivity Quality of Life Questionnaire. Eur Ann Allergy Clin Immunol. 2020;52(2):62-5. doi: 10.23822/EurAnnACI.1764-1489.11.
7. Baiardini I, Bousquet PJ, Brzoza Z, Canonica GW, Compalati E, Fiocchi A, et al. Recommendations for assessing patient-reported outcomes and health-related quality of life in clinical trials on allergy: a GA(2)LEN taskforce position paper. Allergy. 2010;65(3):290-5. doi: 10.1111/j.1398-9995.2009.02263.x.
8. Gastaminza G, Ruiz M, Andrés B, Barasona J, Cabañas R, García I, et al. Quality of Life in Patients with Allergic Reactions to Medications: Influence of a Drug Allergy Evaluation. J Allergy Clin Immunol Pract. 2019;7(8):2714-21. doi: 10.1016/j.jaip.2019.05.017.

Eur Ann Allergy Clin Immunol Vol 55, N.3, 122-130, 2023

Şadan Soyyiğit[1], Ömür Aidin[1], Derya Seçil[1], Cahit Doğan[2], Derya Gökmen[3], Betül Ayşe Sin[1], Zeynep Misirligil[4], Vesile Dilşad Mungan[1]

Pre-seasonal immunotherapy is effective in both monosensitized and polysensitized patients with allergic rhinitis

[1]Division of Immunology and Allergic Diseases, Department of Chest Diseases, Ankara University, School of Medicine, Ankara, Turkey
[2]Department of Biology, School of Medicine, Hacettepe University, Ankara, Turkey
[3]Department of Biostatistics, School of Medicine, Ankara University, Ankara, Turkey
[4]Faculty of Medicine, Istinye University, Ankara Liv Hospital, Immunology and Allergic Diseases, Turkey

Key words

Pre-seasonal immunotherapy; monosensitized; polysensitized; specific IgE; specific IgG4.

Corresponding author
Şadan Soyyiğit
Division of Immunology and Allergy
Department of Chest Diseases
School of Medicine
Yıldırım Beyazıt University - Ankara City Hospital
Bilkent/Ankara, Turkey 06760
ORCID: 0000-0003-3270-5884
E-mail: sadansoyyigit@gmail.com;
ssoyyigit@ybu.edu.tr

Doi
10.23822/EurAnnACI.1764-1489.252

Impact statement

Pre-seasonal allergoid immunotherapy is clinically and immunologically effective in pollen allergic polysensitized patients.

Summary

Background. *The effectiveness of pre-seasonal allergoid immunotherapy in polysensitized patients is not well-known. The aim of this study was to compare the clinical efficacy and immunological changes of pre-seasonal allergoid immunotherapy in mono and polysensitized patients with grass pollen allergy.* ***Methods.*** *46 patients with seasonal allergic rhinitis undergoing pre-seasonal grass pollen immunotherapy and 28 cases followed by conventional drug treatment were included. These groups were divided into monosensitized and polysensitized ones. All patients were followed between March-September with symptom-medication scores, and visual analogue scale. The quality of life was assessed using the Mini-RQLQ questionnaire. Phleum pratense specific IgE and IgG4 measurements were performed before and after 7 weeks of immunotherapy.* ***Results.*** *In the immunotherapy group, 15th weekly symptom-medication scores and VAS scores between May and August were found to be significantly lower than those in the control group ($p < 0.05$). Phl p specific IgE and IgG4 levels were significantly higher after immunotherapy compared to those before immunotherapy ($p = 0.001$). Furthermore, Phl p specific IgG4 levels after immunotherapy were also significantly higher than in the control group ($p = 0.001$). Improvements in activities-practical problems and non-nose/eye symptoms quality of life scores were significantly different between two groups ($p < 0.05$). There was no difference in terms of clinical and immunological parameters in mono and polysensitized patients ($p > 0.05$).* ***Conclusions.*** *Clinical improvement with pre-seasonal grass pollen immunotherapy is accompanied by important increase in specific IgG4 blocking antibodies. A single-allergen immunotherapy can lead to similar clinical efficacy and immunological changes in polysensitized as well as monosensitized patients with grass pollen allergy.*

Introduction

Allergen-specific immunotherapy represents an effective treatment for allergic rhinitis caused by pollen allergy. Pre-seasonal short-term immunotherapy is a different immunotherapy program than the conventional immunotherapy protocols. The use of allergoids as immunotherapy compounds is expected to result in earlier immunological and clinical effects (1-4).

The prevalence of polysensitization is greater than monosensitization in allergic population, and it is reported to account for more than 50% of patients with respiratory allergies (4). Polysensitization is defined as the co-sensitization to two or more non-cross-reacting allergens from diverse sources evaluated either by skin prick testing (SPT) or serum-specific IgE assays. However, polysensitized patients may not always be polyallergic. Due to the absence of general recommendations by guidelines, the clinical management approach to polysensitized patients is not standardized (5, 6). Although large-scale clinical trials of grass pollen sublingual tablets showed that polysensitized patients benefited at least as much from allergen immunotherapy as monosensitized patients, the effects of pre-seasonal allergoid immunotherapy by injection route are not known on the clinical efficacy and immunologic response in polysensitized patients (7).

The aim of the present study was to compare the clinical efficacy and immunological changes of pre-seasonal allergoid immunotherapy in monosensitized and polysensitized patients with seasonal allergic rhinitis with grass pollen allergy.

Materials and methods

Study design

A total of 74 patients aged between 18-60 years old with seasonal allergic rhinitis were included in the study. Their inclusion criteria were: IgE-mediated moderate to severe persistent seasonal allergic rhinitis with symptoms during the pollen seasons (between March and September), symptoms of allergic rhinoconjunctivitis requiring medication during the last season and the presence of positive skin-prick test reactivity to grass pollen. The study was designed as an experimental study with two arms: one arm being the pre-seasonal immunotherapy group treated with 7 injections before the pollen season, and the second arm being the control group who were prescribed oral antihistamines and/or nasal corticosteroids when needed during the pollen season. The immunotherapy group consisted of 46 patients who had moderate to severe persistent seasonal allergic rhinitis receiving grass pollen allergoid immunotherapy. As the control group, 28 cases with moderate to severe persistent seasonal allergic rhinitis were included in the study and treated with medical treatment.

The subjects were divided into two groups as monosensitized and polysensitized according to their skin prick test sensitivity in both the immunotherapy and control groups. Patients sensitized to only grass pollens were categorized as monosensitized patients. In addition to grass pollen sensitivity, patients who showed sensitivity to other non-cross-reactive allergens from diverse sources (house dust mites and/or cat and/or dog dander and/or mold spores and or *Blattella germanica*) were categorized as polysensitized ones. This group had no history of clinically allergy to other allergens except grass pollen (presence of polysensitization but clinically monoallergic).

The time course of the study along with the clinical and laboratory investigations performed are outlined in **figure 1**. All subjects gave their written informed consent, and the Local Ethics Committee of Ankara University (Turkey) approved the protocol. The study was performed in accordance with the 1964 Helsinki declaration.

Skin prick tests

Skin prick tests were carried out with standard panel consisting of grass mix *(Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis* and *Fescuta pratensis*), cereal mix (*Hordeum vulgare*, *Avena sativa* and *Tricutum sativa*), *Secale cereale*, weed mix (*Artemisia vulgaris*, *Urtica dioica*, *Taraxacum vulgare*, *Plantago lanceolata* and *Chenopodium album*), trees mix 1 (*Salix caprea, Populus alba*, *Ulmus scabra*, *Alnus glutinosa*, *Coryllus avellana*), trees mix 2 (*Betula verrucosa*, *Fagus silvatica*, *Quercus robur* and *Planatus orientalis)* mold mix 1 (*Alternaria alternata*, *Cladosporium herbarum*, *Botrytis cinerea*, *Curvularia lunata*, *Fusarium moniliforme* and *Helminthosporium halodes*), mold mix 2 (*Aspergillus fumigatus*, *Mucor mucedo*, *Penicillium notatum*, *Pullularia pullulans*, *Rhizopus nigricans* and *Serpula lacrymans*), feather mix, cat and dog dander, house-dust mites *(Dermatophagoides pteronyssinus* and *D. farinae),* cockroach *(Blatella germanica)* and Latex (Allergopharma, Reinbek, Germany). Wheal (edema with erythema) of at least 3 mm or greater in diameter than the negative control after 20 minutes was considered positive reaction. Histamine dihydrochloride (10 mg/ml) was used for the positive control and physiologic saline was used for the negative control.

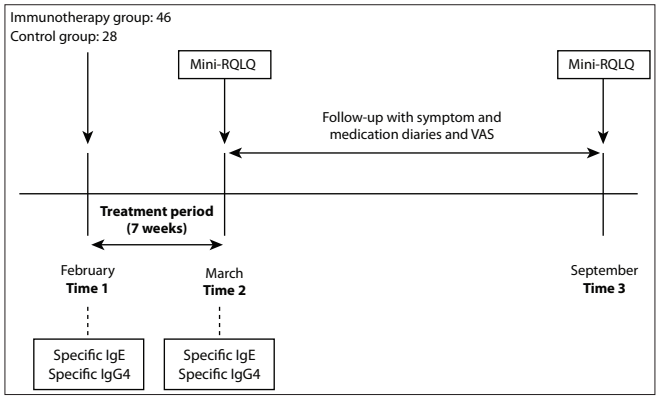
Determination of specific IgE and IgG4 levels

Phleum pratense (Phl p) specific IgE (sIgE) and specific IgG4 (sIgG4) (UNI-CAP 100, Phadia) antibody measurements were performed at baseline (Time 1) and after immunotherapy (Time 2) in the immunotherapy and control groups. The levels of sIgE and sIgG4 were quantified using the CAP fluoroenzyme immunoassay system according to the recommendations of the manufacturer's (Phadia, Uppsala, Sweden). For Phl p sIgE, the reference value was taken as > 0.35 kUA/L, and > 0.17 mgA/L for sIgG4.

Immunotherapy protocol

The immunotherapy product was a preparation of extracts of grasses treated with formaldehyde to produce an allergoid and then adsorbed on to aluminum hydroxide (Allergopharma, GmbH&Co, Germany). It was supplied in two concentrations, 1,000 therapeutic units TU/mL (vial A) and 10,000 TU/mL (vial B). Pre-seasonal immunotherapy treatment protocol was

***Figure 1** - The design and time course of the study.*



Time 1: Before immunotherapy (Baseline); Time 2: After immunotherapy; Time 3: After pollen season.

administered by injection weekly for seven weeks before starting pollen season. Subcutaneous injections commenced with 0.1 ml of strength-A in February followed by an approximate doubling of the dose weekly up to 0.6 ml of strength-B. Dose adjustments were made according to the individual tolerance.

Assessment of clinical efficacy

All patients were followed between 1st March to 1st September with symptom and medication scores, and visual analogue scale (VAS). Nasal (itching, sneezing, rhinorrhea and obstruction) and ocular (itching or watery-eyes) symptoms were recorded daily on a scale of 4: 0 − no symptoms, 1 − mild symptoms, 2 − moderate symptoms, and 3 − severe symptoms. The rhinoconjunctivitis symptom score (SS) was calculated as the mean of the daily symptom score (8). For rescue medication, patients were instructed to use a stepwise regimen (step 1: 5 mg of oral desloratadine, step 2: fluticasone furoate nasal spray and step 3: 4 mg of oral metilprednisolone). Medication scores (MS) were assigned as follows: 0 − no medication, 1 − desloratadine, 2 − nasal fluticasone furoate and 3 − oral metilprednisolone. The highest score for a given day was recorded as the MS (8). Weekly scores were obtained by adding up and averaging daily scores for each given week. Every month, patients assessed the severity of allergic symptoms on a 10-cm visual analogue scale (VAS) (with 0 cm indicating no symptoms and 10 cm indicating the highest level of symptoms). The QoL was evaluated using the Turkish version of the Mini Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ) (9). Mini-RQLQ questionnaire was administered twice, once before pollen season (beginning of March − Time 2) and once after pollen season (beginning of September − Time 3).

Pollen counts

Airborne pollen measurements were carried out in Ankara, during the pollen season from 1st March to 1st September with a Burkard volumetric 7-day spore trap. A Burkard spore trap was used for 7-day sampling onto Melinex tape coated with a thin film of Lubriseal (Thomas Scientific, Swedesboro, NJ). Tapes were changed weekly, cut into 48 mm segments, and mounted on microscope slides. Slides were colored with glycerin jelly containing basic fuchsine and examined microscopically at 400x magnification using a single longitudinal traverse lens. Microscope counts were converted into atmospheric concentrations and expressed as pollen grains/m^3.

Statistical analysis

Statistical analysis was performed using SPSS software version 15 (SPSS, Chicago, III., USA). Normality of distribution was analyzed with the Shapiro-Wilk test. Comparisons between groups were performed using the Mann-Whitney U test. Intragroup comparisons were made Friedman test or the Wilcoxon signed-rank test. A value of $p < 0.05$ was considered statistically significant. The primary end point was a difference between monosensitized and polysensitized patients with regard to the SS and MS, VAS and quality of life scores and serum levels of sIgE and sIgG4 during pollen season. The secondary end point was a difference between immunotherapy and control groups with regard to the SS and MS, VAS and quality of life scores and serum levels of sIgE and sIgG4 during pollen season.

Results

A total of 46 patients with seasonal allergic rhinitis undergoing pre-seasonal grass pollen immunotherapy and 28 control cases followed by conventional drug treatment were included in the present study. There was no difference between two groups in terms of demographic characteristics (**table I**). The number of monosensitized/polysensitized patients were 37/9 and 20/8 in immunotherapy and control groups, respectively. Distribution of sensitization profile against other inhalant allergens except grass pollen in polysensitized group was shown in **figure 2**. Skin prick test reactivity was observed mostly against house dust mites and cat as perennial allergens in this group.

Clinical assessment in immunotherapy and control groups

Symptom-medication score and VAS

In the immunotherapy group 11th, 13th, 14th, 15th, 16th 17th, 18th, 19th, 21th and 22th weekly SS at the peak of the grass pollen period were found to be significantly lower than those in the control group ($p = 0.02$, $p = 0.004$, $p = 0.006$, $p = 0.002$, $p = 0.01$, $p = 0.01$, $p = 0.008$, $p = 0.003$, $p = 0.03$, $p = 0.01$, respectively) (**figure 3a**). MS recorded in 15th week were found to be lower in the immunotherapy group in the peak pollen time ($p = 0.02$) (**figure 3b**). VAS scores were also decreased in May-June-July-August in the immunotherapy group ($p = 0.003$, $p < 0.001$, $p = 0.007$, $p = 0.002$) (**figure 4a**).

Quality of life
There was no difference between the immunotherapy and control groups with regard to overall score and domains of Mini-RQLQ questionnaire before the pollen season (Time 2) (p = 0.17, p = 0.18, p = 0.44, p = 0.33, p = 0.46, p = 0.57, respectively) (**figure 5a**). However, improvements in activities and practical problems and non-nose/eye symptoms quality of life domain scores were significantly better in the immunotherapy group after the pollen season (Time 3) (p = 0.001, p = 0.03, p = 0.01, respectively) (**figure 5b**).

Clinical assessment in monosensitized and polysensitized patients

Symptom-medication scores and VAS
No difference was found between monosensitized and polysensitized patients with respect to weekly SS and MS in the immunotherapy group (p > 0.05) (**figure 3c,d**). VAS scores of the polysensitized group during March, April and June was significantly lower than monosensitized patients in the immunotherapy group (p = 0.04, p = 0.02, p = 0.04) (**figure 4b**).

Quality of life
All domains of Mini-RQLQ quality of life were significantly higher in the monosensitized group compared with the polysensitized group before the pollen season (Time 2) (p = 0.002, p = 0.01, p = 0.005, p < 0.001, p = 0.01, p = 0.002, respectively) (**figure 5c**). After the pollen season (Time 3), there was no difference between the monosensitized and polysensitized patients with regard to overall score and domains of Mini-RQLQ questionnaire (p = 0.31, p = 0.37, p = 0.24, p = 0.19, p = 0.11, p = 0.23, respectively) (**figure 5d**).

Allergen-specific IgE and IgG4 levels in the immunotherapy and control groups
Phl p sIgE values just after immunotherapy were higher than baseline levels in the immunotherapy group (p < 0.001). There were no significant differences in terms of IgE values between the immunotherapy and control groups after immunotherapy (p = 0.1). In the immunotherapy group, Phl p sIgG4 values after immunotherapy were found to be significantly higher than baseline levels (p < 0.001). Phl p sIgG4 levels after immunotherapy were significantly higher in the immunotherapy group than in the control group (p < 0.001) (**figure 6a**).

Allergen-specific IgE and IgG4 levels in monosensitized and polysensitized patients
There was no difference in Phl p sIgE levels between mono and polysensitized patients in the immunotherapy group at two time points (p = 0.38, p = 0.42, respectively).
Furthermore, Phl p sIgG4 values did not differ between monosensitized and polysensitized patients at baseline, and just after immunotherapy (p = 0.999, p = 0.5, respectively) (**figure 6b**).

Correlations
A weak negative correlation was observed between the baseline activities-practical problems-nasal symptoms-overall QoL domain scores, 5th week SS and sIgG4 values after immunotherapy

Figure 2 *- Distribution of sensitivity to inhalant allergens other than grass pollen in polysensitized patients in the immunotherapy and control groups.*

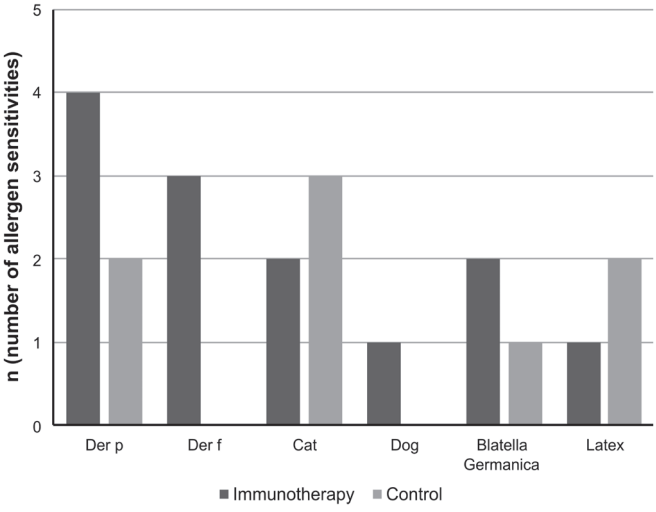
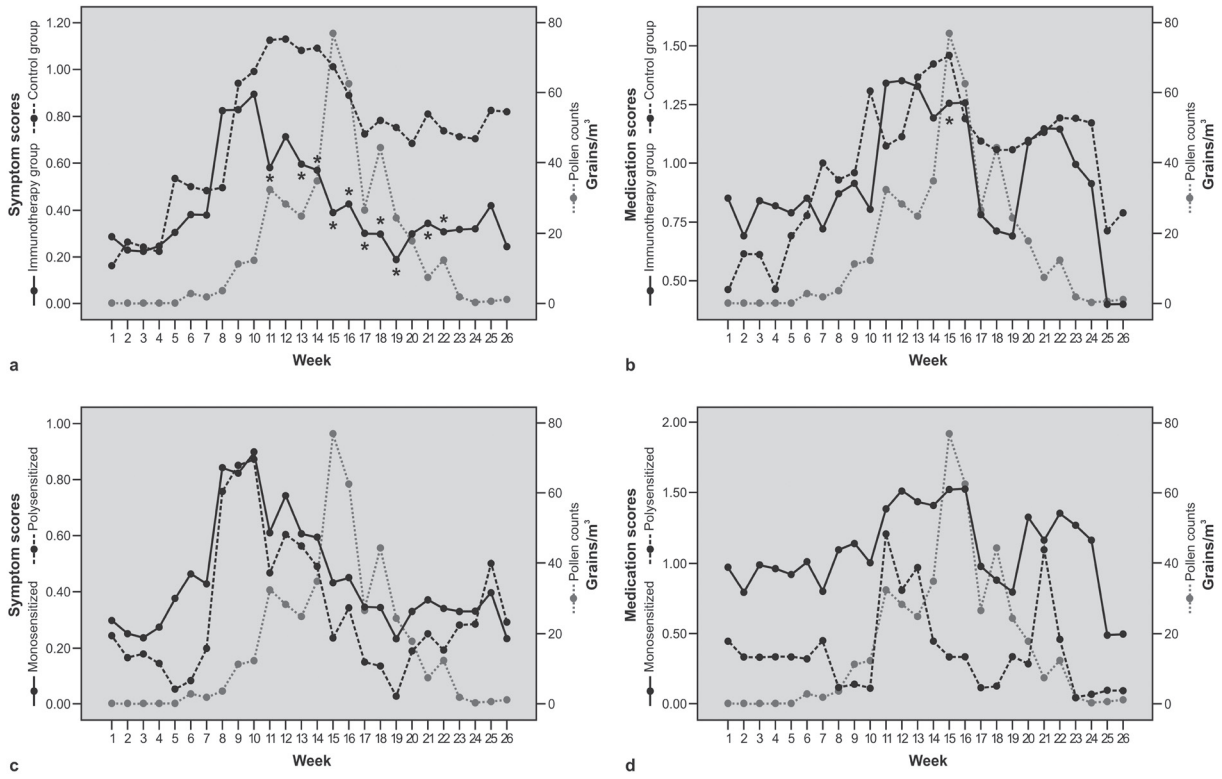


Table I *- Characteristics of the study population.*

	Immunotherapy group	Control group	P-value
Sex (F/M)	29/17	17/11	0.8
Age, years (Mean ± SD)	34.9 ± 10.6	34.2 ± 12	0.5
Median duration of rhinitis, years (min-max)	1-30	1-25	0.3
Monosensitized/Polisensitized	37/9	20/8	0.3
Results of skin-prick testing, mm*	7.9 ± 3.8	7.7 ± 3.4	0.7

*Values are the mean ± SD wheal diameter (to a mixture of six grasses).

Figure 3 *- Weekly symptom-medication scores and pollen counts:* ***(a,b)*** *immunotherapy and control groups);* ***(c,d)*** *monosensitized and polysensitized patients in the immunotherapy group.*



*p < 0.05.

(r = -0.36, p = 0.01; r = -0.32, p = 0.03; r = -0.37, p = 0.01; r = -0.33, p = 0.02; r = -0.34, p = 0.02, respectively). There was no significant correlation between sIgG4 levels and MS or VAS scores in the immunotherapy group.

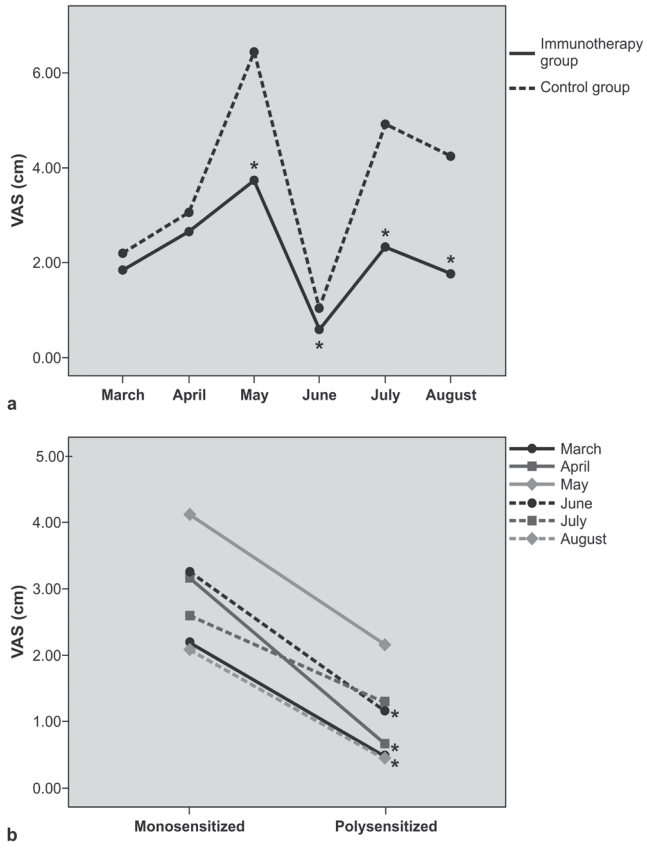
Discussion

As an important finding, this study demonstrated that clinical improvement with pre-seasonal allergoid immunotherapy is accompanied by a significant increase in sIgG4 blocking antibodies despite short-term injections. Furthermore, this effect was comparable between polysensitized but monoallergic and monosensitized patients. To our knowledge this is the first study to show the clinical and immunological efficacy of pre-seasonal allergoid immunotherapy in monosensitized and polysensitized patients with seasonal allergic rhinitis.

Allergen-specific immunotherapy is the only immunomodulatory treatment modality that leads to the development of long-term tolerance to allergens. The formation of peripheral T cell tolerance to allergens with immunotherapy plays a critical role (10). In this study we measured specific IgG4 to assess the immunological effect of pre-seasonal allergoid immunotherapy. However, it should be emphasized that the production of IgG4 blocking antibodies is also associated with a number of other immunological mechanisms. Mast cell and basophil desensitization are responsible for the early effects after initiation of therapy. Then, modulation of T and B cell responses, induction of peripheral T regulatory (Treg) cells, increase in IL-10 and TGF-β levels, changes in allergen-specific antibody responses (decrease in IgE, increase in blocking antibodies such as IgG4 and IgA) occur. In the late response, the production of mast cells, eosinophils and their mediators is reduced in the target tissue (11). IgG4-related immunological effects are also responsible for clinical effects following reduction of allergic inflammation (12).

Although there are studies demonstrating that pre-seasonal allergoid immunotherapy is clinically effective, there is limited data regarding its immunological effects. It is expected that immunological and clinical effects of allergoid immunotherapy emerge earlier and become more marked in contrast to conventional immunotherapy (3, 4). In the placebo-controlled study of Pas-

Figure 4 *- Monthly VAS scores:* ***(a)*** *immunotherapy and control groups;* ***(b)*** *monosensitized and polysensitized patients in the immunotherapy group.*



*p < 0.05.

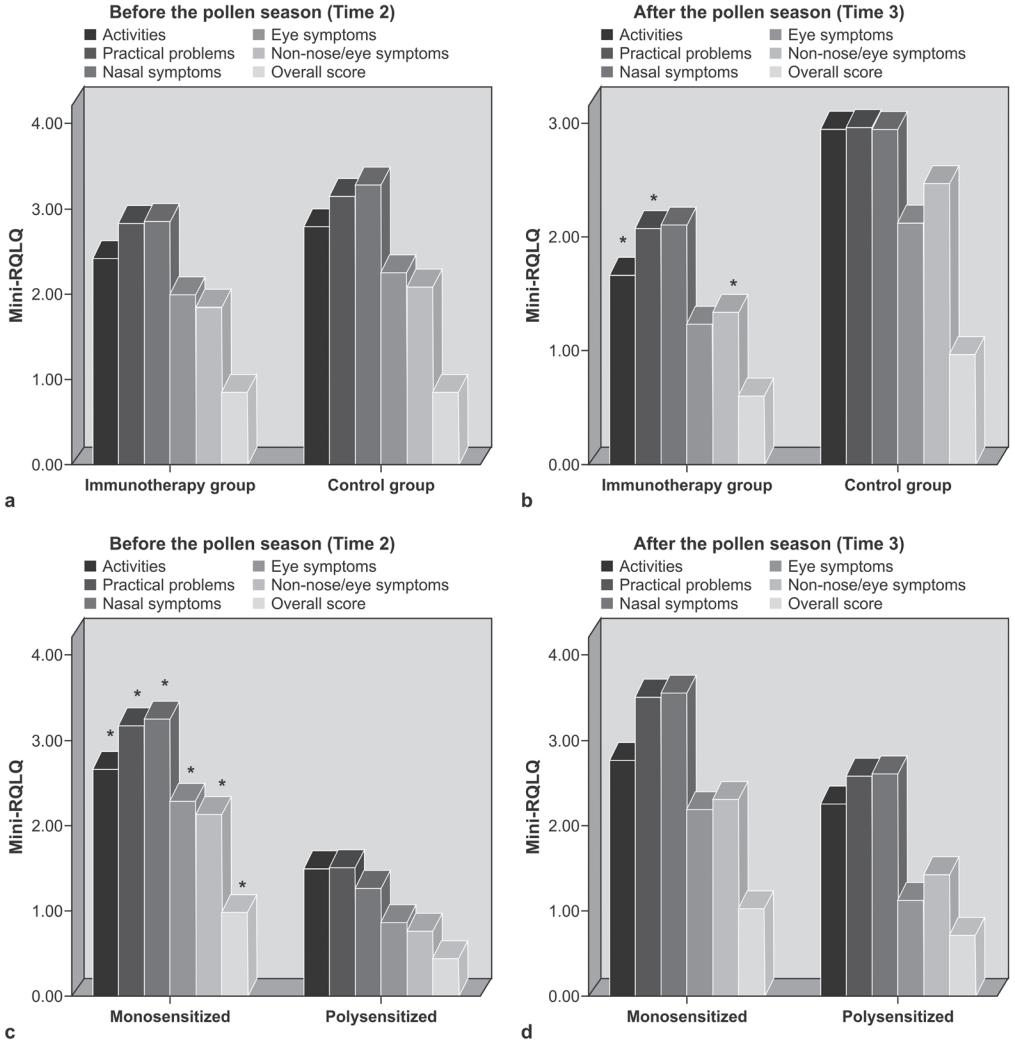
torella *et al.*, it was reported that symptom-medication scores in May were significantly lower than placebo group and there was a significant increase in sIgE, sIgG1 and sIgG4 levels in the early period in active groups with seasonal allergic rhinitis. However, higher sIgG4/sIgG1 ratio was found to be associated with high symptom-medication scores (13). In the placebo-controlled study of Corrigan *et al.* in 154 patients with seasonal allergic rhinoconjunctivitis responsible from grass pollen, it was demonstrated that symptom and medication scores were significantly lower and sIgG1 *vs* sIgG4 levels were higher than placebo group in the pre-seasonal immunotherapy group (2). In a study comparing perennial and pre-seasonal immunotherapy, the increase in sIgG4 levels at the end of 2nd year was found to be higher in the perennial group, however the difference between two groups was not significant indicating that pre-seasonal immunotherapy had also an early immunological effect (11, 14). Additionally, an early improvement in clinical outcomes and quality of life accompanied by sIgG4 increase was also demonstrated with pre-seasonal immunotherapy (15, 16). The findings of this study were in accordance with previous studies in which significant clinical improvement was shown with allergoid immunotherapy.

We know that conventional immunotherapy induces increase in the allergen-specific IgG4 antibody production within a few weeks. In our study, we also looked for the answer to question on how allergoid immunotherapy affects specific IgG4 levels in early period. Phl p sIgG4 levels were found to be increased after 7 weeks of allergoid immunotherapy in the active group compared to control subjects as well as it was accompanied by significant improvement in symptom and drug scores in this study. Increase in sIgG4 with allergoid immunotherapy is important as it indicates the emergence of humoral immune response in B lymphocytes in early period of allergoid immunotherapy. In our opinion the sustained immunological benefit achieved after short term allergoid immunotherapy is also a notable finding of this study. In support of our findings, in another study performed in our clinic, we found that sIgG4 levels were significantly higher after pre-seasonal allergoid immunotherapy in patients with grass pollen allergy (17). It is expected that antigenic stimulation induces specific IgE production during the early period generally first 6 months of immunotherapy and then starts to decrease synthesis of IgE antibodies. In accordance with this findings, we detected increase in specific IgE antibody levels in patients receiving immunotherapy. Nevertheless, there was no difference between active and control groups in terms of sIgE levels after 7 weeks of immunotherapy.

According to epidemiological and clinical studies, it was established that 50-80% of cases with allergic rhinitis diagnosed polysensitization. Polysensitized patients display a different clinical profile than monosensitized ones since their condition is associated with more severe disease that influences quality of life more markedly (18). It was usually believed that immunotherapy was less effective in polysensitized than monosensitized patients in previous years, however it has been recently demonstrated that immunotherapy was efficacious in polysensitized patients as well (1, 6). In contrast to previous studies, we observed that single allergen immunotherapy with grass pollen extract in which it was most relevant allergen responsible for the most bothersome symptoms, can lead to both clinical improvement and also humoral changes such as increase in blocking antibody production in polysensitized but clinically monoallergic patients.

In the literature, most of the studies has been reported about the effectiveness of sublingual and tablet forms for grass pollen extract. It is seen that previous comparison studies between monosensitized and polysensitized patients were focused on sublingual route (19, 20). However, Passalacqua *et al.* highlighted that the optimal regimen is pre-seasonal immunotherapy in patients with seasonal allergic rhinitis (21). In a single study, conventional subcutaneous immunotherapy performed with a

Figure 5 *- Mini-RQLQ domains:* ***(a,b)*** *immunotherapy and control groups;* ***(c,d)*** *monosensitized and polysensitized patients in the immunotherapy group.*

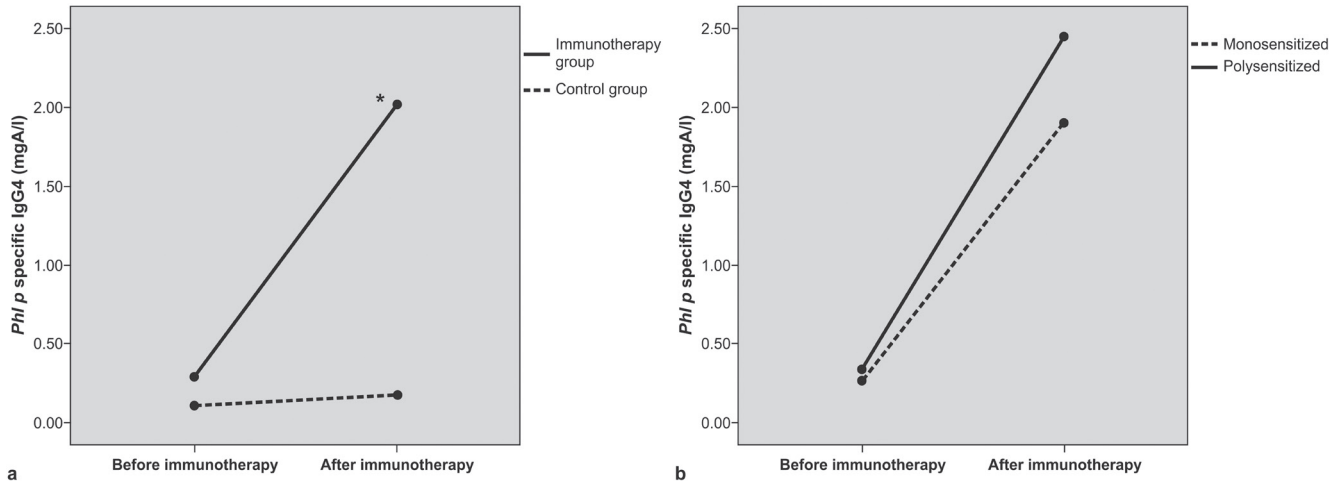


*p < 0.05.

single grass pollen in patients with seasonal allergic rhinitis, was found to be effective and safe, and no difference was found between monosensitized and polysensitized patients with respect to symptom scores and quality of life (22). Additionally, authors recently consider that in case of polysensitized patients, if they have no seasonal symptoms related to grass pollens and most relevant perennial allergen responsible for clinical symptoms, it may be recommended single-AIT (23). In another study carried out in our clinic, we found that increase in sIgG4, sIgE and total IgE antibodies after cluster immunotherapy performed with single Der p allergen was more marked in polysensitized patients than that in monosensitized patients (24). In addition to these data, in this study we demonstrated that the clinical effectiveness of single (Der p) allergen immunotherapy was comparable between monosensitized and polysensitized patients who had clinically monollergy to most relevant house dust mite allergen. In our study, sensitization profile in polysensitized patients was shown in **figure 2**. House dust mites and cat allergen sensitization was found as predominant perennial allergens. However, all patients had described only seasonal allergic symptoms due to grass pollen sensitization suggesting clinically relevant monoallergy.

Main limitation of the present study is that it is not a double-blind placebo-controlled study. However, we used a group receiving only drug treatment as control group who have similar

Figure 6 *- Phl p specific IgG4.* ***(a)*** *Immunotherapy and control groups;* ***(b)*** *monosensitized and polysensitized patients in the immunotherapy group.*



*p < 0.05.

clinical characteristics with the active treatment group. We believe that using such control groups is also valuable in immunotherapy studies, as we compared both groups with objective parameters. Another limitation is that the number of polysensitized patients is lower than the number of monosensitized patients.

Based upon the data obtained in this preliminary study, it may be suggested that in patients with seasonal allergic rhinitis, pre-seasonal short-term allergoid immunotherapy leads also to production of protective type sIgG4 blocking antibodies during early period despite the increase in sIgE as well in conventional immunotherapy. In addition, clinical improvement in the patients is quite promising for the early period of pre-seasonal immunotherapy. Importantly, improvement in symptom-medication scores and quality of life after allergoid immunotherapy was found to be similar between monosensitized and polysensitized groups despite lower number of polysensitized patients in contrast to false beliefs. This finding was accompanied by the increases in sIgG4 after immunotherapy both in monosensitized and also polysensitized patients. In conclusion, although our study suggests that in early period of allergoid grass pollen immunotherapy polysensitized monoallergic patients may benefit as much as monosensititized patients do, these results need to be further supported by clinical and immunological effectiveness of immunotherapy in large-scale studies.

Fundings

This study was supported by Ankara University (16H023002) and Necmettin Erbakan University (171218001) Scientific Research Foundation.

Contributions

DM: conceptualization. DM, ŞS: study design, funding. ZM, BAS: supervision. ŞS, DS, CD: materials. ŞS, DS: data collection and/or processing. DG: statistical analysis and/or data interpretation. ŞS: literature review, manuscript preparation. ŞS, DM, ZM, BAS: critical review.

Conflict of interests

The authors declare that they have no conflict of interests.

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;2007(1):CD001936. doi: 10.1002/14651858.CD001936.pub2.
2. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A; Study Group. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. Allergy. 2005;60(6):801-7. doi: 10.1111/j.1398-9995.2005.00790.x.
3. Keskin O, Tuncer A, Adalioglu G, Sekerel BE, Saçkesen C, Kalayci O. The effects of grass pollen allergoid immunotherapy on clinical and immunological parameters in children with allergic rhinitis. Pediatr Allergy Immunol. 2006;17(6):396-407. doi: 10.1111/j.1399-3038.2006.00442.x.
4. 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):S1-55. doi: 10.1016/j.jaci.2010.09.034.
5. Bahceciler NN, Yuruker O. Planning and approach to allergen-specific immunotherapy in polyallergic patients. Immunotherapy. 2020;12(8):577-85. doi: 10.2217/imt-2019-0182.

6. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Management of the polyallergic patient with allergy immunotherapy: a practice-based approach. Allergy Asthma Clin Immunol. 2016;12:2. doi: 10.1186/s13223-015-0109-6.
7. Calderón MA, Cox L, Casale TB, Moingeon P, Demoly P. Multiple-allergen and single-allergen immunotherapy strategies in polysensitized patients: looking at the published evidence. J Allergy Clin Immunol. 2012;129(4):929-34. doi: 10.1016/j.jaci.2011.11.019.
8. Clark J, Schall R. Assessment of combined symptom and medication scores for rhinoconjunctivitis immunotherapy clinical trials. Allergy. 2007;62(9):1023-8. doi: 10.1111/j.1398-9995.2007.01469.x.
9. Yuksel H, Yilmaz O, Alkan S, Bayrak Değirmenci P, Kirmaz C. Validity and reliability of Turkish version of rhinitis and mini-rhinitis quality of life questionnaires. Allergol Immunopathol (Madr). 2009;37(6):293-7. doi: 10.1016/j.aller.2009.04.006.
10. Kucuksezer UC, Ozdemir C, Cevhertas L, Ogulur I, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy and allergen tolerance. Allergol Int. 2020;69(4):549-60. doi: 10.1016/j.alit.2020.08.002.
11. Celebi Sözener Z, Mungan D, Cevhertas L, Ogulur I, Akdis M, Akdis C. Tolerance mechanisms in allergen immunotherapy. Curr Opin Allergy Clin Immunol. 2020;20(6):591-601. doi: 10.1097/ACI.0000000000000693.
12. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol. 2011;127(1):18-27; quiz 28-9. doi: 10.1016/j.jaci.2010.11.030.
13. Pastorello EA, Pravettoni V, Incorvaia C, Mambretti M, Franck E, Wahl R, et al. Clinical and immunological effects of immunotherapy with alum-absorbed grass allergoid in grass-pollen-induced hay fever. Allergy. 1992;47(4 Pt 1):281-90. doi: 10.1111/j.1398-9995.1992.tb02054.
14. Tworek D, Bochenska-Marciniak M, Kuprys-Lipinska I, Kupczyk M, Kuna P. Perennial is more effective than preseasonal subcutaneous immunotherapy in the treatment of seasonal allergic rhinoconjunctivitis. Am J Rhinol Allergy. 2013;27(4):304-8. doi: 10.2500/ajra.2013.27.3935.
15. Williams A, Henzgen M, Rajakulasingam K. Additional benefit of a third year of specific grass pollen allergoid immunotherapy in patients with seasonal allergic rhinitis. Eur Ann Allergy Clin Immunol. 2007;39(4):123-6. Available at: https://pubmed.ncbi.nlm.nih.gov/17523386/.
16. Rajakulasingam K. Early improvement of patients' condition during allergen-specific subcutaneous immunotherapy with a high-dose hypoallergenic 6-grass pollen preparation. Eur Ann Allergy Clin Immunol. 2012;44(3):128-34. Available at: http://www.eurannallergyimm.com/cont/journals-articles/282/volume-early-improvement-patients-condition-during-752allasp1.pdf.
17. Kepil Özdemir S, Sin BA, Güloğlu D, İkincioğulları A, Gençtürk Z, Mısırlıgil Z. Short-term preseasonal immunotherapy: is early clinical efficacy related to the basophil response? Int Arch Allergy Immunol. 2014;164(3):237-45. doi: 10.1159/000365628.
18. Ciprandi G, Incorvaia C, Puccinelli P, Soffia S, Scurati S, Frati F. Polysensitization as a challenge for the allergist: the suggestions provided by the Polysensitization Impact on Allergen Immunotherapy studies. Expert Opin Biol Ther. 2011;11(6):715-22. doi: 10.1517/14712598.2011.576246.
19. Malling HJ, Montagut A, Melac M, Patriarca G, Panzner P, Seberova E, et al. Efficacy and safety of 5-grass pollen sublingual immunotherapy tablets in patients with different clinical profiles of allergic rhinoconjunctivitis. Clin Exp Allergy. 2009;39(3):387-93. doi: 10.1111/j.1365-2222.2008.03152.x.
20. Nelson H, Blaiss M, Nolte H, Würtz SØ, Andersen JS, Durham SR. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized subjects. Allergy. 2013;68(2):252-5. doi: 10.1111/all.12074.
21. Passalacqua G, Bagnasco D, Ferrando M, Heffler E, Puggioni F, Canonica GW. Current insights in allergen immunotherapy. Ann Allergy Asthma Immunol. 2018;120(2):152-4. doi: 10.1016/j.anai.2017.11.001.
22. Frew AJ, Powell RJ, Corrigan CJ, Durham SR; UK Immunotherapy Study Group. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006;117(2):319-25. doi: 10.1016/j.jaci.2005.11.014.
23. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Management of the polyallergic patient with allergy immunotherapy: a practice-based approach. Allergy Asthma Clin Immunol. 2016;12:2. doi: 10.1186/s13223-015-0109-6.
24. Soyyigit S, Guloglu D, Ikinciogullari A, Secil D, Oztuna D, Mungan D, et al. Immunologic alterations and efficacy of subcutaneous immunotherapy with Dermatophagoides pteronyssinus in monosensitized and polysensitized patients. Ann Allergy Asthma Immunol. 2016;116(3):244-51.e2. doi: 10.1016/j.anai.2016.01.002.

ORIGINAL ARTICLE | Eur Ann Allergy Clin Immunol | Vol 55, N.3, 131-140, 2023

Ana Margarida Pereira[1-3,*], Mariana Pereira[1,2,4,*], Luís Miguel Araújo[1,2,5], Maria Graça Castel-Branco[1], Ana Morete[1], João Almeida Fonseca[1-4]

Self-reported adverse reactions to subcutaneous airborne allergen immunotherapy: a real-life, single center study

[1]Allergy Unit, CUF-Porto (Hospital & Instituto), Porto, Portugal
[2]Center for Health Technology and Services Research (CINTESIS), Faculty of Medicine, University of Porto, Porto, Portugal
[3]Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Porto, Portugal
[4]Medicina, EDucação, I&D e Avaliação, Lda (MEDIDA), Porto, Portugal
[5]Basic & Clinical Immunology, Department of Pathology, Faculty of Medicine, University of Porto, Porto, Portugal
*The authors contributed equally to this work

Key words

Adverse reactions; subcutaneous allergen immunotherapy; multiple allergen immunotherapy; extracts dilutional effect.

Corresponding author
Ana Margarida Pereira
Center for Research in Health Technologies and Information Systems (CINTESIS)
Faculty of Medicine
University of Porto
Rua Plácido da Costa, s/n
4200-450 Porto, Portugal
ORCID: 0000-0002-5468-0932
E-mail: ambrpereira@gmail.com

Doi
10.23822/EurAnnACI.1764-1489.212

Summary

Background. *To estimate the prevalence of self-reported adverse reactions (AdR) to subcutaneous airborne allergen immunotherapy (SCIT) and to describe factors associated with its occurrence.* ***Methods.*** *Real-life, observational, descriptive study of all patients treated with SCIT at a Portuguese allergy unit between 03/2017 and 06/2019, and who answered ≥ 1 time to a pre-SCIT evaluation questionnaire assessing the occurrence of local and/or systemic AdR in the previous administration.* ***Results.*** *939 questionnaires from 231 patients (42% female, 35% with asthma) were included. Most (60%) SCIT preparations had multiple allergens with concentration adjusted to prevent dilution (MA-NoDil), 26% were single allergen with standard concentration (SA-SC), 10% single allergen with higher than standard concentration (SA-HC), and 4% mixtures without concentration adjustment (MA-Dil). SCIT-related AdR were self-reported in 313 (33%) administrations, 97% at the injection site and 11% grade 1 systemic symptoms. In a multivariable model, being a female and having asthma were associated with higher risk of AdR. MA-NoDil SCIT presented a lower risk of AdR compared to SA-SC SCIT.* ***Conclusions.*** *SCIT-related AdR were self-reported in 1/3 of the administrations, most at the injection site. The risk of AdR was higher in females and in patients with asthma. The lower risk of adverse reactions observed in SCIT preparations with multiple allergens with no dilutional effect should be further explored in future, targeted studies.*

Impact statement

Self-reported SCIT-related adverse reactions are common, occurring in 1/3 of the administrations, but almost all at the injection site and most easily tolerable. Females and patients with asthma had a higher odds ratio for self-reported SCIT adverse reactions.

Introduction

Allergen immunotherapy (AIT) is the only disease-modifying treatment for allergic diseases (1). It is usually administered by sublingual (SLIT) or subcutaneous (SCIT) route and both have demonstrated efficacy in reducing both allergic symptoms upon exposure to aeroallergens and the need for rescue medications (1). To achieve long-term benefits, AIT should be continued for a minimum of 3 years (2, 3).

Allergen immunotherapy safety, especially with SCIT, has been a significant concern. In fact, adverse reactions (AdR) associated with SCIT administration are common with some studies reporting that over 85% of patients receiving SCIT experience local, injection site reactions (LR) (1). Conversely, systemic reactions (SR) with SCIT are unusual but potentially severe, including the risk of anaphylaxis (1, 4). Therefore allergen immunotherapy should be administered by or under the close supervision of a trained physician who can recognize early symptoms and signs of anaphylaxis and administer emergency treatment (4). Moreover, all patients should be kept under surveillance at the healthcare facility for at least 30 minutes following injections (4). The rate of SCIT-associated SR of varying severity is relatively low, at around 0.1-0.2% (1). In Portugal, published data shows that SCIT-associated SR are also infrequent, occurring in about 0.1% of all SCIT administrations (5). There are several commonly described risk factors for SCIT-associated SR, including poorly-controlled asthma, infections, physical exercise, administration during pollen season, prior history of SCIT-associated SR, some concomitant medications (such as beta-adrenergic blockers or ACE inhibitors), frequency of administration, dosing error and incorrect administration technique (4, 6-9). Although SR can be severe and even lead to death (1), LR are much more common and can have impact on patient compliance and SCIT schedule or dose (10, 11). Nevertheless, risk factors for SCIT-associated LR or AdR as a whole (including both local and systemic AdR) were seldom evaluated.

In the last couple of years, new SCIT formulations have been released by different manufacturers. These include the possibility to prescribe mixtures of non-homologous allergens without significant loss of efficacy and the use of SCIT preparations with higher than standard allergen concentration. Although the current European guidelines on AIT do not recommend prescribing SCIT with mixtures of non-homologous allergens (2), 60 to 80% of the patients consulting allergists are polysensitized (12). When treating a polyallergic patient with AIT, some allergists use a single-allergen formulation (selecting the most clinically relevant allergen), whereas others prefer to prescribe either a mixture of two or more allergen extracts (preferably adjusting for dilutional effect) or two or more separate allergens (12). The possibility to use mixtures of non-homologous allergens within the same SCIT preparation seems very interesting to treat polyallergic patients. Still, there are unclarified concerns regarding the stability of the preparation (12) and a possible increase in the risk of AdR.

Dose-finding clinical trials suggested that SCIT efficacy increases with higher allergen concentrations, but this may be hampered by an increased risk of adverse reactions (13). Nevertheless, most allergen preparations commercialized in Portugal have no published studies regarding the optimal concentration (efficacy combined with tolerability) nor the associated risk of AdR.

This study aimed to estimate the prevalence of self-reported local and/systemic AdR to SCIT with airborne allergens and to describe factors associated with the occurrence of self-reported AdR, focusing on a possible increased risk in relation to the use of allergen mixtures and higher allergen concentrations.

Materials and methods

Study design

This was an observational, descriptive study that analyzed real-world data collected anterogradely during administrations of SCIT with airborne allergens in a private allergy unit from Northern Portugal, between March 2017 and June 2019. During this period, 497 individuals had SCIT administered at the site.

Participants

This study included data from all individuals who answered at least once to the self-administered questionnaire that is applied prior to SCIT administration as part of the usual clinical care provided at the allergy unit. Patients without any information on SCIT AdR in the filled the questionnaires were excluded. No additional exclusion criteria (*e.g.*, regarding the time since the beginning of SCIT or SCIT composition) were applied. All data were collected during routine care and the analysis was performed using an anonymized dataset with no personal identifier. Therefore, Ethics Committee approval was not required.

Data collection

Data on SCIT AdR were collected using a self-administered paper questionnaire that was implemented in 2017 to have a structured assessment of the conditions for a safe SCIT administration. The questionnaire was delivered to the patient after arriving to the allergy unit and filled while waiting for SCIT administration under the supervision of a healthcare professional that clarified any doubt about the interpretation of the questions, but avoided direct influence on answer selection; this support was only provided when requested by the patient. Children under thirteen years old answered the questionnaires together with their parents; older children were asked to answer the questionnaire by themselves but could ask for parent support when they felt it was needed.

Additional data on allergic disease diagnosis, date of first SCIT administration and physician perception on the relation between SCIT administration and self-reported systemic reactions were collected from the electronic medical records and, when necessary, from specific SCIT administration paper records. No information regarding local AdR was collected from the electronic medical records.

Data on SCIT characterization, including type of extract (*e.g.*, polymerized, depot or aqueous), allergen composition and concentration (with or without dilutional effect) were collected from the SCIT packaging and manufacturer's information.

All the patient data were collected as part of the usual clinical care and they were anonymized before analysis.

Questionnaire description

The questionnaire is provided as **figure 1**.

The collected data on adverse reactions reported to the last SCIT administration and included a symptom checklist considering both local and systemic symptoms. The checklist for local reactions included the presence of swelling and its approximate size (< 5 cm, 5 to 8 cm, and > 8 cm), redness, itching and subcutaneous nodule. The checklist for systemic symptoms ("apart from injection site") was stratified according to the systems that are commonly used for severity classification (14): skin, respiratory, gastrointestinal and cardiovascular systems. Within each body system, the most frequent or particularly relevant symptoms were specifically included. A few additional symptoms that do not directly fit into any of the referred systems but are frequently described in the literature (14) (*e.g.*, metallic taste, headache, itchy and watery red eyes) were also included. Patients could also report other symptoms as free text.

When an AdR was reported, the patient was asked to provide additional details regarding the timing of onset (< 30 minutes, 30 to 60 minutes and > 60 minutes), associated discomfort and impact (not troublesome; mild discomfort − easily tolerable; moderate discomfort − tolerable; and severe discomfort − interfering with daily activities/sleep), need for medical observation and treatment. Additional data regarding recent/current acute illness, and current allergic disease control, including CARAT (Control of Allergic Rhinitis and Asthma Test) and a visual analogue scale assessing eye symptoms, were also collected, but are not used in this analysis.

Classifications and definitions

The classification of swelling dimensions considered in the questionnaire checklist (< 5 cm, 5 to 8 cm, and > 8 cm) was based on the cut-offs that are commonly used to decide on SCIT dose increase (when applicable), keep as is or decrease (15).

The severity of systemic reactions to SCIT was computed using the self-reported systemic symptoms and classified according to the classification proposed by the World Allergy Organization (WAO) (14), including 5 different grades. SCIT allergen composition was classified according to the number of non-homologous allergens into single *vs* multiple allergen (MA) SCIT. Homologous allergens were considered when a high cross-reactivity is reported in the literature, such as between *D. pteronyssinus* and *D. farinae*, and they were considered as a single allergen. Single allergen (SA) SCIT was further classified according to allergen concentration into standard (SC) or higher than standard concentration (HC; *e.g.*, preparations described as "strong" by SCIT manufacturers). MA SCIT was classified according to the presence of dilutional effect, according to the manufacturer's information regarding that specific SCIT preparation: if the manufacturer reported that the dilutional effect of allergen mixture was compensated, the preparation was considered as without dilutional effect (NoDil); if no concentration adjustment was explicitly indicated, the preparation was considered as having dilution effect (Dil). Moreover, to classify the mixtures according to the presence of allergens of different groups, single allergens were grouped into six major classes: mites (*D. pteronyssinus/D. farinae* and *L. destructor*); epithelia (cat and dog); grass, tree (*Olea europea*, *Betula alba* and *Platanus acerifolia*) and weed (*Parietaria judaica*, *Artemisia vulgaris* and *Plantago lanceolata*) pollens; and molds (*Alternaria alternata*).

Statistical analysis

Categorical data were described with absolute and relative frequencies. Continuous variables with normal distribution (*e.g.*, age) were described with mean and standard deviation (SD); those with non-parametric distribution (*e.g.*, time since the beginning of SCIT) were presented as median and percentile 25-percentile 75. Normality was checked using Shapiro-Wilk test and by visual analysis of the variable distribution. A sub analysis including patients that filled at least six questionnaires during the study period was also performed.

Generalized estimating equations were used to develop a repeated measures multivariable logistic regression model to explain the factors associated with the occurrence of AdR. A common anonymized identifier and SCIT composition were used to identify repeated measures (with patient/SCIT composition pairs being the unit of analysis within the model). A univariate analysis was performed with all available variables possibly associated with the occurrence of AdR. Variables with a P-value < 0.250 in the univariate analysis were selected for inclusion in the multivariable regression model. This initial multivariable model was further improved using a stepwise strategy, with additional variables being excluded based on the individual P-value after adjustment and the model's QICC (corrected Quasi Likelihood under Independence Model Criterion). QICC was used to assess goodness-of-fit and the model with the lowest QICC was selected. Results were presented as odds ratio (OR) with 95% confidence intervals (CI). All statistical analyses were performed with IBM SPSS® version 25 (IBM Corporation, Armonk, USA). The forest-plot was created

***Figure 1** - Subcutaneous allergen immunotherapy: pre-administration questionnaire.*

In the last administration of subcutaneous allergen immunotherapy:

A - Did you have any side effects/adverse reactions? ……..**Yes** ☐ **No** ☐

If Yes: a) What were the symptoms (check all the symptoms that occurred)? (If **No** go to **Question B**)

At the injection site	
Swelling - diameter:	
< 5 cm	☐
5-8 cm	☐
> 8 cm	☐
Itching	☐
Redness	☐
Subcutaneous nodule	☐

Systemic symptoms (away from the injection site)					
Skin		Respiratory		Gastrointestinal	
Generalized itching	☐	Rhinitis (runny nose, sneezing, itchy nose, stuffy nose)	☐	Vomit	☐
Urticaria	☐			Diarrhea	☐
Swelling/edema (external)	☐	Itchy throat	☐	Stomachache	☐
		Cough from throat	☐		☐
Other symptoms		Asthma attack **solved** with SOS medication	☐	Cardiovascular	
Metallic taste	☐			Drop in blood pressure	☐
Headache	☐	Asthma attack **not solved** with SOS medication	☐	Loss of consciousness/ fainting	☐
Red, itchy and watery eyes	☐	Swelling of the tongue or tightness in the throat	☐	Other:_____	
Nausea	☐				

b) How long after the injection did the symptoms started?

Less than 30 minutes ☐ **Between 30 and 60 minutes** ☐ **More than 60 minutes** ☐

c) Were the symptoms bothersome? (tick with **x** the answer that best characterizes your symptoms)

☐ - - - - - ☐ - - - - - ☐ - - - - - ☐

0 - no discomfort | 1 - mild discomfort, easily tolerable | 2 - moderate discomfort, tolerable | 3 - severe discomfort that interferes with daily activities/sleep

d) Did you need medical observation? ……. **Yes**☐ **No** ☐

d.1) if YES, where/ by whom were you observed?

Allergist ☐ **Emergency Room** ☐ **Primary care center** ☐

e) Did you need treatment? **…….** **Yes** ☐ **No** ☐

e.1) If Yes, which one?_____ (report all the treatments you remember)

If NO go to Question B

Since the last administration of subcutaneous allergen immunotherapy:

B - Did you start or increase any medication? ……..……. **Yes** ☐ **No** ☐

(If **NO** go to **Question C**)

IF YES: c.1) Specify the reason: **Asthma** worsening ☐ **Rhinitis** worsening ☐ **Skin** problems ☐

Infection ☐ **Other** ☐ _____ Please specify

c.2) Which medication did you start/increase?

Name/drug description*		Dose	When
	Started ☐ Increased ☐		
	Started ☐ Increased ☐		
	Started ☐ Increased ☐		
	Started ☐ Increased ☐		

* If you don't remember the name of your medication you can make a short description, for example: "nasal spray with green cap", "purple disk", "oral corticosteroid", antibiotic…

C - Did you miss work/school because of your allergies (asthma, rhinitis, atopic dermatitis)?

I'm not working/studying ☐ **I didn't miss** ☐ **Missed** ☐ **_____Days**

D - Did you go to the Emergency Room or needed an unscheduled medical appointment due to worsening of your allergies? (asthma, rhinitis, dermatitis) **…….** **Yes** ☐ **No** ☐

If NO go to Question C

Over the past 3 days:

E - Have you had fever and/or symptoms of infection?……. **Yes** ☐ **No** ☐

F - Did your allergic diseases get worse? (asthma, rhinitis, dermatitis)? …….. **Yes** ☐ **No** ☐

The questionnaire also assesses symptom control with CARAT and a visual analogue scale evaluating eye symptoms (not shown).

with MS Excel® version 2006 (Microsoft Corporation, Redmond, USA). P-values < 0.05 were defined as statistically significant.

Results

Description of the study participants and administered SCIT

During the study period, 991 questionnaires were filled (250 patients) and 52 were excluded. Overall, 939 questionnaires, from 231 patients, were included (**figure 2**); 55 (23%) patients filled ≥ 6 questionnaires. Nine patients changed SCIT composition during the study period, with a total of 240 patients / SCIT composition pairs available for analysis (**figure 2**). Most study patients were male and had ≥ 18 years old at the time of the last registered SCIT administration. All had allergic rhinitis and one third had asthma (**table I**). At the time of the questionnaire, the median (P25-P75) time since the beginning of SCIT was 17 (7-30) months; in 37% (n = 343) of the administrations SCIT was ongoing for three or more years. Mites and grass pollens were the most commonly used extracts in the administered SCIT. Almost two thirds were preparations with MA extracts and only 31% of them had allergens from a single group. Most mixtures had concentrations adjusted to prevent dilutional effect (**table I**). All but one (an *Alternaria alternata* extract) were polymerized.

Self-reported AdR: prevalence and characterization

Self-reported SCIT-related AdR were registered in 313 (33%) administrations, corresponding to 111 (48%) patients with at least one AdR. Most (97%) were local AdR and presented with injection site swelling and/or itching. There were 11% (n = 34, corresponding to 4% of all SCIT administrations) with self-reported systemic symptoms (all grade 1; **table II**). Nevertheless, none of these self-reported systemic reactions was recorded by the administering physician as being related to SCIT and there were no SCIT interruptions or schedule/dose changes in relation with these self-reported systemic symptoms.

Thirty-five percent of the AdR started less than 30 minutes after SCIT administration (within the watching period), 30% between 30 and 60 minutes and 35% after 60 minutes. Only four AdR required medical observation, all presenting with local symptoms and one with associated headache; three of them were treated with topical corticosteroid and/or systemic antihistamine (the one with headache had no need for treatment). Three quarters (n = 232) of the self-reported AdR had some associated discomfort, but most (77%) were considered mild and easily tolerable. Only 3 patients (1.2% of those who classified AdR severity) reported severe discomfort that interfered with sleep or daily activities.

Considering patients that filled ≥ 6 questionnaires during the study period, 38 (69%) reported at least one AdR. Twenty of them (53%) reported AdR in less than 50% of the administrations and five (13%) reported SCIT-related AdR in all administrations.

Table I *- Patient (n = 231) and SCIT (n = 240) characteristics.*

	n	%
Sex, female	98	42
Age group, < 18 years old	100	43
Age, mean (SD)	23.6	13.8
Clinical diagnosis		
Allergic rhinitis	231	100
Asthma	80	35
Allergen extracts in administered SCIT		
Mites	182	76
Epithelia	21	9
Grass pollens	124	52
Tree pollens	14	6
Weed pollens	23	10
Molds	2	0.8
Number of non-homologous allergens in SCIT		
One allergen	86	36
Multiple allergens	153	64
Two allergens	111	46
Three allergens	41	17
Four allergens	1	0.4
Number of allergen groups		
One allergen group	49	31
Two allergen groups	93	58
Three allergen groups	17	11
Type of SCIT		
Single allergen, standard concentration	63	26
Single allergen, higher concentration	23	10
Multiple allergens, with dilutional effect	10	4
Multiple allergens, without dilutional effect	143	60

Data is presented as n (%), except when otherwise indicated; SD: standard deviation.

Self-reported AdR: factors associated with reporting

In the univariate analysis, the self-report of AdR to SCIT was significantly associated with female gender, asthma diagnosis, the number of allergens groups included in the SCIT preparation and the type of SCIT (**table III**). Age group, time since the beginning of SCIT and the specific allergen groups included in treatment were not significantly associated with self-reported AdR to SCIT. In the adjusted model, being a female and having asthma were associated with increased risk of reporting adverse reactions to SCIT (OR 1.71 (1.19-2.46) and OR 1.89 (1.30-2.75), respec-

Figure 2 *- Study flowchart.*

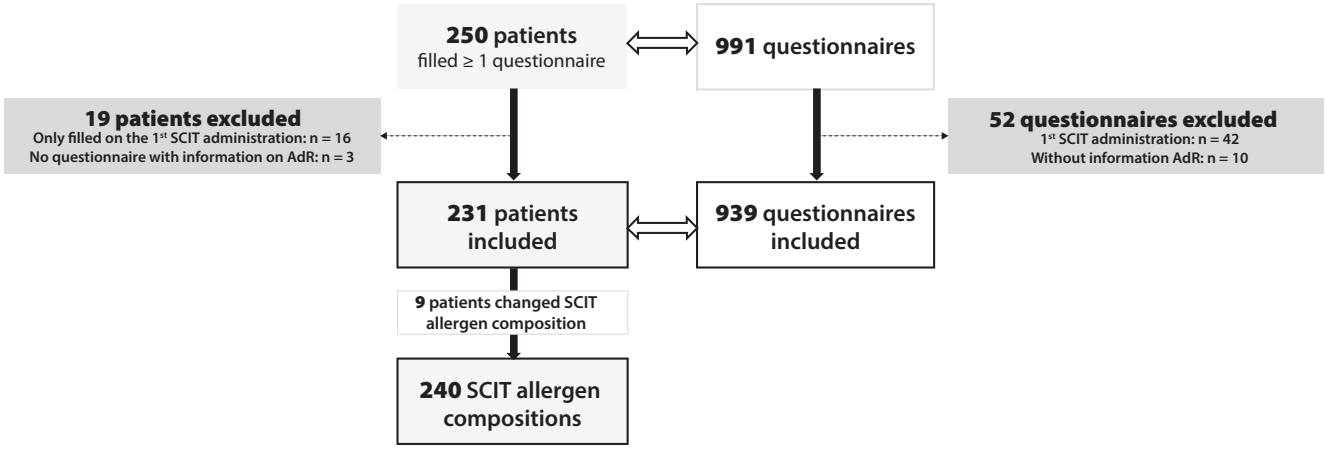


Table II *- Self-reported SCIT adverse reactions, considering all questionnaires (n = 939).*

	n	%
Self-reported adverse reaction	313	33
Local adverse reactions	304	32
Edema (any size)	256	27
< 5 cm	180	19
5-8 cm	58	6
> 8 cm	18	2
Itching	211	22
Erythema	161	17
Subcutaneous nodule	136	14
Systemic adverse reactions	34	4
Generalized itching or urticaria	14	1
Angioedema	7	0.7
Rhinitis	15	2
Conjunctivitis	9	1
Throat itching	1	0.1
Other respiratory symptoms*	0	0
Stomach pain	1	0.1
Vomiting or diarrhea	0	0
Cardiovascular symptoms¥	0	0
Other symptoms†	2	0.2

Percentages for local and systemic adverse reactions were computed based on the total number of administrations; SD: standard deviation; *including cough and asthma exacerbation; ¥including hypotension and syncope; †including metallic taste (n = 0) and headache (n = 2).

tively; **table III** and **figure 3**). The type of SCIT was also significantly associated with AdR, with those under SCIT with MA-NoDil presenting a lower risk of AdR (OR 0.52 (0.35-0.78)). SCIT with SA-HC was not a significant risk factor for self-reported SCIT-related AdR (**table III** and **figure 3**). The number of allergen groups included in the SCIT preparation was not included in the final adjusted model.

Discussion

In this study, patients treated with SCIT with airborne allergens reported adverse reactions in 33% of the administrations. Most adverse reactions were local and with only mild discomfort, easily tolerable. Although systemic symptoms were self-reported in 4% of the administrations, none was considered as SCIT-associated by the administering physician. In the adjusted logistic regression model, the risk of self-reported SCIT-associated AdR was higher in female and patients with asthma. The use of SCIT preparations with MA-NoDil was associated with a lower risk of AdR.

This study assessed the patient's perspective regarding SCIT-associated AdR, using real-life data. To our knowledge, this is one of the few published studies assessing SCIT related AdR based on self-reported patient information; most of the other studies report only physician information, which might be more objective and correspond to a more robust evaluation of the underlying causality relationship, but lack the patient's perspective. Our findings are in agreement with those from previous studies based on self-reported SCIT-related adverse reactions, with a high proportion of local adverse reactions, some reports of systemic symptoms (with higher frequency than when based on physician assessment) and low discomfort. One study in the USA, by Coop *et al.* (16), found a high proportion of patients (reaching 71%) that reported at least one local reaction during SCIT; nevertheless, 82% of

Figure 3 *- Forest plot representing the final adjusted model for risk of self-reported SCIT-related adverse reactions.*

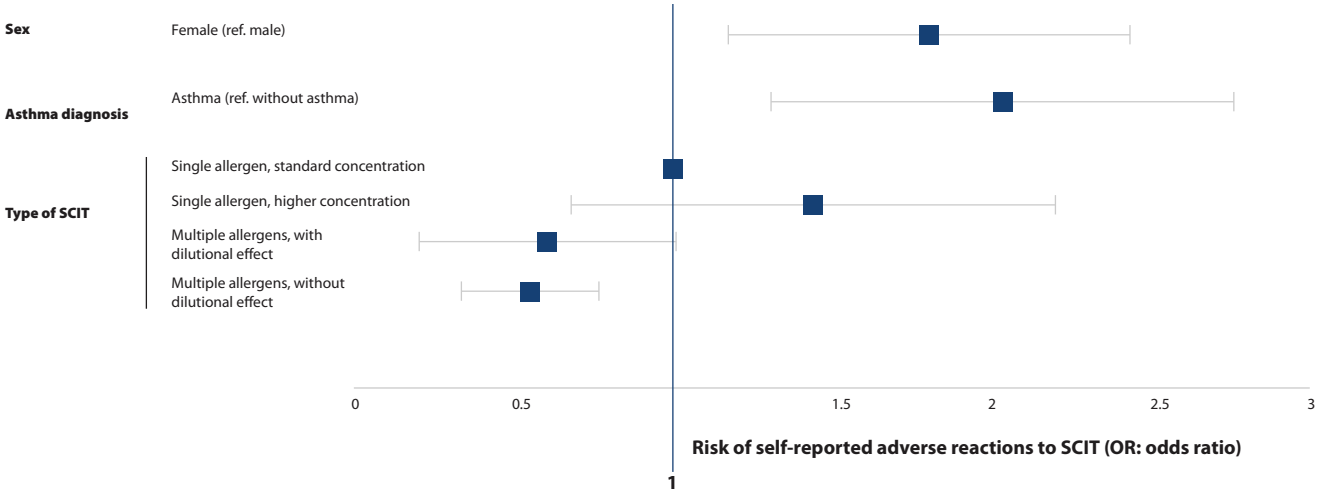


Table III *- Unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI) for the risk of self-reported SCIT related adverse reactions.*

	Unadjusted			Adjusted		
	OR	**95%CI**	**P-value**	**OR**	**95%CI**	**P-value**
Female (ref. male)	1.84	1.28-2.66	**0.001**	1.71	1.19-2.46	**0.004**
< 18 years old (ref. ≥ 18 years)	0.76	0.54-1.08	0.125		Exc.	
Asthma diagnosis (ref. no asthma diagnosis)	1.75	1.22-2.51	**0.002**	1.89	1.30-2.75	**0.001**
Time since the beginning of SCIT			0.780		NI	
1 year	1.03	0.72-1.47	0.864			
2 years	0.94	0.68-1.30	0.708			
≥ 3 years	Ref.					
SCIT with mites (ref. without mites)	0.80	0.53-1.20	0.273		NI	
SCIT with epithelia (ref. without epithelia)	0.89	0.55-1.46	0.654		NI	
SCIT with grass pollens (ref. without grass pollens)	0.90	0.63-1.28	0.543		NI	
SCIT with tree pollens (ref. without tree pollens)	0.81	0.35-1.85	0.612		NI	
SCIT with weed pollens (ref. without weed pollens)	0.57	0.24-1.35	0.204		Exc.	
Number of allergen groups in SCIT			**0.028**		Exc.	
One allergen group	Ref.					
Two allergen groups	0.61	0.42-0.89	**0.010**			
Three allergen groups	0.65	0.32-1.33	0.239			
Type of SCIT			**0.002**			**0.001**
Single allergen, standard concentration (SA-SC)	Ref.			Ref.		
Single allergen, higher concentration (SA-HC)	1.08	0.60-1.96	0.804	1.25	0.70-2.24	0.460
Multiple allergens, with dilutional effect (MA-Dil)	0.53	0.17-1.62	0.265	0.45	0.19-1.06	0.066
Multiple allergens, without dilutional effect (MA-NoDil)	0.51	0.34-0.77	**0.001**	0.52	0.35-0.78	**0.002**

Molds were not included due to the low number of patients with this SCIT composition, which precluded an adequate risk estimation. Ref.: reference category; NI: not included in the adjusted model due to P-value > 0.25 in the univariate analysis; Exc.: excluded from the final model.

them considered that they were not bothersome at all or were only slightly troublesome. Ninety-six per cent stated they would not stop immunotherapy because of these local reactions (16). Another study, held in Portugal, by Santos *et al.* (17), found that almost 50% of the patients self-reported at least one adverse reaction during SCIT treatment (with at least one year long), most at the injection site. However, there were several patients (13% of the whole study population) reporting asthenia, fatigue, rhinitis and headache, among other systemic symptoms; the authors state that none of the reactions was severe, and most were ill-defined. Nevertheless, it should be highlighted that these self-reported systemic symptoms were noted at a higher frequency than those usually described in the literature, where the usual rate is around 0.1-0.2% per administration (corresponding to 0.6-4.7% of patients) (1, 6, 18). In fact, our results are difficult to compare directly with other studies where the frequency of SCIT-related adverse reactions was assessed and registered by a healthcare professional (6, 18). The patient perspective gives value to additional aspects that are not easily evaluated by the healthcare professional, such as symptomatic, intellectual, psychosocial, spiritual and goal-oriented dimensions of the disease and its treatment (19), and is recognized as being of significant importance in several clinical areas, including pulmonary hypertension (19) and allergic diseases (20, 21). A previous study, by Baiardini *et al.* (21), found that patient's and physician's satisfaction and perceptions related to allergen immunotherapy had a good correlation/agreement. Still, the agreement in the report of adverse reactions was not assessed. In our study, the relatively high frequency of self-reported systemic symptoms that were not recorded by the administering physician as related to SCIT, might be related with these differences in patient's and physician's perspectives, but also with reporting errors. Most questionnaires were completed by the patients themselves. Although there was supervision by a healthcare professional, we cannot exclude that some patients misinterpreted the question on SCIT-related adverse reactions and reported all symptoms that occurred after the last SCIT administration (*e.g.*, rhinitis worsening) even if they were not genuinely perceived as SCIT-related. Our findings regarding risk factors for adverse reactions are also very relevant and can support a more personalized healthcare delivery to patients having their allergic disease treated with SCIT. Although the risk factors for systemic reactions are commonly described (6-9), few studies reported on the risk factors for adverse reactions as a whole (including both local and systemic reactions). We acknowledge that systemic reactions, although rare and usually of moderate severity, especially with polymerized SCIT extracts (6, 22, 23) − that are frequently used in Portugal − are a major understandable concern due to the impact on patient safety and treatment continuation or schedule. Nevertheless, local reactions to SCIT are reported to occur in up to 85% of the patients (1) and, even though they don't seem to be predictive of a higher risk of systemic reactions (1, 16, 24), they could be a major reason for noncompliance with allergen immunotherapy (10, 11). Although several studies failed to support lower SCIT compliance with the occurrence of local reactions (16, 25, 26), most allergists adjust SCIT dose due to local reactions based on the concerns that they cause discomfort that may lead to patient noncompliance and that they may be predictive of future local reactions (27). In this study, most AdR were classified as mildly discomfortable and easy to tolerate but they were frequently recurrent (18 out of 55 patients reported AdR in 50% or more questionnaires and 5 patients reported SCIT-related AdR in all administrations). We could not assess if any dose adjustment or treatment interruption were performed based on these self-reported local AdR.

We found that female sex and having asthma were significantly associated with self-reported SCIT-related AdR. Still, there was no significant increase in the risk of AdR with neither higher than standard SCIT concentration nor multiple allergens (compared to SCIT with a single allergen at standard concentration). We found no significant association between SCIT-related AdR and any specific allergen extract. A previous study, based on physician assessment of pediatric patients, found that AdR were more common in patients undergoing SCIT with multiple allergens and house dust mite (18), which disagrees with our findings. This might be related to the different setting, data collection methods and age group. It is interesting to highlight that, in our study, having SCIT with MA-NoDil seemed to protect against AdR, which is not easy to explain. We cannot exclude that this finding might be related to a sample bias favouring a low reporting of adverse reactions to these SCIT preparations. However, although unpredicted, it may represent a real effect and should be futher assessed in future, targeted studies. These unexpected findings are not new in SCIT. In fact, a few year ago, contrary to the hypothesized, rush SCIT build-up schedules proved at least as safe as traditional, slower build-up schemes (28, 29). In regard of SCIT preparations with MA, one might also argue that mixing non-homologous extracts might lead to inactivation of some relevant components, leading to lower potency. This was a traditional concern regarding natural extracts and the basis for the recommendation against mixing extracts from unrelated allergen groups even in polyallergic patients (2, 12). Nevertheless, in the last couple of years, several immunotherapy manufacturers have been releasing new SCIT polymerized formulations that allow mixing non-homologous allergens keeping the concentration from the SA SCIT. Most manufacturers have internal data supporting high stability and efficacy maintained until the expiry date; however, most stability data regarding these mixtures were not published in peer-reviewed journals.

Another interesting finding in our data is the absence of a significantly increased risk of AdR with SA-HC SCIT concentration. In fact, a previous phase two clinical trial testing a SCIT mite preparation has shown that clinical efficacy incresed at higher SCIT doses; however, it reached a plateau at a concentration of

50,000 AUeq/mL, with the highest concentration being as effective but presenting higher frequency of adverse events (13). The reported adverse events were not severe, but the 50,000 AUeq/mL concentration was chosen for further development (13). However, this kind of data were not available for most SCIT preparations commercially available in Portugal, including for those with SA-HC. Although our data is limited by the low number of these SCIT preparations (corresponding to only 10% of the total), real-world data, collected during routine care, can give valuable insights on the risk of local and systemic AdR in relation to SA-HC preparations. Nevertheless, having published data on the stability of non-homologous SCIT mixtures and performing well-designed clinical trials or large observational studies assessing clinical efficacy and safety of SCIT mixtures and of preparations with higher allergen concentrations is, currently, an unmet need in allergen immunotherapy-related knowledge.

As previously stated, a strength of this study is being one of the few published studies assessing SCIT related AdR based on self-reported patient information and one of the few exploring risk factors for adverse reactions as a whole. However, this study has several limitations. First, this was a questionnaire-based self-assessment without healthcare professional input which might lead to reporting errors (*e.g.*, due to question misinterpretation) or incorrect evaluation of the causality relation between SCIT and AdR. We tried to minimize these bias by supervising and providing support to questionnaire filling whenever asked by the patient; nevertheless, it was not possible to assure that all patients understood all questions correctly. Secondly, during the study period (March 2017 to June 2019, 28 months), considering the 231 patients that were included, we should have around 6,468 questionnaires. This means that our response rate was 15% which is low and limits the interpretation and generalizability of our results. Although the pre-SCIT administration questionnaire was implemented at our site in 2017, it was usually applied with the support of a specific colleague (MP), that could only consistently collect these data on specific week periods. We are now working on a more accessible and straightforward solution, taking advantage of new technologies, that will allow collecting these same data using a readily accessible smartphone or tablet while the patient waits for SCIT administration. Finally, we had no data regarding some variables of interest, including the level of allergic disease control, medication intake (*e.g.*, antihistamine or systemic corticosteroid) that could prevent or largely minimize AdR, and allergen exposure and practice of physical exercise before or readily after SCIT administration. It should be noted that the information regarding disease control is part of the pre-SCIT administration questionnaire. Nevertheless, as the data on SCIT-related AdR are collected only at the following administration, we need to have sequential questionnaires to be able to match the information on AdR with control assessment. Due to the low response rate this was not possible, and we decided not to include data on allergic disease control in this analysis. Future research should include a larger set of clinical variables, namely allergic disease control.

Adverse reactions to subcutaneous allergen immunotherapy were self-reported in one-third of the included administrations. Most adverse reactions were exclusively at the injection site, and most were only mildly troublesome and easily tolerable. The risk of adverse reactions was higher in female sex and patients with asthma, and lower in patients treated with SCIT preparations with multiple allergens and concentrations adjusted to prevent dilutional effect. Additional, well-designed studies, including clinical trials and larger observational studies using real-world data, are urgently needed.

Fundings

None.

Contributions

AMP, MP: data management and analysis. AMP: writing - original draft. MP: writing - original draft support. All authors: data collection, critically review, final version agreement.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. James C, Bernstein DI. Allergen immunotherapy: an updated review of safety. Curr Opin Allergy Clin Immunol. 2017;17(1):55-9. doi: 10.1097/ACI.0000000000000335.
2. 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):765-98. doi: 10.1111/all.13317.
3. Grupo de Interesse de "Alergénios e Imunoterapia" da Sociedade Portuguesa de Alergologia e Imunologia Clínica (SPAIC). Normas de Orientação em Imunoterapia Específica. Rev Port Imunoalergologia. 2011;19(4):199-213. Available at: https://www.spaic.pt/client_files/rpia_artigos/normas-de-orientacao-em-imunoterapia-especifica.pdf.
4. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol. 1998;102(4 Pt 1):558-62. doi: 10.1016/s0091-6749(98)70271-4.
5. Santos N, Pereira A, Plácido J, Castel-Branco M. Subcutaneous Specific Immunotherapy: local and systemic reactions. Allergy. 2010;65:568. Available at: https://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2010.02393.x.
6. Santos N, Pereira AM, Silva R, Torres da Costa J, Plácido JL. Characterisation of systemic reactions to subcutaneous immunotherapy with airborne allergens and classification according to WAO 2010. Allergol Immunopathol (Madr). 2015;43(1):25-31. doi: 10.1016/j.aller.2013.10.006.

7. Lieberman P. The risk and management of anaphylaxis in the setting of immunotherapy. Am J Rhinol Allergy. 2012;26(6):469-74. doi: 10.2500/ajra.2012.26.3811.
8. Calderón M, Vidal C, Rodríguez del Río P, Just J, Pfaar O, Tabar A, et al. European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment. Allergy. 2017;72(3):462-72. doi: 10.1111/all.13066.
9. Sánchez-Borges M, Bernstein DI, Calabria C. Subcutaneous Immunotherapy Safety: Incidence per Surveys and Risk Factors. Immunol Allergy Clin North Am. 2020;40(1):25-39. doi: 10.1016/j.iac.2019.09.001.
10. Alessandrini AE, Berra D, Rizzini FL, Mauro M, Melchiorre A, Rossi F, et al. Flexible approaches in the design of subcutaneous immunotherapy protocols for Hymenoptera venom allergy. Ann Allergy Asthma Immunol. 2006;97(1):92-7. doi: 10.1016/S1081-1206(10)61376-2.
11. Cadario G, Marengo F, Ranghino E, Rossi R, Gatti B, Cantone R, et al. Higher frequency of early local side effects with aqueous versus depot immunotherapy for hymenoptera venom allergy. J Investig Allergol Clin Immunol. 2004;14(2):127-33. Available at: https://pubmed.ncbi.nlm.nih.gov/15301302/.
12. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Management of the polyallergic patient with allergy immunotherapy: a practice-based approach. Allergy Asthma Clin Immunol. 2016;12:2. doi: 10.1186/s13223-015-0109-6.
13. Pfaar O, Nell MJ, Boot JD, Versteeg SA, van Ree R, Roger A, et al. A randomized, 5-arm dose finding study with a mite allergoid SCIT in allergic rhinoconjunctivitis patients. Allergy. 2016;71(7):967-76. doi: 10.1111/all.12860.
14. 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, 574.e1-574.e7. doi: 10.1016/j.jaci.2009.10.060.
15. Malling H, Weeke B. Position paper: Immunotherapy. Allergy. 1993;48(14 Suppl):9-35. doi: 10.1111/j.1398-9995.1993.tb04754.x.
16. Coop CA, Tankersley MS. Patient perceptions regarding local reactions from allergen immunotherapy injections. Ann Allergy Asthma Immunol. 2008;101(1):96-100. doi: 10.1016/S1081-1206(10)60841-1.
17. Santos MAS, Viegas L, Ferreira M, Barbosa MP. Subcutaneous specific immunotherapy: The patients' perspective. Rev Port Imunoalergologia. 2010;18:539-60. Available at: https://www.spaic.pt/client_files/rpia_artigos/imunoterapia-especifica-subcutanea:-a-percepcao-dos-doentes.pdf.
18. Nacaroglu HT, Erdem SB, Sumer O, Karaman S, Unsal Karkıner CS, Asilsoy S, et al. Local and systemic reactions to subcutaneous allergen immunotherapy: Ten years' experience in a pediatric clinic. Ann Allergy Asthma Immunol. 2016;116(4):349-53. doi: 10.1016/j.anai.2016.01.015.
19. McGoon MD, Ferrari P, Armstrong I, Denis M, Howard Luke S, Lowe G, et al. The importance of patient perspectives in pulmonary hypertension. Eur Respir J. 2019;53(1):1801919. doi: 10.1183/13993003.01919-2018.
20. Jutel M, Angier L, Palkonen S, Ryan D, Sheikh A, Smith H, et al. Improving allergy management in the primary care network – a holistic approach. Allergy. 2013;68(11):1362-9. doi: 10.1111/all.12258.
21. Baiardini I, Puggioni F, Menoni S, Boot JD, Diamant Z, Braido F, et al. Patient knowledge, perceptions, expectations and satisfaction on allergen-specific immunotherapy: A survey. Respir Med. 2013;107(3):361-7. doi: 10.1016/j.rmed.2012.11.004.
22. 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.
23. Caminati M, Dama AR, Djuric I, Montagni M, Schiappoli M, Ridolo E, et al. Incidence and risk factors for subcutaneous immunotherapy anaphylaxis: the optimization of safety. Expert Rev Clin Immunol. 2015;11(2):233-45. doi: 10.1586/1744666X.2015.988143.
24. 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):840-3. doi: 10.1067/mai.2000.110468.
25. More DR, Hagan LL. Factors affecting compliance with allergen immunotherapy at a military medical center. Ann Allergy Asthma Immunol. 2002;88(4):391-4. doi: 10.1016/S1081-1206(10)62370-8.
26. Silva D, Pereira A, Santos N, Plácido JL. Costs of treatment affect compliance to specific subcutaneous immunotherapy. Eur Ann Allergy Clin Immunol. 2014;46(2):87-94. Available at: http://www.eurannallergyimm.com/cont/journals-articles/40/volume-costs-treatment-affect-compliance-specific-100allasp1.pdf.
27. Coop CA, Tankersley MS. Dose adjustment practices among allergists for local reactions to immunotherapy. Ann Allergy Asthma Immunol. 2007;99(1):77-81. doi: 10.1016/S1081-1206(10)60625-4.
28. 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(3):e31-8. doi: 10.2500/aap.2010.31.3334.
29. Gomes Dos Reis Pimentel RA, Oliveira G, Ferreira Chaves Loureiro ELCS. Accelerated subcutaneous immunotherapy in pediatric population - Systematic review. Pulmonology. 2018;24(3):182-93. doi: 10.1016/j.rppnen.2017.07.009.

Maria Angela Tosca[1], Irene Schiavetti[2], Gian Luigi Marseglia[3], Giorgio Ciprandi[4]

The gender effect in children and adolescents with asthma: practical outcomes from the "ControL'Asma" study

[1]Allergy Center, Department of Pediatrics, Istituto Giannina Gaslini, Genoa, Italy
[2]Department of Health Science, University of Genoa, Genoa, Italy
[3]Pediatrics Clinic, Department of Pediatrics, Policlinico San Matteo, University of Pavia, Pavia, Italy
[4]Allergy Clinic, Department of Outpatients, Casa di Cura Villa Montallegro, Genoa, Italy

Key words
Asthma; asthma control; children; adolescents; gender.

Corresponding author
Giorgio Ciprandi
Allergy Clinic
Department of Outpatients
Casa di Cura Villa Montallegro
via Montezovetto 27
16132 Genoa, Italy
ORCID: 0000-0001-7016-8421
E-mail: gio.cip@libero.it

Doi
10.23822/EurAnnACI.1764-1489.235

To the Editor,

gender medicine is attracting more and more attention also in clinical practice (1). Differences between genders exist in many diseases. The evaluation of the gender impact on asthma arouses current and outstanding interest and is an interesting research field, as recently pointed out (2). Currently, asthma control is the cornerstone strategy in the management of patients with asthma, as stated by the Global Initiative for Asthma (GINA) document (3). The asthma control evaluation should be based on a global assessment of symptoms, lung function, medications' use, limitations, and respiration perception. The asthma control perception may be assessed in a standardized way by the Asthma Control Test (ACT) questionnaire. In this regard, a recent study evaluated a large group of outpatients with asthma in a real-world setting (4). Interestingly, the asthma control, assessed by objective and subjective measures, was not influenced by gender. However, differences between female and male adults concerned only lung function and smoking. Asthmatic women had higher FVC and FEV1 values than men, but men smoked more than women. Otherwise, there were no significant differences between genders. Consistently, we reported no difference between female and male children with asthma concerning the lung function and the perception of breathlessness (5). However, some pediatric studies do not investigate the assessment of asthma control. In this regard, the Italian Society of Paediatric Allergy and Immunology recently established a prospective study ("ControL'Asma") to investigate the asthma control in children and adolescents managed in clinical practice. As asthma and allergy are dynamic events, the present study aimed to compare genders about asthma control and other clinical-functional characteristics in children and adolescents recruited in a real-world setting, such as Italian pediatric third-level allergy and asthma clinics.

This cross-sectional study included 471 children and adolescents consecutively visited across 10 Italian pediatric third-level allergy clinics. Asthma diagnosis was performed following the GINA document criteria. All patients were currently treated according to the GINA guidelines based on the asthma control level.

The Ethics Committee of the Istituto Giannina Gaslini of Genoa initially approved the procedure (code number: 22253/2017, in the Italian Project "ControL'Asma" promoted by the Italian Society of Paediatric Allergy and Immunology). All the other Review Ethics Committees further approved the study procedure and written informed consent was obtained from all parents. Clinical data were recorded by an electronic case report form designed expressly for this study. Due to the nature of this study, no sample size justification was needed as no formal *a priori* hypothesis was tested.

Descriptive data summary was expressed as frequency (percent); mean ± standard deviation; median and interquartile range (IQR). Two separate analyses were performed, independently considering children and adolescents. Any relationship between categorical variables was assessed by Chi-square test or Fisher's exact test, as appropriate. The independent samples t-test or Mann-Whitney U test was used to compare the continuous variables.

Table I reports the outcomes, considering children and adolescents separately. Male gender was prevalent both in children- and adolescents-group.

In children, there was no significant difference between females and males concerning BMI, rhinitis, type 2 high phenotype, ARIA classes, lung function, asthma control level, cACT, and perception of asthma symptoms by children's parents and doctors. Lung function differed between genders in adolescents: males had lower FVC and FEV1 values than females ($p = 0.006$ and 0.02, respectively).

These outcomes highlighted no significant difference between female and male children, mainly concerning the asthma control level, assessed both by GINA criteria and cACT. Other clinical variables, including the perception of breathlessness, comorbidities, and lung function, were similar in both genders. Substantially, the same findings were observed in adolescents, but lung function, although the higher values observed in females were without clinical relevance.

Curiously, there was an inversion between genders about the quote of subjects with uncontrolled asthma. Uncontrolled asthma was more prevalent in male children (14.8% *vs* 10%) and female adolescents 14.1% *vs* 8.1%), even though without statistical significance.

These results confirmed previous findings obtained in adulthood (4). Therefore, the impact of gender seems to be scarcely important in patients with asthma, if not for the different prevalence: higher in male children and adolescents, but higher in women. These outcomes could represent a risk of bias. However, these results were obtained in a real-life setting, as derived from ten Italian pediatric clinics. These data reflected what occurred in clinical practice and outlined the relevance of gender in affecting asthma prevalence.

The present outcomes were conflicting with a recent Chinese study showing that maternal sleep, physical activity, and screen time during pregnancy were significantly associated with the risk of childhood allergies, mainly in males (6). However, the setting was different and asthma control was not investigated.

Another study evaluated subjects (age range 10-18 years) from the Isle of Wight birth cohort (7). That study showed that there was a gender difference concerning the DNA methylation associated with the risk of asthma. However, also that study did not address the asthma control.

A Korean study demonstrated that there was a between gender difference concerning factors associated with bronchial hyperresponsiveness (8), but asthma control was not investigated.

On the other hand, the current real-world study had one main limitation because it was performed as a cross-sectional, so further longitudinal studies should be performed to confirm these findings. On the other hand, the real-world setting allowed to represent a third-level asthma clinic's daily practice, including a wide range of asthma severity. In addition, no sample size calculation was provided *a priori* due to the exploratory nature of this study.

In conclusion, the ControL'Asma study showed no clinically relevant differences between genders, about asthma control, symptom perception, lung function, and comorbidities, in Italian children and adolescents with asthma.

Fundings

None

Contributions

MAT: study design. IS: data analysis. GLM: discussion of results. GC: writing - original draft, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgements

We would thank the "ControL'Asma Study Group" members: Elisa Anastasio, Carlo Caffarelli, Federica Caricato, Loredana Chini, Elisabetta Del Duca, Valentina De Vittori, Maria Elisa Di Cicco, Ahmad Kantar, Maddalena Leone, Amelia Licari, Viviana Moschese, Roberta Olcese, Diego G Peroni, Valeria Talarico, and Martina Votto, who participated in the research.

Table I *- Comparison between gender and age classes in children and adolescents.*

	Children (n = 270)			Adolescents (n = 201)*		
	Female (n = 81)	**Male (n = 189)**	**p**	**Female (n = 64)**	**Male (n = 137)**	**p**
BMI	18.0 ± 3.29	18.6 ± 3.47	0.24	22.3 ± 4.94	21.1 ± 3.80	0.10
Rhinitis comorbidity	68 (84.0)	161 (85.2)	0.85	60 (93.8)	125 (91.2)	0.78
Type 2 high asthma	75 (92.6)	174 (93.0)	0.99	64 (100.0)	131 (97.0)	0.31
ARIA Category						
Mild intermittent allergic rhinitis (MIAR)	22 (32.4)	59 (36.9)	0.62	23 (38.3)	51 (40.8)	0.92
Moderate-severe intermittent allergic rhinitis (MSIAR)	8 (11.8)	12 (7.5)		7 (11.7)	11 (8.8)	
Mild persistent allergic rhinitis (MPAR)	33 (48.5)	81 (50.6)		27 (45.0)	58 (46.4)	
Moderate-severe persistent allergic rhinitis (MSPAR)	5 (7.4)	8 (5.0)		3 (5.0)	5 (4.0)	
FVC (% predicted)	98.2 ± 13.94	98.1 ± 13.44	0.68	104.4 ± 15.21	98.3 ± 12.78	**0.006***
FEV_1 (% predicted)	95.4 ± 13.59	94.7 ± 15.78	0.91	103.0 ± 17.69	96.4 ± 13.30	**0.020***
Bronchial obstruction (FEV_1 < 80%)	9 (12.7)	28 (17.1)	0.44	7 (11.1)	11 (8.7)	0.61
FEV_1/FVC	97.7 (9.72)	96.8 ± 11.24	0.64	98.8 ± 10.33	98.3 ± 9.40	0.72
$FEF_{25–75}$ (% pred.)	87.4 (26.58)	82.9 ± 27.06	0.42	89.3 ± 29.15	84.8 ± 22.38	0.13
Asthma control level (GINA)						
Well-controlled	41 (51.2)	99 (52.4)	0.46	35 (54.7)	86 (63.2)	0.34
Partly controlled	31 (38.8)	62 (32.8)		20 (31.3)	39 (28.7)	
Uncontrolled	8 (10.0)	28 (14.8)		9 (14.1)	11 (8.1)	
Childhood Asthma Control Test (adjusted age)	23.0 (19.0-25.0)	22.0 (19.0-24.0)	0.08	22.0 (17.0-25.0)	23.0 (19.0-24.0)	0.37
VAS (by patient)	8.3 (7.0-9.0)	8.0 (7.0-9.0)	0.94	8.5 (7.0-9.0)	8.0 (7.0-9.0)	0.32
VAS (by patient)	8.0 (7.0-9.0)	8.0 (7.0-9.0)	0.82	8.0 (7.0-9.0)	8.0 (7.0-9.0)	0.45
VAS (by physician)	8.0 (7.0-9.0)	8.0 (7.0-9.0)	0.57	8.3 (7.0-9.3)	8.0 (7.0-9.0)	0.54

Data are expressed as frequency (percent); mean ± standard deviation; median (IQR).

References

1. Lippi D, Bianucci R, Donell S. Gender medicine: its historical roots. Postgrad Med J. 2020;96(1138):480-6. doi: 10.1136/postgradmedj-2019-137452.
2. Raghavan D, Jain R. Increasing awareness of sex differences in airway diseases. Respirology. 2016;21(3):449-59. doi: 10.1111/resp.12702.
3. Global Initiative for Asthma. GINA guidelines. Global Strategy for Asthma Management and Prevention. Available at: htpp://www.ginasthma.org/. Last access date: 02/01/2021.
4. Ricciardolo FLM, Levra S, Sprio AE, Bertolini F, Carriero V, Gallo F, et al. Asthma in the Real-World: The Relevance of Gender. Int Arch Allergy Immunol. 2020;181(6):462-6. doi: 10.1159/000506808.
5. Ciprandi G, Tosca MA, Brambilla I, Arturo Rossi G, Marseglia G. Perception of dyspnea in prepubescent children with mild intermittent asthma: is there any gender difference? J Asthma. 2011;48(9):886-7. doi: 10.3109/02770903.2011.616617.
6. Chen Y, Lyu J, Xia Y, Zhu J, Tong S, Ying Y, et al. Effect of maternal sleep, physical activity and screen time during pregnancy on the risk of childhood respiratory allergies: a sex-specific study. Respir Res. 2020;21(1):230. doi: 10.1186/s12931-020-01497-8.
7. Patel R, Solatikia F, Zhang H, Wolde A, Kadalayil L, Karmaus W, et al. Sex-specific associations of asthma acquisition with changes in DNA methylation during adolescence. Clin Exp Allergy. 2021;51(2):318-28. doi: 10.1111/cea.13776.
8. Kim YH, Jang YY, Jeong J, Chung HL. Sex-based differences in factors associated with bronchial hyperresponsiveness in adolescents with childhood asthma. Clin Exp Pediatr. 2021;64(5):229-38. doi: 10.3345/cep.2020.01585.

Larissa Silva Brandão, Inês Cristina Camelo-Nunes, Luis Felipe Ensina

Anti-thyroid antibodies as biomarkers in Chronic Spontaneous Urticaria

Division of Allergy, Clinical Immunology and Rheumatology, Federal University of São Paulo (UNIFESP), São Paulo, Brazil

Key words

Anti-thyroid antibodies; autoimmunity; biomarkers; urticaria.

Corresponding author
Larissa Silva Brandão
Division of Allergy, Clinical Immunology and Rheumatology
Federal University of São Paulo (UNIFESP)
Rua dos Otonis 731 -Vila Clementino
São Paulo, Brazil 04025-002
ORCID: 0000-0001-8669-0425
E-mail: larissbrando@gmail.com

Doi
10.23822/EurAnnACI.1764-1489.228

To the Editor,

chronic urticaria is a disease characterized by the development of itching hives, angioedema, or both for six weeks or more (1). Among its different presentations, chronic spontaneous urticaria (CSU) is the most common, with a point prevalence of 0.4 to 1.0% in the general population (2). CSU's average duration ranges from 6 months to 5 years but may be longer in patients with angioedema or autoimmune thyroid disease (3-5).

Currently, there are potential biomarkers of CSU activity and response to treatment (6). Still, a definitive blood biomarker to predict CSU duration or prognosis is lacking, and anti-thyroid antibodies have been studied for this purpose. However, its use is controversial since the frequency of this association is variable in different populations (3, 7, 8). Therefore, this study aimed to evaluate anti-thyroid autoantibodies' association with disease duration, presence of angioedema, and response to antihistamines treatment.

This retrospective and cross-sectional study analyzed data from CSU patients followed at the Federal University of Sao Paulo from January 2012 to December 2019. The study was conducted in accordance with Declaration of Helsinki and all participants, or their legal guardians, have given their written informed consent to file their records for clinical research. The registry was approved by the Ethics Committee of the Federal University of Sao Paulo (CAAE: 94104318.0.0000.5505).

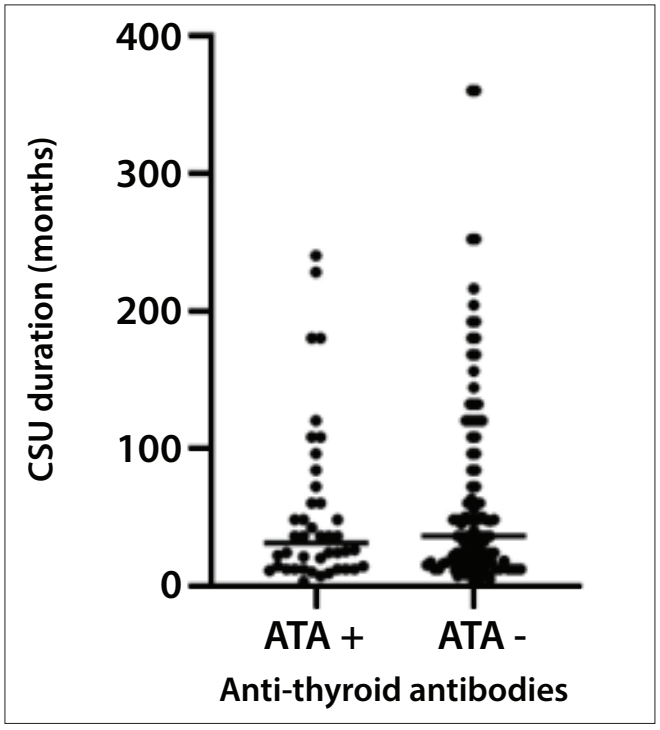
All patients with a clinical diagnosis of CSU and tested for anti-thyroglobulin (anti-TGB) IgG or anti-peroxidase (anti-TPO) IgG antibodies were included. Patients with isolated inducible chronic urticaria or incomplete data charts were excluded.

To access the presence of anti-thyroid antibodies (ATA) in CSU patients, we considered the positivity for any or both anti-TGB/Anti-TPO IgG antibodies. We statistically analyzed this data with different prognostic aspects of CSU according to the nature of variables. The chi-square or Fisher's exact test were used to analyze associations between categorical groups and compare distributions. The median test was used to compare medians, and a P-value ≤ 0.05 was considered statistically significant. The time from the onset of symptoms until the last visit presenting urticaria was chosen to assess disease duration. The response to treatment criteria was met based on the second-generation antihistamines

(anti-H1) doses necessary to control symptoms (UAS7 ≤ 6 and/or UCT > 12) or the refractoriness to these drugs, defined by UAS7 > 6 and/or UCT < 12 with 4-times the standard anti-H1 dose (1). In this study, 147 patients were tested for ATA and included for analysis. The mean age of patients was 36.4 years (SD 17.21), and females were predominant (5:1). Only 42 patients had positive ATA (14 anti-TPO+/14 anti-TGB+/14 positive for both), 85% were women and the mean age was 38.43 years (SD 16.42); however, there was no association between gender and age with ATA (p = 0.86 and p = 0.36, respectively). CSU duration was variable, with a median of 36 months (range: 2 to 360 months). In ATA positive patients, the median CSU duration was 31 months, while in ATA negative was 36 months. There was no significant difference in CSU duration between ATA groups (p = 0.58) as shown in **figure 1**, even when comparing isolated positiveness to Anti-TPO or Anti-TGB (p = 0.58 and p = 0.68, respectively). Sixteen patients had autoimmune thyroid diseases but only nine of them had positive ATA. These diseases were not associated with CSU duration as well (p = 0.73).

Angioedema was more frequent in patients with ATA (64.2%), but not significantly (p = 0.45). Also, ATA's association with angioedema did not influence CSU duration compared with ATA positiveness and angioedema only (p = 0.63).

Figure 1 *- CSU duration in patients with positive and negative anti-thyroid antibodies (ATA).*



The majority of CSU patients had a good response to anti-H1 treatment (107/147), but only 15% controlled with standard doses. One quarter of patients controlled with 2-fold the standard dose, and 32% with 4-fold dose. When comparing ATA groups, ATA positive patients responded to anti-H1 treatment in 69% of cases (29/42), while ATA negatives responded in 74%. Regarding the anti-H1 dose regimen, a standard dose was able to control symptoms in 12% of ATA positives and 16% of negatives; a 2-fold dose in 29% of positives and 24% of negatives; and a 4-fold dose in 29% positives and 26% negatives. In ATA positives, 30% did not respond to the 4-fold dose anti-H1 treatment, while in ATA negatives 26%. Although the ATA positive patients used nonstandard doses more frequently, we found no association of positivity to ATA and response to anti-H1 treatment (p = 0.54) or the necessary dosage to control symptoms (p = 0.79).

The prevalence found of positive ATA in CSU patients (29%) was similar to the literature (5), which was up to 53.6% in some studies (9-11). The exact mechanism that explains this association is still unknown, but autoimmunity has been discussed and could explain part of the physiopathology (11).

The higher prevalence of CSU and positive ATA in women were previously observed and involved the role of adipokines and other cytokines in promoting an inflammatory state capable of compromise the innate immune response to triggers. This erratic response contributes to the inflammatory cascade and breaks the tolerance to thyroid autoantigens (5).

A strong association between ATA presence and CSU duration has been discussed since 2004 when a study reported that in 70% of ATA patients the urticaria lasted for more than one year (4). Furthermore, anti-TPO seems to have a more critical role in predicting CSU duration than anti-TGB (5). However, in our sample, anti-thyroid antibodies were not statistically associated with CSU duration.

In a Thai study, angioedema was not associated with autoimmune thyroiditis or the presence of autoantibodies alone (5). Although angioedema was more frequent in patients with positive autoantibodies in our study, there was also no statistical association between these two variables. The same Thai study described a higher use of nonstandard doses of second-generation anti-H1 in CSU patients with positive ATA than in ATA negatives (61.2% *versus* 37.8%). However, this association was not statistically different in their study (5). Similarly, in our sample, ATA patients used nonstandard doses more frequently but without statistical difference. Therefore, we believe it is not possible to say that positive ATA has an actual interference in response to treatment with anti-H1.

Limitations of this study were a lack of information about CSU activity and control scores in all medical records, preventing the inclusion of these variables in the analyses. Also, 15 patients lost follow-up, and we considered the last registered outcome to evaluate response to treatment. However, strong points in our study

are the size of our sample and the fact this is the first study to evaluate the role of ATA in a population of CSU Brazilian patients. Therefore, we concluded anti-thyroid autoantibodies might not be suitable biomarkers to predict CSU duration, disease severity, or response to anti-H1 treatment.

Fundings

None.

Contributions

LSB: conceptualization, data curation, methodology, writing - original draft, writing - review & editing. LFE, ICC-N: writing - original draft, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy Eur J Allergy Clin Immunol. 2018;73(7):1393-414. doi: 10.1111/all.13397.
2. Balp MM, Weller K, Carboni V, Chirilov A, Papavassilis C, Severin T, Tian H, et al. Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. Pediatr Allergy Immunol. 2018;29(6):630-6. doi: 10.1111/pai.12910.
3. Kolkhir P, Metz M, Altrichter S, Maurer M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: A systematic review. Allergy. 2017;72(10):1440-60. doi: 10.1111/all.13182.
4. Toubi E, Kessel A, Avshovich N, Bamberger E, Sabo E, Nusem D, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: A prospective study of 139 patients. Allergy Eur J Allergy Clin Immunol. 2004;59(8):869-73. doi: 10.1111/j.1398-9995.2004.00473.x.
5. Chanprapaph K, Iamsumang W, Wattanakrai P, Vachiramon V. Thyroid autoimmunity and autoimmunity in chronic spontaneous urticaria linked to disease severity, therapeutic response, and time to remission in patients with chronic spontaneous urticaria. Biomed Res Int. 2018;2018:9856843. doi: 10.1155/2018/9856843.
6. Fok JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. Allergy. 2021;76(10):2965-81. doi: 10.1111/all.14757.
7. Kolkhir P, André F, Church MK, Maurer M, Metz M. Potential blood biomarkers in chronic spontaneous urticaria. Clin Exp Allergy. 2017;47(1):19-36. doi: 10.1111/cea.12870.
8. Deza G, Ricketti PA, Giménez-Arnau AM, Casale TB. Emerging Biomarkers and Therapeutic Pipelines for Chronic Spontaneous Urticaria. J Allergy Clin Immunol Pract. 2018;6(4):1108-17. doi: 10.1016/j.jaip.2018.02.024.
9. Alen Coutinho I, Regateiro FS, Fernandes RA, Pita JS, Gomes R, Coelho C, et al. Refractory chronic urticaria in adults: clinical characterization and predictors of severity. Allergy Asthma Clin Immunol. 2020;16(1):97. doi: 10.1186/s13223-020-00496-0.
10. Folci M, Heffler E, Canonica GW, Furlan R, Brunetta E. Cutting Edge: Biomarkers for Chronic Spontaneous Urticaria. J Immunol Res. 2018;2018:5615109. doi: 10.1155/2018/5615109.
11. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: What we know and what we do not know. J Allergy Clin Immunol. 2017;139(6):1772-81.e1. doi: 10.1016/j.jaci.2016.08.050.

L'INFORMATORE FARMACEUTICO

2023

LA DIFFICOLTÀ DI ALCUNE SCELTE, LA CERTEZZA DI POTERSI AFFIDARE

Edizione completa

Medicinali e Tascabile

Medicinali

L'***unico*** prontuario ***completo*** e ***affidabile***

TUTTE LE INFORMAZIONI UTILI SEMPRE A PORTATA DI MANO

clienti.codifa@lswr.it
www.edizioniedra.it/if

edra

EDRA SpA
Tel. 02 88184 317 - 243
Via Spadolini, 7 - 20141 Milano

THE OFFICIAL JOURNAL OF AAIITO
ASSOCIAZIONE ALLERGOLOGI
IMMUNOLOGI ITALIANI
TERRITORIALI E OSPEDALIERI

European Annals of Allergy and Clinical Immunology

THE OFFICIAL JOURNAL OF SPAIC
SOCIEDADE PORTUGUESA
DE ALERGOLOGIA
E IMUNOLOGIA CLINICA

ITALY SUBSCRIPTION
only 60,00 Euro

INTERNATIONAL SUBSCRIPTION
only 85,00 Euro

SUBSCRIBE NOW!
www.eurannallergyimm.com

- 6 print issues per year
- full access to www.eurannallergyimm.com, featuring all current and archived issues

European Annals of Allergy and Clinical Immunology

is a bimonthly peer-reviewed publication

- The official Journal of the "Associazione Allergologi Immunologi Italiani Territoriali e Ospedalieri" (Italian Association of Hospital Allergists and Immunologists - AAIITO) and the "Sociedade Portuguesa de Alergologia e Immunologia Clinica" (Portuguese Society of Allergology and Clinical Immunology - SPAIC)
- indexed in PubMed and Scopus
- collects reviews, original works and case reports concerning etiology, diagnosis and treatment of allergic and immunological disorders
- includes a section of information coming from the main international health associations and authorities.

16045

To submit your paper go to http://eaaci.edmgr.com

EDRA Spa, Via Spadolini 7, 20141 Milano – Tel. 02 88 18 41 – abbonamentiedra@lswr.it