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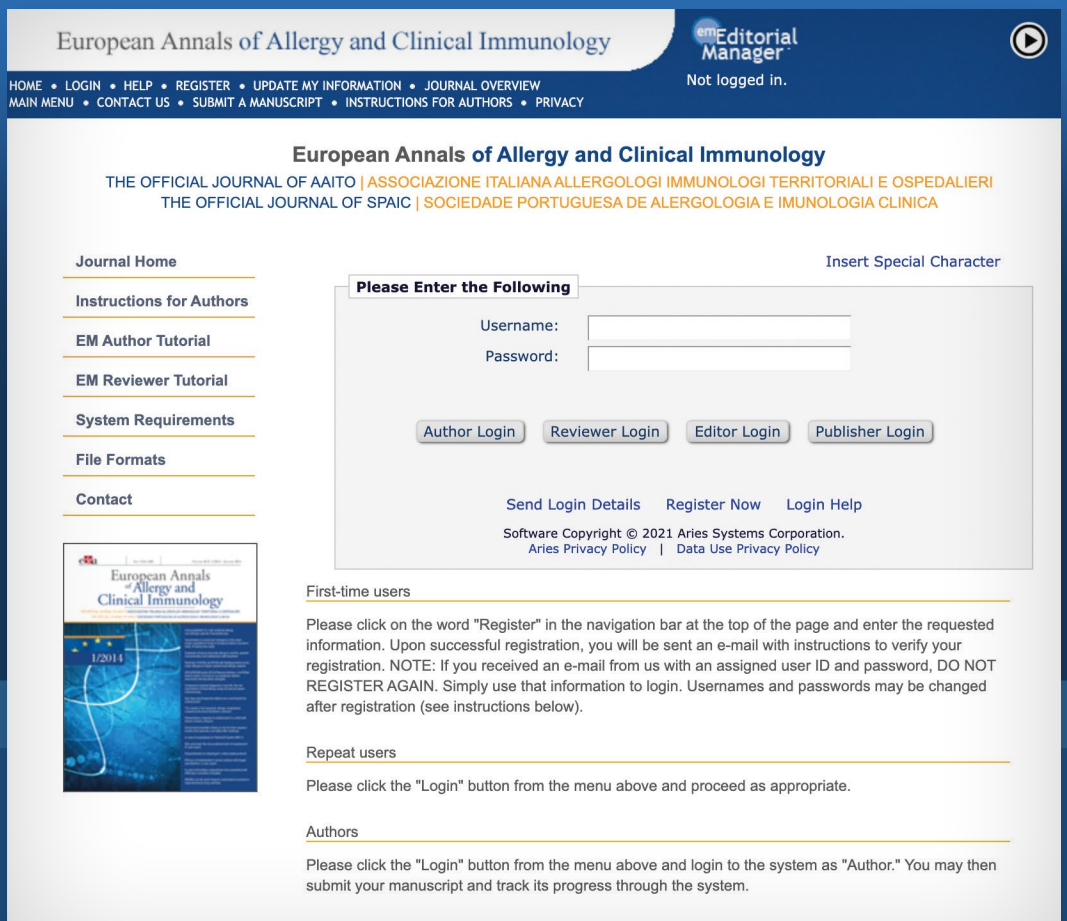

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Editorial Coordinator

Marco Malagutti

Publishing Editor

Jessica Guenzi
editorialoffice@eur-ann-allergy-clin-immunol.com
Ph. 0039 3491716011

Sales

dircom@lswr.it

Edra Media S.r.l.

Viale Forlanini, 21
20134 Milano - Italy
Tel. 0039 (0)2-88184.1
Fax 0039 (0)2-88184.301
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edra MEDIA REVIEW | Eur Ann Allergy Clin Immunol | Vol 58, N.3, 99-110, 2026

Ji-Sun Kim[1], Gulnaz Stybayeva[2], Se Hwan Hwang[3]

Efficacy comparison of combined montelukast-antihistamine and montelukast monotherapy in allergic rhinitis: a meta-analysis of randomized controlled trials

[1]Department of Otolaryngology-Head and Neck Surgery, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester (MN), U.S.A.
[3]Department of Otolaryngology-Head and Neck Surgery, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Key words

Montelukast; allergic rhinitis; antihistamine; drug combinations; meta-analysis.

Corresponding author
Se Hwan Hwang
Department of Otolaryngology-Head and Neck Surgery
Bucheon St. Mary's Hospital
College of Medicine
The Catholic University of Korea
327 Sosa-ro, Bucheon-si, Gyeonggi-do, 14647, Korea
ORCID: 0000-0002-2838-7820
E-mail: yellobird@catholic.ac.kr

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Impact statement

This meta-analysis provides evidence that symptom-specific efficacy of montelukast–antihistamine combinations may inform personalized pharmacologic strategies in allergic rhinitis management.

Summary

Background. *Combination therapy with montelukast and oral antihistamines is commonly used in allergic rhinitis (AR), but its comparative benefit over montelukast monotherapy remains unclear. This meta-analysis aimed to evaluate the efficacy of combination therapy compared to monotherapy, with a focus on symptom-specific outcomes.* ***Methods.*** *A comprehensive search of PubMed, SCOPUS, Embase, Web of Science, and Cochrane databases was conducted through April 2025. We systematically reviewed randomized controlled trials comparing montelukast combined with oral antihistamines to montelukast monotherapy in patients with AR. Outcomes included total symptom scores, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores, and individual symptom domains. Pooled effects were analyzed using standardized mean differences (SMDs) with 95% confidence intervals (CIs).* ***Results.*** *Thirteen RCTs enrolling 2,950 patients were identified. Combination therapy significantly improved daytime symptoms (SMD = 0.25; 95%CI 0.15 to 0.35), with limited benefit for nighttime symptoms (SMD = 0.10; 95%CI -0.01 to 0.21) or RQLQ scores (SMD = 0.11; 95%CI -0.05 to 0.26). In subgroup analysis, all combinations with loratadine, desloratadine, or levocetirizine showed greater efficacy than monotherapy in improving daytime symptoms. However, only the levocetirizine-based combination demonstrated a significant benefit for nighttime symptoms. When analyzed by individual symptoms, the levocetirizine combination resulted in significantly better outcomes than monotherapy, improving sneezing, nasal itching, nasal obstruction, and rhinorrhea.* ***Conclusions.*** *Montelukast combined with antihistamines improves daytime and individual nasal symptoms more effectively than monotherapy. However, the effectiveness of each drug combination varied by symptom domain. These findings may assist clinicians in selecting appropriate combination regimens based on individual symptom patterns.* ***Study registration.*** *We registered study protocol on Open Science Framework (https://osf.io/4sedu/).*

Introduction

Allergic rhinitis (AR) is a common chronic inflammatory disorder of the upper respiratory tract, characterized by symptoms such as nasal congestion, rhinorrhea, sneezing, and nasal itching. It affects approximately 10-30% of the global population, with rising prevalence in both developed and developing countries (1). Beyond its physical symptoms, AR imposes a significant burden on patients' quality of life, including impaired sleep, decreased cognitive performance, and reduced work productivity (2). Despite the availability of various treatment options, many patients with AR remain poorly controlled due to suboptimal symptom relief and limited adherence, contributing to a substantial economic burden (3).

Current pharmacological options for AR include oral and intranasal antihistamines, intranasal corticosteroids, leukotriene receptor antagonists (LTRAs), and decongestants. Among these, second-generation oral antihistamines – such as loratadine, desloratadine, and levocetirizine –are commonly used as first-line therapy due to their rapid onset of action and minimal sedative effects. According to the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines, these agents are recommended as the initial treatment for mild intermittent AR, given their favorable safety profile and symptom-relieving efficacy (4). Montelukast, a LTRA, is often used as an alternative or adjunct, particularly in patients with poor response to antihistamines or comorbid asthma (5). The recent International Consensus Statement on Allergy and Rhinology supports that LTRAs are consistently more effective than placebo and may provide additional benefits for specific symptom domains such as nighttime control. They are not generally recommended as first-line therapy but may be considered in selected patients, particularly in combination strategies to enhance efficacy (6).

The rationale for combining montelukast with antihistamines is based on their complementary mechanisms. Antihistamines target histamine-mediated responses, while montelukast acts on leukotriene pathways, offering broader symptom control (7). This pathophysiological basis supports their potential synergistic effects, especially in patients with moderate-to-severe AR or those with partial response to monotherapy (8). In clinical practice, such combination therapy is frequently employed, although supporting evidence has been inconsistent. While several randomized controlled trials (RCTs) have evaluated the efficacy of combination therapy compared to monotherapy, the results remain inconsistent (9, 10). Importantly, limited number of meta-analyses have comprehensively addressed this specific comparison, leaving a gap in synthesized evidence that could inform guideline recommendations. The objective of this meta-analysis is to systematically evaluate the efficacy of combination therapy with montelukast and antihistamines compared to montelukast monotherapy in patients with AR. Primary outcomes include changes in total symptom scores and quality of life measures, while secondary analyses focus on individual symptom domains. This study also aims to identify whether certain antihistamine combinations provide greater benefit, thereby offering a clearer understanding of the clinical value of combination therapy and guiding optimal treatment strategies for AR.

Materials and methods

Search strategy

A comprehensive literature search was conducted in PubMed, Embase, MEDLINE, Scopus, and the Cochrane Library through April 2025. The search strategy was developed in collaboration with an experienced medical librarian specialized in clinical research synthesis. Studies were eligible if they compared combination therapy with montelukast and oral antihistamines *versus* montelukast monotherapy in patients with AR, with outcomes assessing symptom scores or health-related quality of life. Two reviewers independently screened titles and abstracts, assessed full texts, and resolved discrepancies through consensus with a third reviewer. The study flow is shown in **figure 1**.

Data extraction and risk of bias assessment

Data extraction was performed using a standardized form, capturing study characteristics including patient demographics, treatment allocation, and outcome measures (11, 12). Extracted data included changes from baseline to post-treatment in individual nasal symptoms (sneezing, itching, nasal congestion, and rhinorrhea), eye symptoms, total daytime and nighttime symptom scores, and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores. Outcomes were compared between combination therapy groups (montelukast plus loratadine, levocetirizine, or desloratadine) and monotherapy controls (montelukast alone) to assess the added benefit of combination treatment. Risk of bias for each included randomized controlled trial was evaluated using the Cochrane Risk of Bias 2.0 tool (13).

Statistical analysis

Statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Outcomes were pooled using standardized mean differences (SMDs) to account for variations in measurement scales across studies. Heterogeneity was assessed using Cochran's Q and the I^2 statistic. Publication bias was evaluated through funnel plots and Egger's regression test. Subgroup analyses were conducted to investigate sources of heterogeneity and to examine potential effect modifiers.

Results

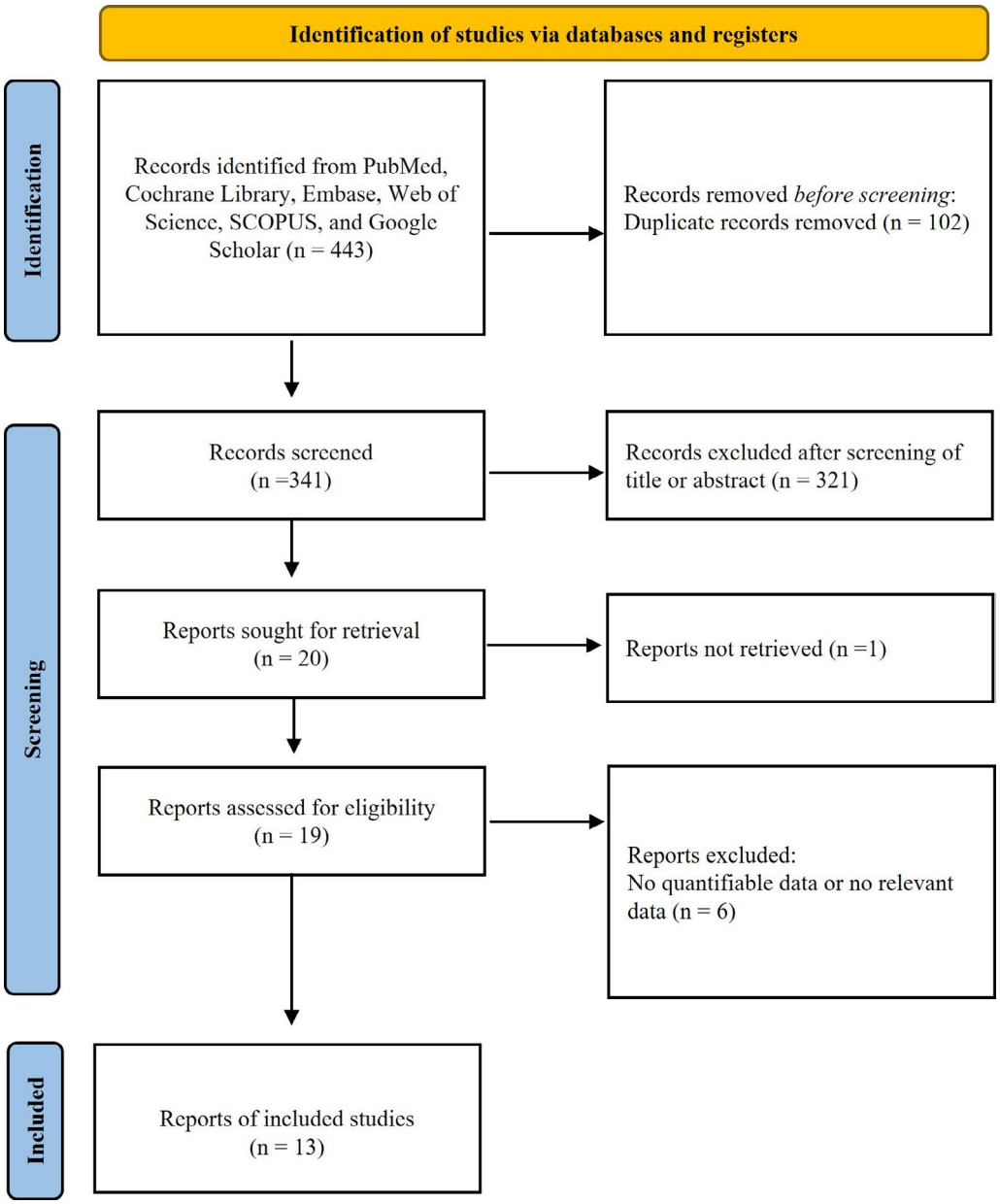
We ultimately analyzed 2,950 subjects evaluated in 13 studies (7, 10, 14-24). The studies are summarized in **table I** and the individual randomized controlled trial methodological quality are listed in **table I(Suppl)**.

Direct comparison of changes in total symptom scores and quality of life between combination therapy and montelukast monotherapy

Combination therapy demonstrated a statistically significant improvement in daytime nasal and eye symptoms compared to montelukast alone (SMD [95%CI] = 0.25 [0.15 to 0.35], I^2 = 51.2%) (**figure 2**). However, no significant differences were observed in nighttime symptoms (SMD [95%CI] = 0.10 [-0.01 to 0.21], I^2 = 0%) or RQLQ scores (SMD [95%CI] = 0.11 [-0.05 to 0.26], I^2 = 0%) (**table II**).

Subgroup analyses based on the type of antihistamine revealed that the combination of levocetirizine and montelukast consistently provided greater benefit in daytime symptoms (SMD [95%CI] = 0.42 [0.03 to 0.81], I^2 = 66.9%) and nighttime symptoms (SMD [95% CI] = 0.22 [0.05 to 0.39], I^2 = 0%) (**table II**). In contrast, loratadine in combination with montelukast showed a

Figure 1 *- Study selection diagram.*



more modest benefit in daytime symptoms (SMD [95%CI] = 0.18 [0.07 to 0.30], I^2 = 0%) with no significant effects on nighttime symptoms or quality of life. Desloratadine combined with montelukast showed a relatively large effect size for daytime symptoms (SMD [95%CI] = 0.83 [0.18 to 1.48]), although based on a single study. Subgroup analyses indicated that levocetirizine-montelukast combinations showed numerically greater benefit in both daytime and nighttime symptoms. However, these trends should be interpreted with caution, as formal tests for subgroup differences did not reach statistical significance (**table II**).

Direct comparison of changes in individual symptom scores between combination therapy and montelukast monotherapy

Combination therapy with montelukast and antihistamines was generally more effective than montelukast monotherapy in relieving most nasal symptoms, including sneezing, itching, obstruction, and rhinorrhea (**figure 3**). Considerable heterogeneity (I^2 > 50%) was observed in several outcomes. The analysis was based on pooled data without stratification by the type of antihistamine. Subgroup comparisons were performed to explore differences in treatment response across antihistamines (**table III**). For sneezing, combination therapy demonstrated a clear benefit over monotherapy (SMD = 0.54 [0.23 to 0.84], I^2 = 62.4%). The largest effect was observed in the desloratadine group (SMD = 0.72 [0.23 to 1.21], I^2 = 0%), followed by levocetirizine (SMD = 0.66 [0.14 to 1.18], I^2 = 66.2%). Loratadine-based therapy did not show a statistically significant improvement (SMD = 0.18 [-0.01 to 0.38]). In nasal itching, the overall effect of combination therapy was modest (SMD = 0.23 [0.09 to 0.37], I^2 = 0%). Desloratadine (SMD = 0.53 [0.05 to 1.01]) and levocetirizine (SMD = 0.32 [0.09 to 0.55]) both showed meaningful improvements, while loratadine did not result in a significant effect (SMD = 0.12 [-0.07 to 0.31]). Nasal obstruction improved significantly with combination therapy overall (SMD = 0.58 [0.21 to 0.95], I^2 = 79.2%). Deslorata-

Table I *- Summary of the studies included in our meta-analysis.*

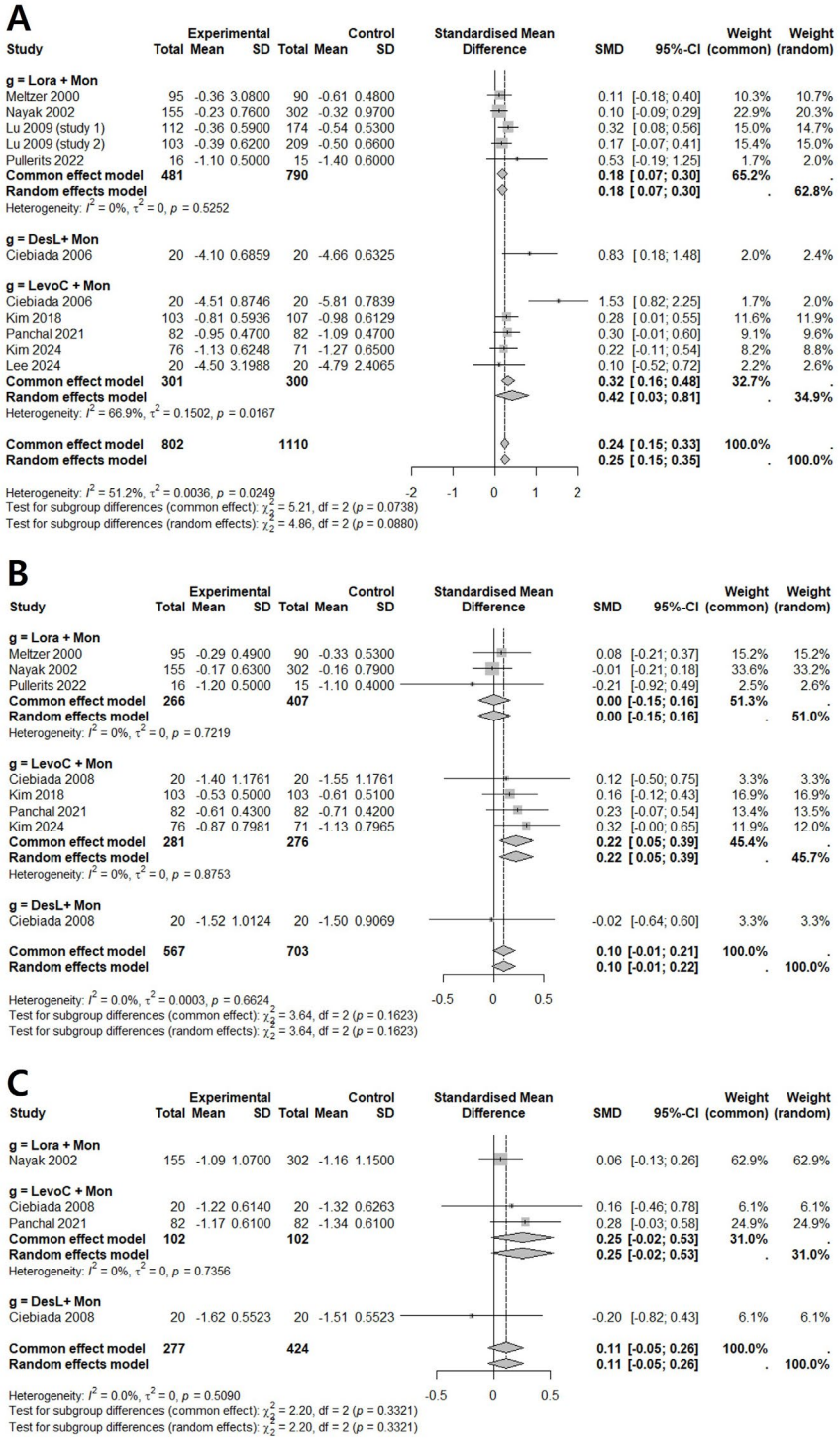
Study	Year	Study Type	Total number	Age (yrs)	Country	Rhinitis Type	Treatment	Duration (wks)	Outcomes
Meltzer	2000	Multicenter RCT with 5 parallel treatment groups (placebo-controlled)	460	15-75	USA	SAR	Montelukast (10/20 mg), loratadine 10 mg, combination (montelukast + loratadine), or placebo	2	Daytime nasal symptoms, Daytime eye symptoms, Nighttime nasal symptoms
Nayak	2002	Multicenter double-blind RCT (placebo-controlled)	758	15-82	USA	SAR	Montelukast (10/20 mg), loratadine 10 mg, combination (montelukast + loratadine), or placebo	2	Daytime nasal symptoms, individual nasal symptoms, Daytime eye symptoms, Nighttime nasal symptoms, Rhinoconjunctivitis Quality-of-Life
Ciebiada	2006	Double-blind, placebo-controlled crossover RCT	40	18-65	Poland	PAR	Montelukast 10 mg, desloratadine 5 mg, combination, or placebo	6	Daytime nasal symptoms, individual nasal symptoms, Daytime eye symptoms
Ciebiada	2008	Double-blind, placebo-controlled crossover RCT	40	18-65	Poland	PAR	Montelukast 10 mg, desloratadine 5 mg, combination, or placebo	6	Nighttime nasal symptoms, Rhinoconjunctivitis Quality-of-Life
Lu (study 1)	2009	Phase 2 randomized parallel-group study	402	15-85	Belgium	SAR	Beclomethasone 200 µg, placebo, combination (montelukast 10 mg + loratadine 10 mg), montelukast 10 mg, or loratadine 10 mg	2	Daytime nasal symptoms

→

Study	Year	Study Type	Total number	Age (yrs)	Country	Rhinitis Type	Treatment	Duration (wks)	Outcomes
Lu (study 2)	2009	Phase 2 randomized parallel-group study	476	15-85	Belgium	SAR	Beclomethasone 200 µg (study 1 only), placebo, combination (montelukast + loratadine), montelukast, or loratadine	2	Daytime nasal symptoms
Ciebiada	2011	Double-blind, placebo-controlled, 2-arm crossover RCT	40	18-65	Poland	PAR	Montelukast 10 mg, desloratadine 5 mg, combination (montelukast 10 mg + desloratadine 5 mg), or placebo	6	individual nasal symptom
Andhale	2016	Prospective RCT	75	15-75	India	PAR	Montelukast 10 mg or combination (montelukast 10 mg + levocetirizine 5 mg), or levocetirizine 5mg alone	2	individual nasal symptoms, Daytime eye symptoms
Kim	2018	Phase 3 multicenter double-blind RCT	210	>15	Korea	Asthma and AR	Montelukast 10 mg or combination (montelukast 10 mg + levocetirizine 5 mg)	4	Daytime nasal symptoms, individual nasal symptoms, Nighttime nasal symptoms
Panchal	2021	Phase 3 multicenter double-blind RCT	186	18-60	India	SAR	Montelukast 10 mg or combination (montelukast 10 mg + levocetirizine 5 mg), or levocetirizine 5mg alone	2	Daytime nasal symptoms, Nighttime nasal symptoms, Rhinoconjunctivitis Quality-of-Life
Pullerits	2022	Double-blind, double-dummy, placebo-controlled parallel-group RCT	31	15-50	Estonia	SAR	Fluticasone 200 µg, montelukast 10 mg, combination (montelukast 10 mg + loratadine 10 mg), or placebo	6	Daytime nasal symptoms, Nighttime nasal symptoms,
Ghanbari	2024	Open-label RCT	45	6-14	Iran	Moderate to severe AR	Desloratadine syrup (2.5–5 mg/day), montelukast 5 mg, combination (desloratadine + montelukast)	8	Daytime nasal symptoms, individual nasal symptoms
Kim	2024	Open-label multicenter RCT	147	6-14	Korea	AR	Montelukast 5 mg or fixed-dose combination (montelukast 5 mg + levocetirizine 5 mg)	4	Daytime nasal symptoms, individual nasal symptoms, nighttime nasal symptom score
Lee	2024	Open-label randomized case-controlled study	40	6-14	Korea	PAR	Montelukast 5 mg or combination (montelukast 5 mg + levocetirizine 5 mg) for 4 weeks	4	Daytime nasal symptoms

RCT: randomized controlled trial; SAR: seasonal allergic rhinitis; PAR: perennial allergic rhinitis; AR: allergic rhinitis.

***Figure 2** - Direct comparison of changes in total symptom scores and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores between combination therapy and montelukast monotherapy.*



***(A)** Daytime total symptom score, **(B)** nighttime total symptom score, and **(C)** RQLQ score. Lora: loratadine; DesL: desloratadine; Levoc: levocetirizine; Mon: montelukast; SMD: standardized mean difference; CI: confidence interval.*

dine (SMD = 0.71 [0.25 to 1.16], I^2 = 28.0%) and levocetirizine (SMD = 0.68 [0.09 to 1.27], I^2 = 82.8%) showed substantial benefit. In contrast, loratadine showed no significant improvement (SMD = 0.02 [-0.17 to 0.21]).

For rhinorrhea, a moderate pooled effect was observed (SMD = 0.42 [0.09 to 0.83], I^2 = 85.5%), with only the levocetirizine subgroup demonstrating a significant improvement (SMD = 0.70 [0.12 to 1.29], I^2 = 87.9%). Desloratadine (SMD = 0.00 [-0.47 to 0.48]) and loratadine (SMD = 0.06 [-0.14 to 0.25]) showed no meaningful effect. Leave-one-out sensitivity analyses indicated that heterogeneity was largely driven by a few trials with large effect sizes, particularly Kim *et al*. (2024) (22) and Ciebiada *et al*. (2006) (7). Excluding Kim (2024) reduced heterogeneity to 60.3% (SMD = 0.23 [-0.02 to 0.47]) (22), and excluding Ciebiada (2006) yielded SMD = 0.31 [-0.04 to 0.65] with I^2 = 84.8% (7). When both studies were removed, the pooled effect remained modest but consistent (SMD = 0.21 [0.05 to 0.37]) with I^2 = 0%, suggesting that the overall direction of effect is robust while the magnitude is influenced by small but influential studies.

Eye symptoms had the largest pooled effect size (SMD = 1.04 [-0.18 to 2.26], I^2 = 97.7%), though the wide confidence interval and high heterogeneity limit the interpretability of this result. The strongest apparent benefit was observed in the levocetirizine group (SMD = 1.84 [-0.11 to 3.79], I^2 = 96.0%), while desloratadine (SMD = 0.42 [–0.21 to 1.05]) and loratadine (SMD = 0.08 [-0.11 to 0.28]) were not associated with significant improvement.

Discussion

In this meta-analysis, combination therapy with montelukast and antihistamines demonstrated superior efficacy compared to montelukast monotherapy in relieving several symptom domains associated with AR. The combination approach was particularly effective in improving daytime symptoms, with a statistically significant pooled effect size. However, it showed limited benefits for nighttime symptoms and health-related quality of life, as measured by the RQLQ. Among the antihistamines analyzed, levocetirizine-based combination therapy consistently provided the most favorable outcomes for both daytime and nighttime symptom scores. Desloratadine also showed a relatively large effect on daytime symptoms, although this finding was derived from a single study. In contrast, loratadine-based combinations did not produce statistically meaningful improvements in any symptom domain.

Cysteinyl leukotrienes (CysLTs) play a key role in the pathophysiology of AR by promoting vascular permeability, mucus secretion, and eosinophilic infiltration in the nasal mucosa (25). Montelukast, a selective CysLT1 receptor antagonist, has demonstrated efficacy in nasal obstruction by reducing mucosal edema, suppress sneezing and itching through inhibition of sensory nerve stimulation, and improve mucociliary clearance by decreasing mucus viscosity (5, 26). Chervinsky *et al*. demonstrated that montelukast monotherapy significantly improved daytime nasal symptoms in patients with seasonal AR, particularly during periods of high pollen exposure (27). Their multi-seasonal analysis supported the responsiveness of montelukast to allergen load, reinforcing its efficacy as a monotherapy.

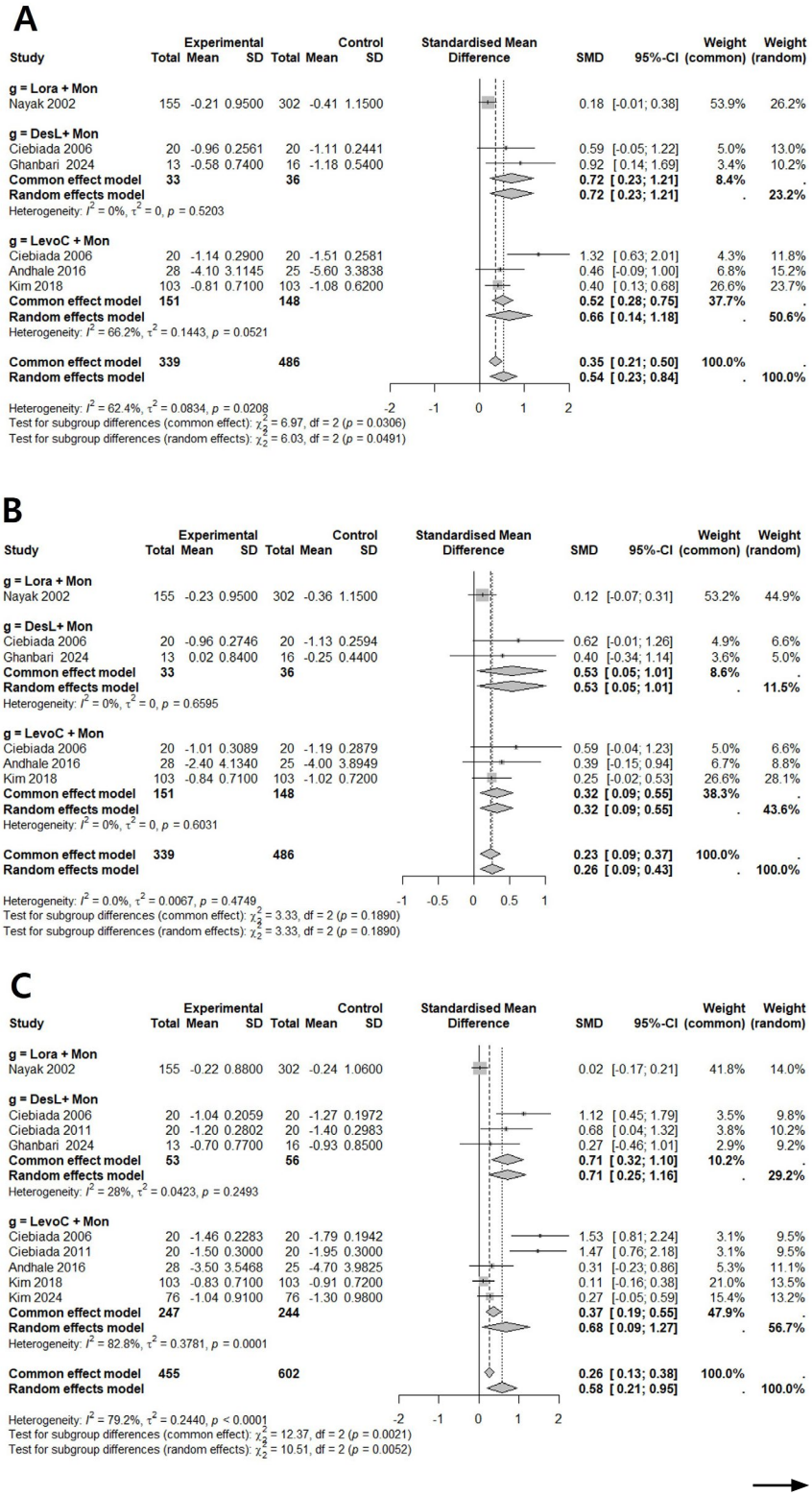
Histamine also plays a key role in the early-phase response of AR (28). Upon allergen exposure, activated mast cells rapidly release histamine, which binds to H_1 receptors in the nasal mucosa (29). These effects occur within minutes, inducing sneezing, itching, and rhinorrhea, and are central to the immediate hypersensitiv-

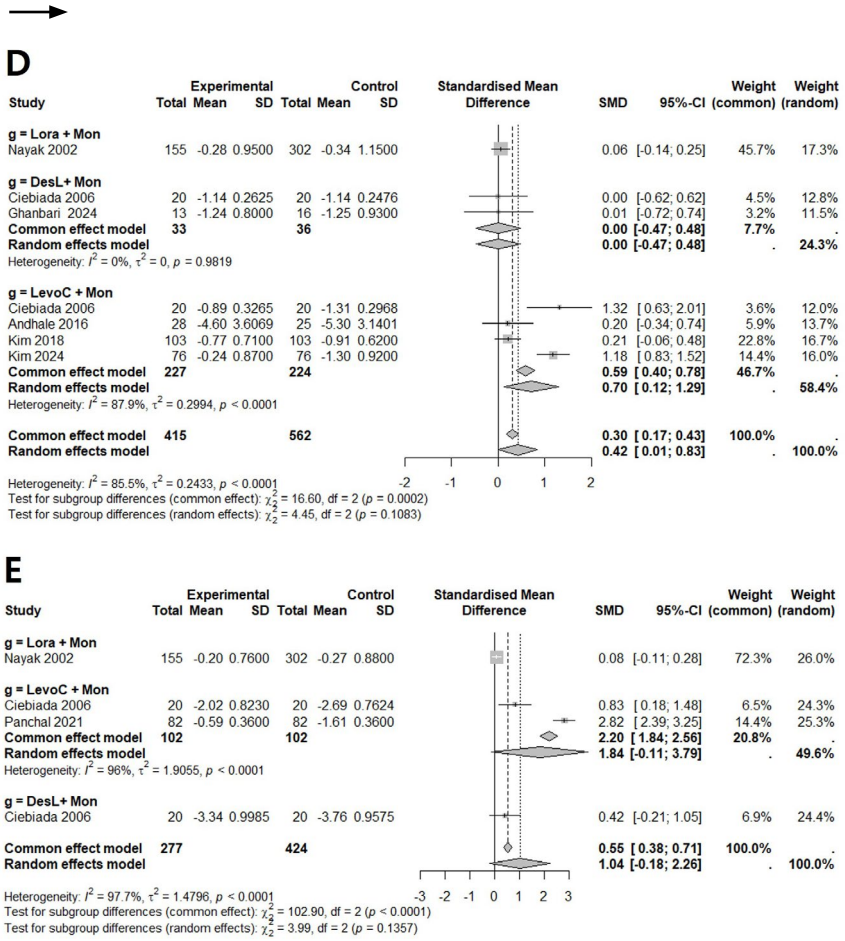
Table II *- Subgroup analysis of changes in total symptom scores and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores between combination therapy (montelukast with antihistamines) and montelukast monotherapy.*

	Daytime	**Nighttime**	**RQLQ**
SMD	0.2498 [0.1478; 0.3518] I^2 = 51.2%	0.1018 [-0.0105; 0.2141] I^2 = 0%	0.1060 [-0.0476; 0.2595] I^2 = 0%
Lora + Mon	n = 5 0.1806 [0.0659; 0.2953] I^2 = 0%	n = 3 0.0037 [-0.1531; 0.1605] I^2 = 0%	n = 1 0.0622 [-0.1315; 0.2559] N/A
DesL+ Mon	n = 1 0.8319 [0.1832; 1.4806] N/A	n = 1 -0.0204 [-0.6402; 0.5994] N/A	n = 1 -0.1952 [-0.8166; 0.4262] N/A
LevoC + Mon	n = 5 0.4201 [0.0264; 0.8138] I^2 = 66.9%	n = 4 0.2216 [0.0549; 0.3883] I^2 = 0%	n = 2 0.2539 [-0.0218; 0.5295] I^2 = 0%
P-value	0.0880	0.1623	0.3321

Lora: loratadine; DesL: desloratadine; Levoc: levocetirizine; Mon: montelukast; SMD: standardized mean difference; CI: confidence interval; RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire; N/A: not applicable.

Figure 3 *- Direct comparison of changes in individual nasal symptom scores and eye symptom scores between combination therapy and montelukast monotherapy.*





***(A)** Sneezing, **(B)** nasal itching, **(C)** nasal congestion, **(D)** rhinorrhea, and **(E)** eye symptoms. Lora: loratadine; DesL: desloratadine; Levoc: levocetirizine; Mon: montelukast; SMD: standardized mean difference; CI: confidence interval.*

***Table III** - Subgroup analysis of changes in individual nasal and eye symptom scores between combination therapy (montelukast with antihistamines) and montelukast monotherapy.*

	Sneezing	Itching	Obstruction	Rhinorrhea	Eye symptoms
SMD	0.5381 [0.2317; 0.8445] I² = 62.4%	0.2313 [0.0900; 0.3727] I² = 0%	0.5773 [0.2076; 0.9470] I² = 79.2%	0.4199 [0.0092; 0.8306] I² = 85.5%	1.0388 [-0.1797; 2.2574] I² = 97.7%
Lora + Mon	n = 1 0.1838 [-0.0102; 0.3778] N/A	n = 1 0.1195 [-0.0744; 0.3133] N/A	n = 1 0.0199 [-0.1737; 0.2136] N/A	n = 1 0.0551 [-0.1386; 0.2488] N/A	n = 1 0.0831 [-0.1107; 0.2768] N/A
DesL+ Mon	n = 2 0.7195 [0.2288; 1.2102] I² = 0%	n = 2 0.5306 [0.0481; 1.0131] I² = 0%	n = 3 0.7078 [0.2515; 1.1640] I² = 28.0%	n = 2 0.0046 [-0.4683; 0.4776] I² = 0%	n = 1 0.4208 [-0.2065; 1.0481] N/A
LevoC + Mon	n = 3 0.6587 [0.1407; 1.1766] I² = 66.2%	n = 3 0.3197 [0.0912; 0.5482] I² = 0%	n = 5 0.6779 [0.0900; 1.2658] I² = 82.8%	n = 4 0.7043 [0.1183; 1.2902] I² = 87.9%	n = 2 1.8391 [-0.1132; 3.7914] I² = 96.0%
P-value	0.0491	0.1890	0.0052	0.1083	0.1357

Lora: loratadine; DesL: desloratadine; Levoc: levocetirizine; Mon: montelukast; SMD: standardized mean difference; CI: confidence interval; N/A: not applicable.

ity reaction observed in AR (28). Second-generation oral antihistamines selectively block peripheral H_1 receptors and are widely recommended as first-line agents for patients with mild to moderate AR (4). Their rapid onset and low sedative potential make them appropriate for daily use. However, their therapeutic benefit is largely limited to histamine-mediated symptoms, with minimal efficacy against nasal obstruction and other manifestations driven by leukotrienes, cytokines, and other inflammatory mediators (30). Moreover, antihistamines exert little effect on the late-phase inflammatory response, which contributes to persistent symptoms and reduced treatment responsiveness in some patients (31). In this context, combination therapy with leukotriene receptor antagonists has been proposed to enhance therapeutic efficacy by targeting multiple inflammatory pathways (22, 24, 32).

Although the overall difference between montelukast-antihistamine combination therapy and montelukast monotherapy was small and RQLQ improvement was not significant, our analysis identified modest improvements in individual symptoms such as sneezing and nasal obstruction. These results are consistent with the modest role of montelukast and with recent evidence showing that intranasal treatments, particularly corticosteroids, are superior to oral therapies (33). However, intranasal corticosteroids are not feasible for all patients because of contraindications, side effects, or poor adherence. In such cases, oral therapy remains a relevant alternative. Our findings therefore suggest that adding an antihistamine to montelukast may provide incremental, symptom-specific benefits, particularly for patients whose predominant complaints are not adequately controlled with monotherapy. RQLQ showed limited responsiveness in our results, which may be because the questionnaire covers broader domains such as emotional well-being and daily functioning. These aspects may require longer treatment durations or stronger anti-inflammatory effects to show measurable improvement. Among the evaluated antihistamines, levocetirizine in combination with montelukast consistently showed statistically significant benefits across multiple studies, suggesting that this regimen may offer more reliable symptom control during both daytime and nighttime. Although desloratadine demonstrated the largest effect size for daytime symptoms, this finding was derived from a single study and should therefore be interpreted with caution until replicated in further trials.

In our analysis, desloratadine-based combinations showed the greatest improvements in sneezing, itching, and nasal obstruction, while levocetirizine-based combinations demonstrated more consistent and statistically robust effects, particularly for rhinorrhea. However, interpretation of the rhinorrhea outcome requires caution because of substantial heterogeneity. A small-scale study by Ciebiada *et al*. (2006) (7), which reported an unusually large effect and had concerns regarding risk of bias, disproportionately increased variability. In addition, the pediatric population in Kim (2024) (22) may have contributed to differences compared with adult studies. These findings suggest that although the overall direction of effect is consistent, the magnitude should be interpreted cautiously. Taken together, these results suggest that the choice of antihistamine in combination therapy may influence both the extent and profile of symptom relief. Analyzing outcomes by individual symptoms provides insights that composite scores may overlook. Since patients often present with distinct symptom patterns, identifying the most appropriate regimen for each profile may support more personalized treatment strategies.

This study has several limitations. Individual patient-level variables, particularly baseline symptom severity, were not consistently reported across studies. Because treatment response in AR varies with initial severity, the absence of severity-based stratification limits the interpretability of pooled effect sizes and may have led to over or underestimation in subgroups. In addition, most included studies had relatively short treatment durations, generally between two and four weeks, which may not be sufficient to capture meaningful changes in quality of life. Some subgroup findings, such as the large effect size observed with desloratadine, were derived from a single trial and should be interpreted with caution until replicated. In addition, most RQoL data were derived from SAR studies, with very limited evidence available for PAR, so the potential impact of rhinitis subtype on quality-of-life outcomes could not be assessed. This distinction may be clinically relevant, since patients with PAR often experience more persistent symptoms than those with SAR. Collectively, these limitations highlight the need for larger and stratified populations, longer follow-up, and standardized reporting of baseline severity. In particular, stratification by predominant symptom profiles will be essential to clarify whether certain AR phenotypes derive greater benefit from montelukast-antihistamine combination therapy.

Conclusions

This meta-analysis indicates that combining montelukast with oral antihistamines improves daytime and individual nasal symptoms more effectively than montelukast alone. Levocetirizine-based combinations showed the most consistent benefits, including nighttime symptom relief. However, treatment effects varied by symptom and antihistamine type. These findings support a personalized, symptom-targeted approach to treatment selection. Future studies should stratify patients by predominant symptoms or AR phenotypes to optimize combination strategies and better assess long-term impacts on quality of life.

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Contributions

JSK, GS, SHH: conceptualization, supervision. JSK, SHH: methodology, formal analysis, investigation data curation, writing - original draft, writing - review & editing, visualization. SHH: software, validation.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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João Cardoso Lopes[1,*], Pedro Botelho Alves[1,*], Helena Pires Pereira[1], Francisca Cunha[1], Inês Farinha[1], Ângela Maresch[2], Rosário Cunha[2], Graça Loureiro[1], Ana Todo-Bom[1,3], Beatriz Tavares[1]

Molecular profiling in bee venom allergy: clinical and therapeutic characterization in a Portuguese cohort

[1]Department of Allergy and Clinical Immunology, Coimbra Hospital and University Center, Coimbra, Portugal
[2]Department of Clinical Pathology, Coimbra Hospital and University Center, Coimbra, Portugal
[3]Coimbra Clinical Academic Center, Faculty of Medicine, University of Coimbra, Coimbra, Portugal
*Contributed equally to the work

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Corresponding author
João Cardoso Lopes
Department of Allergy and Clinical Immunology
Coimbra Hospital and University Center
Praceta Prof. Mota Pinto
3000-075 Coimbra, Portugal
ORCID: 0000-0002-1265-9449
E-mail: joaolopes1493@gmail.com

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Impact statement

Molecular allergens to Apis mellifera appear to be useful in stratifying severity of bee venom allergy index reactions but also in predicting the efficacy and safety of venom immunotherapy in a Portuguese population.

Summary

Background. *Bee venom allergy (BVA) can trigger local and systemic allergic reactions, including anaphylaxis. Recently, the molecular sensitization profile has gained importance in the reaction's stratification and venom immunotherapy (VIT).* ***Methods.*** *Retrospective analysis of patients with hypersensitivity to BVA, confirmed by sIgE to Apis mellifera ≥ 0.35 kU/L and/or positive skin tests to bee venom commercial extract, evaluated in specialized consultation. Demographic, clinical, and laboratory data were analyzed, looking for risk factors associated with the severity of the index reaction and reactions during VIT.* ***Results.*** *93 patients were included (55.9% male; median age of 46 years), 57.3% with atopic comorbidities, and 23.4% with cardiovascular comorbidities. The median specific IgE to Apis mellifera was 6.7 (IQR 1.0-20.3) kU/L. Regarding the molecular profile, the median IgE to Api m 1 was 0.5 kU/L (57.5% positive out of all measurements); Api m 4 - 0.01 kU/L (11.9% positive), and Api m 10 - 0.3 kU/L (50.0% positive). The severity of the index reaction correlated positively with older ages (p = 0.040; r = 0.249), in contrast to monosensitization to Api m 1, which was an independent predictor of milder reactions (p = 0.015). Sensitization to Api m 10 was associated with a higher likelihood of reactions during VIT (p = 0.038) but showed a trend toward fewer systemic reactions at re-stings (p = 0.097).* ***Conclusions.*** *Molecular sensitization profile appears to be relevant not only to the severity of index reactions but also during VIT. Studies of a large cohort of patients with molecular profiles are essential to validate these results and improve the clinical and therapeutic approach to BVA.*

Introduction

Insect stings by Hymenoptera species such as honeybees are very common, with data indicating that 56.6%-94.5% of the general population has been stung at least once in their lifetime (1). The most frequent clinical presentations of bee venom allergy (BVA) are large local reactions (LLR) at the sting site and systemic sting reactions (SSR). A LLR has been defined as a swelling exceeding a diameter of 10 cm that lasts for longer than 24 h (2). In SSR, mild symptoms usually manifest as generalized skin conditions including flushing, urticaria, and angioedema. Typically, dizziness, dyspnea, and nausea are examples of moderate reactions, while shock and loss of consciousness, or even cardiac or respiratory arrest, define a severe SSR. Severe reactions are life threatening and have been attributed to fatalities. The rate of self-reported SSR in European epidemiological studies ranges

from 0.3 to 7.5% in adults (3), while LLRs occur in 2.4% to 26.4% of the general population (4).

The only treatment that can potentially prevent further SSR is venom immunotherapy (VIT), which is reported to be effective in 77 to 84% of patients treated with honeybee venom (5, 6). It is known that specific immunotherapy with bee venom *versus* wasp venom is usually associated with lower therapeutic efficacy and a higher risk of systemic reactions during treatment (7). It is therefore extremely important to identify potential biomarkers for assessing therapeutic efficacy and severity.

A total of 12 allergenic fractions from the honeybee (*Apis mellifera*) are known and registered, and they can be found in the official database of allergens of the World Health Organization/International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature Sub-Committee (8). As many as 11 of these allergens come from bee venom (*Api m 1-10*, *Api m 12*), while two allergenic isoforms are derived from bee secretions from the royal jelly-producing glands (*Api m 11a* [0101] and *Api m 11b* [0201]). Currently, commercially available Hymenoptera allergens for component-resolved allergy testing include *rApi m 1*, *rApi m 2*, *rApi m 3*, *rApi m 5* and *rApi m 10* for honeybee venom, whereas *Api m 4* has emerged as a molecular allergen of potential clinical relevance.

In addition to their already recognized role in the proper diagnosis of BVA patients, the molecular components of bee venom can play an important role in identifying potential cross-reactivity, as well as an important role as markers in assessing efficacy and severity (9).

Some components are better characterized in the literature than others, such as *Api m 1* (a major bee venom allergen) and *Api m 2* (considered a marker of cross-reactivity), while others have yet to be fully studied. Some studies associate sensitization to *Api m 10* with less effective immunotherapy (10, 11) and lower tolerance to immunotherapy in patients sensitized to *Api m 4* – a minor allergen in the venom but with a high percentage of dry weight (12, 13).

Thus, characterizing the molecular sensitization profile has become increasingly important in stratifying the severity of reactions to stings, as well as in the efficacy of VIT and in predicting adverse reactions throughout treatment. We decided to characterize the clinical and laboratory profiles of BVA patients in a Mediterranean cohort.

Materials and methods

Study design

This cross-sectional study was conducted in the Allergy and Clinical Immunology Unit of a tertiary hospital in Portugal. We included patients that were followed-up at our outpatient clinic between January/2012 and July/2023 and were sensitized to bee venom. Sensitization was defined as having serum specific IgE (sIgE) to *Apis mellifera* venom ≥ 0.35 kU/L and/or positive skin prick/intradermal tests to *Apis mellifera* venom (Roxall Medicina, Spain). Subsequently, we collected demographic, clinical and additional laboratory data using electronic hospital records (*SClínico)* and national health registry (*Registo de Saúde Eletrónico – RSE)*.

Participants

A total number of 93 allergic patients were enrolled in this study. Patients had to meet two criteria to be classified as being allergic to bee venom-bee venom sensitization and reported systemic symptoms after bee sting.

Data collection

The collected data included demographic, clinical and laboratory variables.

Patient's gender, age at index-reaction, age at time of data collection and beekeeping-related occupations were selected as our demographic variables.

Index-reaction was characterized as the most severe among the earliest sting reactions in BVA patients. Farmers and hobbyists associated with beekeeping were also defined.

Clinical data included atopic and cardiovascular comorbidities, the severity of the index reaction, the number of stings during the index reaction, and bee VIT. Data was registered in a case report form, based on electronic registries. The clinical background of atopic comorbidities was assessed individually for asthma, allergic rhinitis and food allergy. Arterial hypertension, diabetes, ischemic cardiopathy, dyslipidemia and obesity were considered cardiovascular comorbidities. Information about the severity of the index allergic reaction was collected and stratified according to the Mueller classification of systemic reactions to insect stings (2, 14). Severity ranged from grade 1 (urticaria, itching, malaise, and anxiety) to the more severe grade 4 (mucocutaneous, respiratory and/or gastrointestinal symptoms, plus two or more of the following: fall in blood pressure, collapse, loss of consciousness, incontinence, cyanosis). A cluster protocol for VIT patients was performed in our allergy center. Patients that concluded or were still undergoing bee VIT were also characterized according to the occurrence of systemic reactions during immunotherapy and/or with re-stings.

The following laboratory data was collected: basal tryptase (Thermo Fisher Scientific, United States), *Apis mellifera* venom sIgE and venom component sIgE (ImmunoCAP, Thermo Fisher Scientific, United States), at the time of the first observation at our clinic. For VIT patients, sIgE to *Apis Mellifera* is expected to vary over time. As such, it was collected in two time periods – before and more than 12 months after VIT. *Apis mellifera* and venom component sIgE were considered positive when levels were ≥ 0.35 kU/L. Component-specific sIgE included the allergens *Api m 1, Api m 4* and *Api m 10*.

Statistical analysis

All statistical analyses were done using STATA software (version 16.1, StataCorp LLC, Texas, USA) in order to assess for correlations between the severity of systemic index reactions and demographic, clinical and laboratory data. Patient characteristics were described as a percentage for categorical data and either as mean (standard deviation) or median (interquartile range) for continuous data, depending on observation of normality. Normality was assessed through histogram interpretation. P-values of < 0.05 were considered statistically significant. Chi-squared or Exact Fisher tests were used for correlation between categorical variables. Correlation between continuous and categorical data was assessed using t-test or Mann-Whitney U, depending on observation of normality. Multivariate linear regression was used to control for confounding.

Results

Patient characteristics at allergy onset

Our study included 93 BVA patients. The median age at index-reactions was 36 (IQR 26-48) years, and 52 (55.9%) were males. Forty (43.0%) patients were associated with beekeeping activities. Atopic comorbidities were highly prevalent (57.3% of 75 patients), whereas roughly a quarter (23.4% of 77 patients) presented with cardiovascular comorbidities. No patients were diagnosed with mast-cell diseases or hereditary alpha tryptasemia.

Eighty-five patients with BVA reported index-reactions with a median severity of 3 (IQR 2-3), with most (n = 53, 62.4%) presenting with highly severe reactions (grades 3 and 4). Forty patients were able to discriminate the number of bee stings, with 30 (75.0%) reporting a single one. The clinical characteristics and demographics of the study participants are depicted in **table I**.

Bee venom immunotherapy

In our cohort, 47 (50.5%) patients underwent VIT. Patients who did not have VIT mainly refused treatment, and a few were contraindicated for it (due to pregnancy or active malignancy). Treatment was completed (median of 5 [IQR 5-6] years) in 19 (40.4%), 2 patients (4.2%) abandoned treatment (one due to loss to follow-up and the other discontinued after several systemic reactions to VIT) and 26 (55.4%) are still under treatment. Sixteen patients (35.6%) reported systemic reactions during immunotherapy (mostly grades 1 and 2). Additionally, 25 (53.2%) patients were re-stung, of which only four reported SSR. Most of these re-stung patients were related to beekeeping activities (n = 18, 72.0%).

Laboratory data

The median (IQR) *Apis mellifera* sIgE levels of our cohort were 6.7 (1.0-20.3) kU/L. In our sub-group of VIT patients, pre-treatment levels were higher (13.7; 5.3-43.5), dropping significantly during follow-up to 3.3 (1.1-7.9) kU/L.

Regarding molecular sIgE sensitization, patients were tested for *Api m 1* (n = 73), *Api m 4* (n = 42) and *Api m 10* (n = 64). Overall, *Api m 1* was positive in 42 patients (57.5%) and *Api m 10* in 32 (50.0%), whereas only 5 patients (11.9%) had positive *Api m 4* levels. Three (5.3%) patients of all cohort were sensitized to all three allergens. Median (IQR) sIgE levels for *Api m 1, 4* and *10* were 0.47 (0.10-1.57), 0.01 (0.00-0.08) and 0.32 (0.08-1.62), respectively.

In the VIT subgroup, among patients whose molecular components were available, 18 (72.0% of 25 measurements) were sensitized to *Api m 1*, and 15 (65.2% of 23) to *Api m 10*, in contrast with only 2 (10.5% of 19) patients with positive sIgE to *Api m 4*. These two patients were also polysensitized to the other molecular allergens. Detailed sensitizations to molecular allergens are depicted in **table I**.

Associations between systemic reactions and demographic, clinical or laboratory variables

Severity of index-reaction to bee sting was associated with age and molecular sensitization profiles to Apis mellifera

Severity of the reaction at allergy onset was classified in 85 patients. There was a weak but significant positive correlation with age at onset, with older patients presenting more severe reactions (Spearman's coefficient [*rho*] = 0.249, p = 0.040). Inversely, patients that were only sensitized to *Api m 1* (among the three measured proteins) had milder reactions in comparison to non-monosensitized patients – 2 (IQR 2-2*) vs* 3 (IQR 3-4), p = 0.015. When fitted in a multivariate linear regression model that included variables with $p < 0.100$ (age, atopic comorbidities and sensitization solely to *Api m 1*) and used a backward stepwise approach, the *Api m 1* mono-sensitization profile retained its significance (p = 0.031) and was considered an independent predictor for milder systemic index-reactions to bee sting. Statistical analysis for all demographic, clinical and laboratory variables is described in **table II**.

Occurrence of systemic reactions during VIT was associated with sensitization to Api m 10

Patients that concluded or were still undergoing VIT were analyzed. No significant associations were found between demography, clinical and laboratory variables and the proportion of VIT patients with systemic reactions, with one notable exception – patients sensitized to *Api m 10*, regardless of potential co-sensitizations, were significantly more associated with systemic adverse reactions during VIT when compared to non-systemic reactions (90.0 *vs* 46.2%, p = 0.038). Statistical analysis for potential associations is depicted in **table III**.

Table I *- Characteristics of patients with bee sting reactions (n = 93).*

Variables	Values	Total patients
Demographic data		
Current age	46 (34-55)	93
Male gender, n (%)	52 (55.9)	93
Allergic comorbidities, n (%)	43 (57.3)	75
Asthma, n (%)	15 (22.4)	67
Rhinitis, n (%)	30 (43.5)	69
Food allergy, n (%)	4 (9.1)	44
Cardiovascular comorbidities, n (%)	18 (23.4)	77
Beekeeper, n (%)	40 (43.0)	93
Clinical Data – index-reaction		
Age at reaction, M (IQR)	36 (26-48)	68
Severity classification (Mueller), M (IQR)	3 (2-3)	85
Grade 1, n (%)	12 (14.1)	85
Grade 2, n (%)	20 (23.5)	85
Grade 3, n (%)	35 (41.2)	85
Grade 4, n (%)	18 (21.2)	85
Number of stings in the same reaction, n (%)		
Once, n (%)	30 (75.0)	40
Twice, n (%)	4 (10.0)	40
Three or more times, n (%)	6 (15.0)	40
Clinical data – specific immunotherapy		
Patients undergoing VIT, n (%)	47 (50.5)	93
Completed treatment (median: 5 years), n (%)	19 (40.4)	47
Discontinued treatment, n (%)	2 (4.2)	47
Under treatment, n (%)	26 (55.4)	47
Adverse reactions during VIT, n (%)	16 (35.6)	45
Re-stung patients, n (%)	25 (53.2)	47
Systemic reactions, n (%)	4 (16.0)	25
Severity classification (Mueller)	2 (1-2)	4
Laboratory data		
Basal tryptase	4.2 (3.4-5.6)	72
Basal tryptase >11.4 ug/L, n (%)	3 (4.2)	72
Apis mellifera IgE (total)	6.7 (1.0-20.3)	93
Apis mellifera IgE (VIT: pre-treatment)	13.7 (5.3-43.5)	47
Apis mellifera IgE (VIT: >12M treatment)	3.3 (1.1-7.9)	42
Api m 1 IgE	0.5 (0.1-1.6)	73
Positive (>0.34 kU/L), n (%)	42 (57.5)	73
Api m 4 IgE	0.01 (0.0-0.08)	42
Positive (>0.34 kU/L), n (%)	5 (11.9)	42
Api m 10 IgE	0.3 (0.1-1.6)	64
Positive (>0.34 kU/L), n (%)	32 (50.0)	64
Api m 1 (+) / 4 (-) / 10 (-), n (%)	5 (11.9)	42
Api m 1 (-) / 4 (+) / 10 (-), n (%)	0 (0.0)	42
Api m 1 (-) / 4 (-) / 10 (+), n (%)	2 (4.8)	42
Polysensitized *Api m 1/4/10 (+)*, n (%)	3 (7.1)	42

IQR: interquartile range; M: median.

Table II *- Associations between the variables analyzed and the severity of the index-reaction (n = 85).*

Variables	Reaction severity grading (Mueller)				Total patients	P-value	Spearman Coefficient
	1 (n = 12)	2 (n = 20)	3 (n = 35)	4 (n = 18)			
Male gender, n (%)	7/12 (58.3)	11/20 (55.0)	21/35 (60.0)	9/18 (50.0)	85	0.782	
Age at time of index-reaction, M (IQR)	28.0 (12.0-40.0)	35.5 (27.0-45.5)	40.0 (29.0-53.0)	40.5 (28.5-55.0)	68	**0.040**	0.249
Allergic comorbidities, n (%)	5/11 (45.4)	7/13 (53.8)	18/30 (60.0)	11/14 (78.6)	68	0.090	
Cardiovascular comorbidities, n (%)	1/11 (9.1)	4/18 (22.2)	8/28 (28.6)	4/15 (26.7)	72	0.308	
Beekeepers, n (%)	5/12 (41.7)	7/20 (35.0)	16/35 (45.7)	7/18 (38.9)	85	0.849	
Basal tryptase, M (IQR)	5.2 (3.6-5.9)	3.7 (2.8-4.4)	4.2 (3.4-5.7)	5.0 (4.0-5.6)	64	0.179	0.170
Apis mellifera IgE (kU/L), M (IQR)	6.4 (0.01-12.4)	5.3 (1.1-10.6)	10.6 (1.9-42.8)	2.8 (0.4-34.7)	83	0.409	0.092
Api m 1 IgE (kU/L), M (IQR)	0.3 (0.02-1.3)	0.5 (0.2-1.3)	0.5 (0.1-1.6)	0.5 (0.01-2.1)	70	0.804	0.030
Positive (>0.34 kU/L), n (%)	5/11 (45.4)	12/17 (70.6)	14/25 (56.0)	9/17 (52.9)	70	0.856	
Api m 4 IgE (kU/L), M (IQR)	0.39 (0.01-0.77)	0.01 (0.01-0.02)	0.0 (0.0-0.04)	0.04 (0.01-0.18)	41	0.734	0.055
Positive (>0.34 kU/L), n (%)	1/2 (50.0)	1/10 (10.0)	1/17 (5.9)	2/12 (16.7)	41	0.869	
Api m 10 IgE (kU/L), M (IQR)	1.06 (0.23-1.31)	0.24 (0.07-0.44)	0.41 (0.11-1.99)	0.14 (0.02-2.59)	62	0.580	-0.072
Positive (>0.34 kU/L), n (%)	4/6 (66.7)	7/16 (43.8)	13/25 (52.0)	7/15 (46.7)	62	0.765	
Api m 1 (+) / 4 (-) / 10 (-), n (%)	1/2 (50.0)	3/10 (30.0)	1/17 (5.9)	0/12 (0.0)	41	**0.015**	
Api m 1 (-) / 4 (+) / 10 (-), n (%)	N/A	N/A	N/A	N/A	41	N/A	
Api m 1 (-) / 4 (-) / 10 (+), n (%)	0/2 (0.0)	1/10 (10.0)	1/17 (5.9)	0/12 (0.0)	41	0.658	
Polysensitized *Api m 1/4/10 (+)*, n (%)	1/2 (50.0)	0/10 (0.0)	1/17 (5.9)	1/12 (8.3)	41	0.736	

M: median; IQR: interquartile range.

Absence of systemic reactions with bee re-stings was potentially associated with sensitization to Api m 10 in VIT patients

In the VIT subgroup, no statistically significant associations were found between systemic reactions to re-stings and molecular sensitization profiles. However, re-stung patients non-sensitized to *Api m 10*, regardless of potential co-sensitizations, had a tendency for association with systemic adverse reactions (25.0 *vs* 85.7%, p = 0.093). Additionally, lower levels of *Api m 10* also appeared to be marginally associated with systemic reactions in re-stings (0.15 *vs* 1.08 kU/l, p = 0.059). Inversely, *Api m 4* sensitization (in addition to the other two molecular allergens) was marginally associated with systemic reactions (66.7 *vs* 0.00%, p = 0.087), but there was no association with sIgE levels. Statistical analysis for potential associations is summarized in **table IV**.

Discussion and conclusions

Our study aimed to characterize the clinical and laboratory profiles of a Portuguese cohort of BVA patients. We also sought to establish a relationship between molecular allergic profiles with index reactions' severity, VIT efficacy, and adverse events such as reactions during VIT and re-stings.

Several similarities were shared between our cohort and previously published studies, but there are also notable differences. Regarding demographic and clinical background, most of our patients were young male beekeepers, which is known to fit with the national profile and is also the occupational activity most commonly associated with BVA (15). Atopic comorbidities were highly prevalent, which has also been observed in other cohorts (16). No patients were diagnosed with mast-cell diseases nor had elevated basal tryptase levels, which are known predisposing factors for anaphylaxis to Hymenoptera, but were absent in our cohort (17).

As for molecular allergen profiling, it should be noted that at least half our patients were sensitized to *Api m 1* and/or *Api m 10*, highlighting their importance as major honeybee venom allergens (18-20). Sensitization to *Api m 4*, on the other hand, was far less common in our cohort (11.9% of measurements). Despite *Api m 4* being mainly defined as a minor allergen, recent studies have reported a higher prevalence of this allergen in comparison with our results (12, 13, 21). Our acquisition of *Api m 4* for ImmunoCAP measurement has been very recent and, therefore, much of this data was obtained significantly after index-reaction, which may have influenced results. Additionally, some studies reporting

Table III - *Associations between the variables analyzed and the proportion of patients with reactions during VIT (n = 45).*

Variables	Reactions during VIT (n = 45)		Total patients	P-value
	Yes (n = 16)	No (n = 29)		
Male gender, n (%)	10/16 (62.5)	20/29 (69.0)	45	0.660
Age at time of most severe reaction, M (IQR)	38 (31-42)	30 (21-37)	25	0.113
Severity of most severe reaction, M (IQR)	3 (3-4)	3 (2-3)	37	0.142
Allergic comorbidities, n (%)	6/13 (46.2)	9/25 (36.0)	38	0.544
Cardiovascular comorbidities, n (%)	1/14 (7.1)	1/19 (5.3)	33	0.999
Beekeeper, n (%)	11/16 (68.8)	16/29 (55.2)	45	0.373
Basal tryptase, M (IQR)	4.4 (3.1-5.0)	4.3 (3.5-5.7)	37	0.340
Apis mellifera IgE (pre-treatment), M (IQR)	16.4 (6.4-32.2)	12.4 (3.3-50.1)	45	0.847
Apis mellifera IgE (>12M treatment), M (IQR)	2.6 (1.1-8.0)	3.8 (0.6-6.7)	37	0.808
Api m 1 IgE (kU/L), M (IQR)	0.6 (0.4-1.0)	1.1 (0.3-2.9)	25	0.397
Positive (>0.34 kU/L), n (%)	8/10 (80.0)	10/15 (66.7)	25	0.550
Api m 4 IgE (kU/L), M (IQR)	0.04 (0.01-0.10)	0.01 (0.0-0.14)	19	0.350
Positive (>0.34 kU/L), n (%)	1/8 (12.5)	1/11 (9.1)	19	0.999
Api m 10 IgE (kU/L), M (IQR)	1.4 (0.5-2.6)	0.3 (0.2-2.9)	23	0.418
Positive (>0.34 kU/L), n (%)	9/10 (90.0)	6/13 (46.2)	23	**0.038**
Api m 1 (+) / 4 (-) / 10 (-), n (%)	0/8 (0.0)	2/9 (18.2)	19	0.485
Api m 1 (-) / 4 (+) / 10 (-), n (%)	N/A	N/A	N/A	N/A
Api m 1 (-) / 4 (-) / 10 (+), n (%)	1/8 (12.5)	0/11 (0.0)	19	0.421
Polysensitized *Api m 1/4/10 (+)*, n (%)	1/8 (12.5)	1/11 (9.1)	19	0.999

IQR: interquartile range; M: median.

higher prevalences have used alternative detection methods, such as Western Blot or ADVIA-Centaur sIgE measurement (13, 21). Index-reactions to bee stings, in most cases, were highly severe (Mueller grades 3 and 4). Severity of index-reaction appeared to be associated with older age, which has already been supported by previous studies (22) and could be explained by a larger proportion of comorbidities in these patients and its co-factorial influence on reaction severity. However, findings supporting this explanation have been contradicting, and less than a quarter of our patients reported cardiovascular comorbidities, with this variable being non-significant (22, 23).

Conversely, another interesting finding is that patients monosensitized to *Api m 1* presented with milder reactions in our multivariate model. Studies assessing sting reactions' severity and *Api m 1* sensitizations have conflicting results.

Api m 1 sIgE levels did not correlate with the severity of index-reactions in previous reports (24, 25). However, co-sensitization with *Api m 10* has been linked with severe reactions (21, 25), which could help explain why our patients that were not sensitized to both allergens presented with milder systemic reactions.

Only half of our BVA patients underwent VIT. Even though a few patients were contraindicated for it (*e.g.*, pregnancy, active autoimmune diseases), most declined treatment due to not being able to support costs. This has been explained in recent national studies that report the high economic burden that non-reimbursement of immunotherapy has for patients (26).

Sixteen patients (35.6%) reported systemic reactions during immunotherapy, which were globally milder than index-reactions. Although this proportion appears to be higher than in some studies (27, 28), it is not substantially different from that reported in national studies using similar vaccine manufacturers (29). Treatment protocols and allergen composition could influence the occurrence of reactions during VIT (30). Our patients were treated with a cluster protocol and with aqueous extracts purified from Hymenoptera venom (Roxall Medicina, Spain). Even though sensitization to *Api m 10* appeared to be the single factor in our cohort associated with systemic adverse reactions during VIT, it could subsequently have a protective role in preventing SSR, according to our analysis of re-stung patients.

Out of 47 patients undergoing VIT, twenty-five (53.2%) had re-stings. Only four re-stung patients reported SSR – an 84.0%

Table IV *- Associations between the variables analyzed and the proportion of patients with systemic reactions to re-stings (n = 25).*

Variables	Systemic reactions to re-stings (n = 25)		Total patients	P-value
	Yes (n = 4)	No (n = 21)		
Male gender, n (%)	2/4 (50.0)	15/21 (71.4)	25	0.660
Age at time of most severe reaction, M (IQR)	28 (27-29)	36 (29-42)	11	0.158
Severity of most severe reaction, M (IQR)	3 (3-4)	3 (2-3)	21	0.142
Allergic comorbidities, n (%)	1/1 (100.0)	4/16 (25.0)	17	0.100
Cardiovascular comorbidities, n (%)	0/3 (0.0)	1/13 (7.7)	16	0.999
Beekeeper, n (%)	3/4 (75.0)	15/21 (71.4)	25	0.999
Basal tryptase, M (IQR)	3.0 (2.05-3.7)	4.25 (3.6-4.8)	22	0.055
Apis mellifera IgE (pre-treatment), M (IQR)	6.18 (3.3-37.61)	13.7 (5.89-41.2)	25	0.543
Apis mellifera IgE (>12M treatment), M (IQR)	4.28 (2.82-71.4)	1.97 (0.61-8.32)	23	0.268
Api m 1 IgE (kU/L), M (IQR)	1.02 (0.39-22.34)	0.54 (0.42-1.18)	12	0.397
Positive (>0.34 kU/L), n (%)	3/4 (75.0)	7/8 (87.5)	12	0.999
Api m 4 IgE (kU/L), M (IQR)	1.66 (0.00-3.14)	0.03 (0.01-0.14)	9	0.350
Positive (>0.34 kU/L), n (%)	2/3 (66.7)	0/6 (0.00)	9	0.087
Api m 10 IgE (kU/L), M (IQR)	0.15 (0.14-0.17)	1.08 (0.37-2.63)	11	0.059
Positive (>0.34 kU/L), n (%)	1/4 (25.0)	6/7 (85.7)	11	0.093
Api m 1 (+) / 4 (-) / 10 (-), n (%)	0/3 (0.0)	2/6 (33.3)	9	0.500
Api m 1 (-) / 4 (+) / 10 (-), n (%)	N/A	N/A	N/A	N/A
Api m 1 (-) / 4 (-) / 10 (+), n (%)	0/3 (0.0)	1/6 (16.7)	9	0.999
Polysensitized *Api m 1/4/10 (+)*, n (%)	2/3 (66.7)	0/6 (0.00)	9	0.087

IQR: interquartile range; M: median.

honeybee VIT efficacy, which is in line with the literature (31). It should be noted that only half of our patients were re-stung, stressing the importance of active preventive measures during contact with Hymenoptera, particularly in beekeeping activities (*e.g.*, strengthening of body suit protection).

Despite the low number of analyzed patients, some factors related to molecular sensitization were marginally associated with the VIT efficacy. Particularly, *Api m 10* sensitization and higher *Api m 10* sIgE levels could be associated with local re-sting reactions. This appears to contradict the results of a 2016 study in a Northern European cohort, which hypothesized that their VIT was not enriched with *Api m 10* (32). However, recently published studies in Mediterranean cohort and using similar vaccine manufacturers have hinted at the efficacy of VIT in reducing *Api m 10* levels and the severity of re-stings (20). Additionally, the composition of the Roxall vaccine is known to contain *Api m 10*. This could help explain our results, with patients sensitized to *Api m 10* having systemic reactions during the early stages of VIT but subsequently attaining tolerance to re-stings.

Inversely, sensitization to *Api m 4*, despite being observed in very few patients that were also polysensitized, was marginally associated with SSR. *Api m 4* was not detected in the Roxall vaccine composition, which could explain the inefficacy of VIT observed in these patients. Recent studies also appear to corroborate our findings, reporting systemic reactions during VIT and lower efficacy during sting challenge in patients sensitized to *Api m 4* (13).

There are some limitations to be considered in this study. Its retrospective properties and dependency on clinical records could hinder the quality of collected data, especially regarding clinical characteristics such as cardiovascular comorbidities. Secondly, sIgE to molecular components were assessed according to the clinical history and routine diagnosis, but not in a systematic manner in every patient. In particular, *Api m 4* was only recently available, leading to a lack of measurements at baseline, which prevented a deeper multivariate sIgE analysis and a thorough analysis of molecular sIgE. Lastly, the low number of patients that were re-stung has also limited statistical power for potential associations. This should be properly addressed in prospective studies focused on data gathering, larger cohorts and patient follow-up.

Despite these limitations, we conclude that elderly patients had more severe index reactions, monosensitization to *Api m 1* predicted milder reactions, sensitization to *Api m 10* was associated

with a higher likelihood of reactions during VIT but potentially less systemic reactions at re-stings. Molecular sensitization appears to be relevant not only in stratifying the severity of index reactions but also in assessing VIT safety and efficacy. Studies with bigger BVA and VIT cohorts, as well as a systematic molecular profiling of patients, are essential to validate these results and improve the clinical and therapeutic approach to BVA.

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Contributions

JCL, PBA: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, writing - review & editing. HPP, ICF: data curation, writing - review & editing. FC: data curation, software, writing - review & editing. AM, RC: methodology, data curation, supervision, validation. GC, AT: supervision, validation. BT: conceptualization, project administration, supervision, validation.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Michele Miraglia del Giudice[1], Cristiana Indolfi[1], Gian Luigi Marseglia[2,3], Maria Angela Tosca[4], Anna Maria Zicari[5], Giorgio Ciprandi[6]

Allergic rhinitis management: a survey on Italian primary care pediatricians

[1]Department of Woman, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli," Naples, Italy
[2]Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[3]Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy
[4]Allergy Center, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[5]Department of Maternal Infantile and Urological Science, Sapienza University of Rome, Rome, Italy
[6]Department of Medicine and Health Sciences, Università del Molise, Campobasso, Italy

Key words

Allergic rhinitis; Italian primary care pediatricians; ARIA guidelines; intranasal corticosteroids; antihistamines; nasal lavage.

Corresponding author
Giorgio Ciprandi
via Paolo Boselli 5
16146 Genoa, Italy
ORCID 0000-0001-7016-8421
E-mail: giocip@me.com

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Impact statement

This survey demonstrated that ARIA guidelines are commonly followed by Italian primary care pediatricians. Intranasal corticosteroids, antihistamines, and nasal lavage are common treatments used for children with allergic rhinitis.

Summary

Background. *Allergic rhinitis (AR) is a widespread condition. The Italian Society of Pediatric Allergology and Immunology (SIAIP) promoted an initiative to update the knowledge on AR in children and adolescents. The present survey directly addressed primary care pediatricians, thus reflecting the real-world management of AR in children and adolescents. The aim was to investigate common practice in managing AR children.* ***Methods.*** *A panel of experts drafted a series of questions concerning the practical management of children with AR in clinical practice. The questionnaire was administered to a large sample of primary care pediatricians (n = 864).* ***Results.*** *864 primary care pediatricians participated to the survey. Each pediatrician on average follows 94 children with AR; globally 81,231 children. More than 70% of participants follow ARIA guidelines. Accordingly, 42% of children have mild AR and 58% moderate/severe. Asthma, conjunctivitis and adenoid hypertrophy are the most common comorbidity. Most pediatricians autonomously follow their patients. The intensity of treatment (use of medication) is directly proportional to the symptom severity. Intranasal corticosteroids are the most common medication used followed by oral antihistamines and nasal lavages (with hypertonic or isotonic solution). Up to 20% of participants prescribed the fixed association topical corticosteroids plus antihistamine.* ***Conclusions.*** *The present survey demonstrated that Italian primary care pediatricians accomplish ARIA guidelines and adapt treatment on the basis of the intensity of symptoms. Corticosteroids and antihistamines are the most common prescribed medications. Nasal lavages are also popular.*

Introduction

Allergic rhinitis (AR) is a widespread disease in childhood and adolescence, as a recent meta-analysis reported a 20% prevalence (1). Moreover, AR significantly affects quality of life and burdens on family and society costs (2). Allergic rhinitis recognizes a type 2 immunity that promotes eosinophilic inflammation (3). Type 2 inflammation closely depends on allergen exposure, leading to typical symptoms, including itching, sneezing, watery rhinorrhea, and congestion (4).

Traditionally, AR classification defines two phenotypes, depending on the duration of the symptoms, such as seasonal AR and perennial AR. Almost 25 years ago, the allergic rhinitis and its impact on asthma (ARIA) initiative defined two distinct pheno-

types based on the duration and intensity of symptoms (5). In particular, symptom severity is classified as mild or moderate/severe, considering their impact on daily activities and quality of life (5). Later, the ARIA document has been partially adapted also for the pediatric population (6).

The management of AR patients relies on pharmacological remedies, mainly on antihistamines and corticosteroids. The choice of the administration route, dosage, and duration should consider the symptom severity, usually self-measured by a visual analog scale (7). Also, AR management should contemplate asthma comorbidity as the association of AR and asthma identifies a distinct disease (8). Both disorders are closely related, and adequate AR treatment *per se* improves asthma (9).

A previous Italian survey investigated the features of allergic rhinitis in children and the prevalence of ARIA phenotypes (10). This survey involved 35 pediatric allergy centers throughout Italy and included data from 2,623 patients. The results confirmed the adequacy of ARIA classification and treatment failure in patients with severe AR.

More than ten years have passed since this survey, and the COVID-19 pandemic significantly affected healthcare, so a new Italian survey has been advanced. The Italian Society of Pediatric Allergology and Immunology (SIAIP) promoted an initiative to update the knowledge on AR in children and adolescents. In particular, the present survey directly addressed primary care pediatricians, thus reflecting the real-world management of AR in children and adolescents.

Materials and methods

A group of experts on AR management drafted a questionnaire to administer to pediatricians. The survey comprised questions concerning the doctor's age, geographical area of work, patient characteristics, and practical AR management. In particular, adherence to ARIA guidelines, consultations with allergologists and otorhinolaryngologists, comorbidity assessment, and medication use were considered. The questionnaire was previously validated by the SIAIP (10).

The survey included a panel of randomly selected Italian primary care pediatricians, guaranteeing a representative sample of the whole country.

Table I reports the questions. **Table II** reports the detailed classes of medications used in the questionnaire. Table III includes the main comorbidities investigated.

The questionnaire was administered in paper form, collected, and sent for processing. The collection was handled to ensure full anonymity of responses. The administration selected pediatricians who usually consult the second- or third-level allergy centers homogeneously distributed along the entire national territory. For this purpose, the group of experts invited the chiefs of these centers to select the most cooperative pediatricians.

Table I *- Questions included in the survey.*

Questions
How old are you
What geographic area do you work in
How many children (approximate absolute number) with Allergic Rhinitis do you visit each year?
Do you follow ARIA guidelines in your clinical practice?
If yes, how many children (%) have the mild form?
Do you manage them independently?
Do you also send them to the Allergist?
Do you also send them to the ENT specialist?
What medications are you currently prescribing to your patients with mild AR?
How many patients do you have with moderate-severe allergic rhinitis?
Do you manage them independently?
Do you also send them to the Allergist?
Do you also send them to the ENT specialist?
What medications are you currently prescribing to your patients with moderate/severe AR?
What are the main comorbidities observed?
How many children (approximate absolute number) with asthma do you visit each year?
How many (%) of these do you send to a Referral Center?
Do you think rhinitis treatment also improves asthma?
Have you ever used the combination Azelastine/Fluticasone nasal spray?

Table II *- The most common comorbidities investigated by primary care pediatricians.*

Comorbidity	%
Asthma	64.9
Conjunctivitis	58.1
Adenoid hypertrophy	55.6
Sleep disorders	53.7
Chronic rhinosinusitis without nasal polyps	38.1
Tonsil hypertrophy	19.1
Chronic rhinosinusitis with nasal polyps	13.5
Other	1.7

The statistical analysis was descriptive, and data were expressed as absolute numbers, means, or percentages.

Results

The survey included 864 Italian primary care pediatricians. The mean age was 57.1 (ranging from 31 to 76). Regarding the geographic area where they work, 31% work in Northwest Italy, 26% in Northeast Italy, 22% in central Italy, and 21% in South Italy and Islands.

The pediatricians visit 95 children with AR on average yearly. As a result, the total number of children with AR managed by the participants was 81,231; 39,561 (48.7%) were preschoolers, and 41,670 (51.3%) were schoolers.

Most primary care pediatricians (71.6%) adopt the ARIA guidelines in their clinical practice. Regarding the severity of AR symptoms, 34,392 (42.3%) children had mild AR, and 46,839 (57.7%) had moderate/severe AR.

The main comorbidities were asthma in 64.9% of children, conjunctivitis in 58.1%, adenoid hypertrophy in 55.6%, sleep disorders in 53.7%, chronic rhinosinusitis without nasal polyps (CRSsNP), tonsil hypertrophy 19.1%, chronic rhinosinusitis with nasal polyps (CRSwNP), and other in 1.7%.

Primary care pediatricians visit an average of 63 children with asthma per year. The total number of children with asthma visited yearly was 54,302; 23,546 (43.4%) were referred to a specialistic center. Most pediatricians (91%) are convinced that AR treatment also improves asthma.

Mild AR

In children with mild AR, 704 (81.5%) pediatricians managed autonomously; 66.3% consulted an allergist, and 52.8% also had an ear, nose, and throat (ENT) specialist.

Regarding the currently prescribed treatments (**table III**), 77% of participants use intranasal corticosteroids, 68.2% oral antihistamines, 54% hypertonic saline solution, and 46% isotonic saline solution, 10.6% the fixed combination intranasal antihistamine plus corticosteroid, 5.6% antileukotriene, 4.2% oral corticosteroids, and 1.5% chromones; 5% also used other treatments. The answers could be multiple.

Moderate-severe AR

In children with mild AR, 474 (55%) pediatricians managed the children autonomously; 81% consulted an allergist, and 64% an ear, nose, and throat (ENT) specialist.

Regarding the currently prescribed treatments (**table III**), 86.5% of participants use intranasal corticosteroids, 79.2% oral antihistamines, 50.1% hypertonic saline solution, and 36.6% isotonic saline solution, 20.7% the fixed combination intranasal antihistamine plus corticosteroid, 14.9% antileukotriene, 14% oral corticosteroids, and 1.5% chromones; 5.4% also used other treatments. The answers could be multiple.

Discussion and conclusions

The Italian health service guarantees every citizen primary care with the assignment of a doctor. For the pediatric age group (0-14 years), each child is followed by a pediatrician. Each primary care pediatrician may care for up to 880 children except for 120 patients with "expiring cards" (*i.e.*, residents in neighboring areas, non-residents, and non-EU citizens). The current number of Italian primary care pediatricians is 6,962 (early June 2024), and the pediatric population is about six million seven hundred thousand children. As a result, each primary care pediatrician follows 960 children.

Table III *- Medications used for children with mild or moderate/severe allergic rhinitis (AR).*

Pharmacological class	Mild AR (%)	Moderate/severe AR (%)
Intranasal corticosteroids	77	86.5
Oral antihistamines	68.2	79.2
Hypertonic saline solution	54	50.1
Physiologic saline solution	46	36.6
Nasal decongestants	25.4	25.7
Nasal antihistamine/corticosteroid	10.6	20.7
Antileukotriene	5.6	14.9
Oral corticosteroid	4.2	14
Chromones	1.5	1.5
Other	5	5.4

The present survey included 864 primary care pediatricians, with a mean age of 57, which is in line with the average age of general practitioners, which is 60.

The sample of children followed by these doctors is approximately 750,000 subjects. As a result, the mean AR prevalence is about 11%. This result may be underestimated compared to the prevalence in the literature (about 20%). Still, it is well known that many AR patients do not seek medical care or do so occasionally (1).

Interestingly, most participants (72%) implement ARIA guidelines in clinical practice. This finding is consistent with a recent survey conducted on Philippine doctors, which reported that the majority of respondent physicians (77%) used the ARIA guidelines for the diagnosis and management of AR (11).

Regarding AR comorbidities, asthma is the most prevalent comorbidity, as about 65% of children with AR also have asthma. This finding confirms previous studies conducted on Italian children. Namely, a multicenter initiative promoted by SIAIP (Control'Asma) pointed out that 88% of asthmatic children had AR (12-14). However, a previous Italian survey reported a prevalence of asthma of 40% in children with AR (10). Another Italian multicenter study reported an asthma comorbidity of 39% in children with pollen-induced rhinitis (15). However, both studies were performed in early 2010. On the contrary, a survey conducted on 100 primary care pediatricians confirmed an asthma prevalence of 10% and frequent AR comorbidity (> 50%) in about 70,000 Italian children (16). Lastly, a very recent monocenter study reported asthma comorbidity in 67% of children with AR (17).

Allergic conjunctivitis affected about 58% of AR children; this finding consists of a recent review that reported a quote of association ranging from 30 to 71% (18).

Adenoid (mostly) and tonsil hypertrophy represent common comorbidities in children with AR, as widely reported in the literature. Both conditions contribute to affecting airflow and infection susceptibility (19, 20). Chronic rhinosinusitis frequently affects children with AR as AR is a predisposing factor for sinus inflammation (21, 22). However, an interesting outcome provided by the present survey was the high comorbidity of nasal polyps as reported in 13.5% of subjects. This finding is conflicting with previous studies reporting a low prevalence in children (23). This result deserves adequate in-depth analysis and requires confirmatory studies.

Finally, sleep disorders are common comorbidity and often a consequence of AR, as widely reported in the literature (24, 25). All these comorbidities contribute to increasing the burden of AR in children and their families.

As regards the symptom severity assessed according to ARIA guidelines, 42% of children had mild symptoms and 58% moderate-severe. The previous study conducted in 35 Italian pediatric allergy centers showed that 55.9% of children with AR had mild and more than 40% moderate-severe symptoms (10). Similarly, another Italian multicenter study reported a prevalence of 48.9% for mild symptoms and 51.1% for moderate-severe (15). The present survey reported a higher prevalence of moderate-severe symptoms, probably because the severity of AR could increase in the population over time. Further studies should address this issue.

Regarding treatments, the present survey demonstrated that intranasal corticosteroids were the most common medications for managing children with AR. The second pharmacological class concerned oral antihistamines. Nasal lavages are common, mainly using hypertonic solutions. Surprisingly, 25% of participants declared to prescribe decongestants for treating AR. Italian Agency for Drugs (AIFA) contraindicated decongestants in children aged less than 12 years. Probably, many participants have misinterpreted the meaning of decongestants by also considering products that are not a-adrenergic but can reduce nasal congestion (*e.g.*, glycyrrhetic acid, hypertonic compounds, mechanical devices, balsams).

Participants used more drugs in moderate-severe patients than in mildly symptomatic patients. Comparing these results with the previous Italian survey, the present survey showed a higher use of intranasal corticosteroids than oral antihistamines, the opposite of the last study. However, it is necessary to point out that the percentage of doctors prescribing a particular therapeutic class in the present study is investigated. In contrast, the previous research directly analyzed how many children used that specific therapeutic class. Thus, the results cannot be directly compared. However, this comparison may explain why most primary care pediatricians consider it important to use corticosteroids. As evidence of the different contextualization of the results, a recent study showed that in a group of children with suspected AR sent to a specialist center, the use of oral antihistamines was significantly higher than that of topical corticosteroids, such as 50% *versus* 16% (17).

Finally, the fixed combination of topical antihistamine plus corticosteroid represents a common option for participants, mainly if children have moderate-severe symptoms. Comparing this option with the previous study is not possible as it was unavailable at that time. Notably, this association is indicated only after 12 years of age. However, there is evidence that it is effective also in younger children (26).

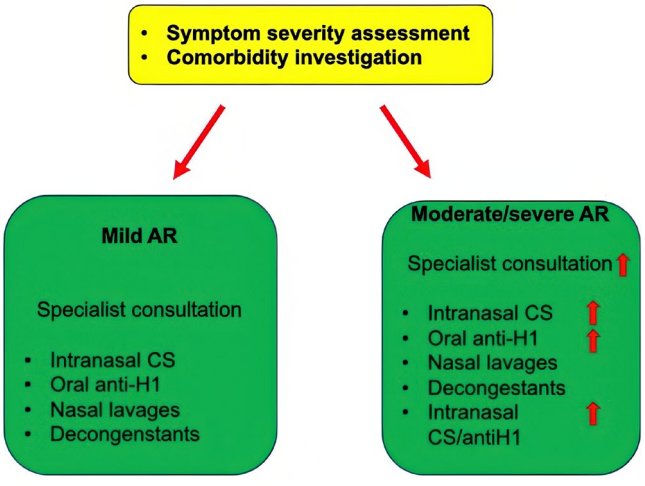
The present survey had some limitations, including the collection of personal opinions, the lack of objective measures, and mostly the absence of clinical data. In addition, it has to be noted that no explanation was given to participants on the diagnostic criteria for the different diseases and their severity as the aim of the survey was to define the current knowledge on this issue without affecting it. However, this partial lack of standardization of answers could represent a potential limitation of the outcomes. Another potential limitation was the selection of participants based on a personal choice of chiefs of second/third-level allergy centers along Italy. This choice could not mathematically represent

the exact number of pediatricians working in the different geographical areas. Namely, regional differences in healthcare practices and access could introduce a potential bias. Moreover, the invited pediatricians might have a particular interest in allergic rhinitis management, potentially skewing the results towards those who are more knowledgeable or proactive in managing AR. As a result, further surveys could investigate this interesting aspect. Furthermore, it has to be considered that the results were reliant on self-reported data from interviewed pediatricians. This method could introduce a possible bias, as primary care pediatricians may over-report adherence to guidelines or perceived effectiveness of treatments, especially if they believed their responses may be scrutinized. Finally, the results may imply a potential for over-generalization as the conclusion drawn about the general adherence to guidelines and management practices may not be universally applicable across different clinical settings or pediatric populations. For this reason, future studies should sample diverse geographic and demographic contexts to confirm and reinforce the present findings.

However, this survey involved more than 800 primary care pediatricians managing more than 80,000 children with AR. Thus, the results provided robust outcomes that also reflected what happens in the real world. Further studies should confirm these findings, adopting adequate methodology. Accordingly, a schematic representation of practical management performed by primary care pediatricians is schematically represented in **figure 1**.

In conclusion, the present survey demonstrated that most Italian primary care pediatricians adopted ARIA guidelines, most children complained of moderate-severe symptoms, asthma was common comorbidity, intranasal corticosteroids and oral antihistamines were first-level choices, and intranasal antihistamine plus corticosteroid was a frequent therapeutic option, mainly in subjects with moderate-severe symptoms.

Figure 1 *- Schematic scenario for AR management in the primary care setting.*



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Contributions

GC: conceptualization, writing – original draft. CI: writing – review & editing. GLM, MMdG, MAT, AMZ: supervision.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Gulseren Tuncay, Ebru Damadoglu, Gul Karakaya, Ali Fuat Kalyoncu

The association between baseline IgE level and urticaria control at six months of omalizumab treatment in chronic urticaria

Division of Allergy and Clinical Immunology, Faculty of Medicine, Hacettepe University, Ankara, Türkiye

Key words

Omalizumab; urticaria; IgE level; D-dimer level; antihistamines.

Corresponding author
Gülseren Tuncay
Division of Allergy and Clinical Immunology
Faculty of Medicine
Hacettepe University
06230 Altındag, Ankara, Türkiye
ORCID: 0000-0001-6529-9750
E-mail: seren_tuncay@hotmail.com

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Impact statement

Poorer urticaria control at six months of omalizumab treatment in CU was not associated with baseline IgE level but was associated with shorter CU duration.

Summary

Background. *There is limited data on the use of baseline IgE level as a predictor of omalizumab response in chronic urticaria (CU). The aim of the present study was to determine if baseline serum total IgE level is associated with response at six months of standard-dose omalizumab.* ***Methods.*** *The study was designed as a retrospective, single-center, cohort survey. This observational real-life study included CU patients receiving omalizumab from September 1, 2014, to July 31, 2022 at a tertiary care allergy center. The control of urticaria was determined by the urticaria control test in the sixth month.* ***Results.*** *A total of 159 patients were enrolled in the study. All patients had received standard-dose omalizumab for six months. At the end of the treatment period, 126 (80%) patients were under control. The median of baseline IgE level was similar in controlled and uncontrolled patients. The baseline D-dimer level and regular antihistamine use during omalizumab treatment use were significantly higher, and CU duration at baseline was shorter in the uncontrolled group (p = 0.03, p = 0.02, p = 0.003, respectively). ROC analysis revealed that CU duration at baseline was related to urticaria control (AUC 0.665, 95%CI [0.586-0.738]).* ***Conclusions.*** *The results of the present study showed that urticaria control at six months of omalizumab treatment in CU was not associated with baseline IgE level but was associated with CU duration at baseline. The shorter CU duration was associated with poorer urticaria control in the sixth month of omalizumab.*

Introduction

Chronic urticaria (CU) is a disease that persists for more than six weeks, with itchy and edematous papules/plaques, and manifests with angioedema due to deep dermis or subcutis involvement, or both (1). The prevalence varies between 0.5-1% (2). It is recommended to use a standard-dose modern 2nd generation H1-antihistamines (sgAHs) as the first-line symptomatic treatment (3). Second generation H1-antihistamines have been used for many years because they are easily available, cheap, and safe, and up to fourfold increase in standard-doses is recommended in cases with insufficient response (4). However, more than 25% of cases are resistant to high-dose sgAHs, and it is recommended to initiate omalizumab as a second-line treatment in patients who do not respond to high-dose sgAHs (5). Patients with CU who do not get sufficient benefit from omalizumab at the licensed dose of 300 mg every 4 weeks can be treated with omalizumab at higher dose, shorter intervals, or both (5). It is unpredictable which patients will not respond well to standard-dose omalizumab treatment. Although baseline IgE level was not correlated with severity of CU in the study of Baek *et al.*, low IgE level was correlated with severity of CU in the cohorts of Asero and Bhati *et al.* (6-8). Currently, there is limited data on baseline IgE level that can be used as a predictor of uncontrolled urticaria (urticaria control test [UCT] score below 12) in patients receiving standard-dose omalizumab. The aim of the present study was to examine the associ-

ation between baseline IgE level and urticaria control in patients receiving standard-dose omalizumab for six months.

Materials and methods

Study design and participants

The study was designed as a retrospective, single-center, cohort survey. This real-life study included a total of 159 CU patients receiving omalizumab from September 1, 2014, to July 31, 2022 at a tertiary care allergy center. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, revised in 2013, and was approved by Hacettepe University Ethics Committee (2024/03-03). The study protocol was reviewed and approved by (Hacettepe University Ethical Committee), approval number (2024/03-03). Written consent of the participants was not required by Hacettepe University Ethical Committee. The study has been granted an exemption from requiring written informed consent, this decision was made by Hacettepe University Ethics Committee (2024/03-03). Inclusion criteria were provision of written informed consent, age ≥ 18 years, and use of omalizumab for six months due to CU (**figure 1**). Omalizumab was initiated in patients who did not respond to high-dose sgAHs within 2-4 weeks. Patients with other dermatological diseases or urticarial vasculitis were excluded from the study.

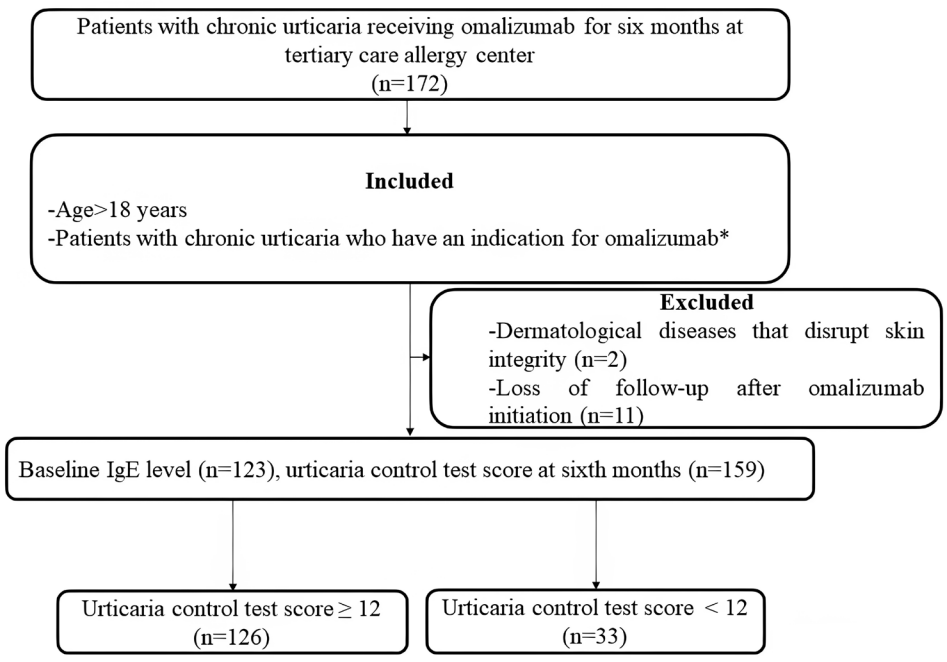
Data collection and laboratory measurements

Information about the clinical characteristics and laboratory values of the patients were obtained from the hospital database and patient files. In addition to the demographic characteristics of the patients, duration of CU, the presence of angioedema, allergic diseases, urticaria exacerbations requiring systemic corticosteroids in the last six months while receiving omalizumab, emergency room admissions because of urticaria attacks, omalizumab doses and intervals, comorbidities, medications, antinuclear antibody (ANA), IgG-anti-thyroidperoxidase (IgG-anti-TPO), specific IgE level and/or skin prick test results, blood eosinophil counts, blood basophil counts, C-reactive protein level, erythrocyte sedimentation rate, D-dimer and total IgE levels at baseline, and UCT scores in the sixth month were recorded. Serum total IgE was measured by a chemiluminescent immunoassay (ImmunoCAP; Thermo Fisher Scientific, Sweden), and the cutoff value of low IgE level was < 43 IU/mL (9).

Assessments of the treatment responses

Whether the disease was under control or not in the last month was determined by the UCT at the sixth month of therapy. Those with scores < 12 points were regarded as uncontrolled, and those ≥ 12 points were regarded as controlled (10). The UCT has been validated by Kocaturk *et al*. (11). In patients who were unresponsive or partially responsive to high-dose sgAHs and had the diagno-

Figure 1 *- The flow chart of the study (5).*



sis of CU confirmed by an allergy specialist, standard-dose omalizumab was initiated considering the EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline (12).

Statistical analysis

Data were analyzed using SPSS vn. 25.0 software. Descriptive data were presented as numbers (n) and percentages (%). Numerical variables showing normal distribution were stated as mean ± standard deviation values, and otherwise as median and interquartile range values. The Chi-Square or Fisher Exact test for categorical variables and the Mann-Whitney U test for continuous variables were used. Spearman correlation coefficient was used for non-normally distributed parameters. For the multivariate analysis, factors identified through univariate analyses – including baseline CU duration, regular antihistamine use during omalizumab treatment, systemic corticosteroid use for urticaria attacks in the past six months, and D-dimer levels – were further included in the logistic regression analysis to determine independent predictors of patient outcomes. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. A 5% type-I error level was

Table I *- Comparison of baseline characteristics of the patients regarding urticaria control in the sixth month of omalizumab treatment.*

Characteristics*	**All patients (n = 159)**	**Controlled group (n = 126)**	**Uncontrolled group (n = 33)**	**P-value**
Age, mean years	44 ± 14	44 ± 21	45 ± 19	0.62
Female, n (%)	100 (63)	80 (63)	20 (61)	0.76
Obesity[1], n (%)	41 (26)	32 (25)	9 (27)	0.83
Ever smoker, n (%)	87 (55)	76 (60)	11 (33)	0.38
Types of chronic urticaria**, n (%)	151 (95)	120 (95)	31 (94)	0.65
CSU	4 (3)	3 (2)	1 (3)	0.48
CındU	4 (3)	3 (2)	1 (3)	0.25
CSU + CındU				
Chronic urticaria duration at baseline, median months	24 (78)	27 (86)	12 (24)	**0.003**
Regular antihistamine use during omalizumab treatment, n (%)	96 (60)	70 (55)	26 (79)	**0.02**
Presence of angioedema, n (%)	105 (66)	84 (66)	21 (64)	0.74
Systemic corticosteroids use due to urticaria attack in the last six months, n (%)	38 (24)	26 (21)	12 (36)	0.06
UCT, median	15 (2)	16 (1)	8 (4)	**<0.001**
Blood eosinophil count[a], median /mm³	107 (160)	100 (170)	100 (150)	0.97
Blood basophil count[a], median / mm³	8 (95)	5 (95)	5 (40)	0.54
C-reactive protein level[a], median mg/dl	0.2 (0.01)	0.32 (0.67)	0.36 (1.04)	0.72
Erythrocyte sedimentation rate[a], median mg/dl	4 (3)	1 (10.3)	1 (2.5)	0.57
D-dimer level[b], median mg/dl	0.20 (0.1)	0.20 (0.3)	0.27 (0.01)	**0.03**
ANA positivity, n (%)	4 (3)	3 (2)	1 (3)	0.83
Anti- TPO positivity, n (%)	14 (9)	16 (13)	5 (15)	0.71
Sensitization to inhalant allergens, n (%)	22 (14)	16 (13)	6 (18)	**0.007**
Baseline IgE level[c], median UI/mL	165 (289)	166 (259.5)	121 (356.5)	0.90
Low IgE[c], n (%)	14 (9)	11 (9)	3 (9)	1.00

*Data is presented as mean ± SD if normally distributed, and median [interquartile range] if not normally distributed. Categorical variables are Presented as number (percentages). **Types of urticaria are described CSU: chronic spontaneous urticaria, CındU; chronic inducible urticaria.

[1]Body mass index ≥30 kg/m². [a]Measured in 127 (80%) patients. [b]Measured in 112 (70%) patients. [c]Measured in 123 (77%) patients (29 [88%] of them in the uncontrolled group, 91 [72%] in the controlled group, and the cutoff value of low IgE level was < 43.8 UI/mL).

Figure 2 *- The association between the baseline IgE level and control of urticaria in the sixth month of omalizumab treatment.*

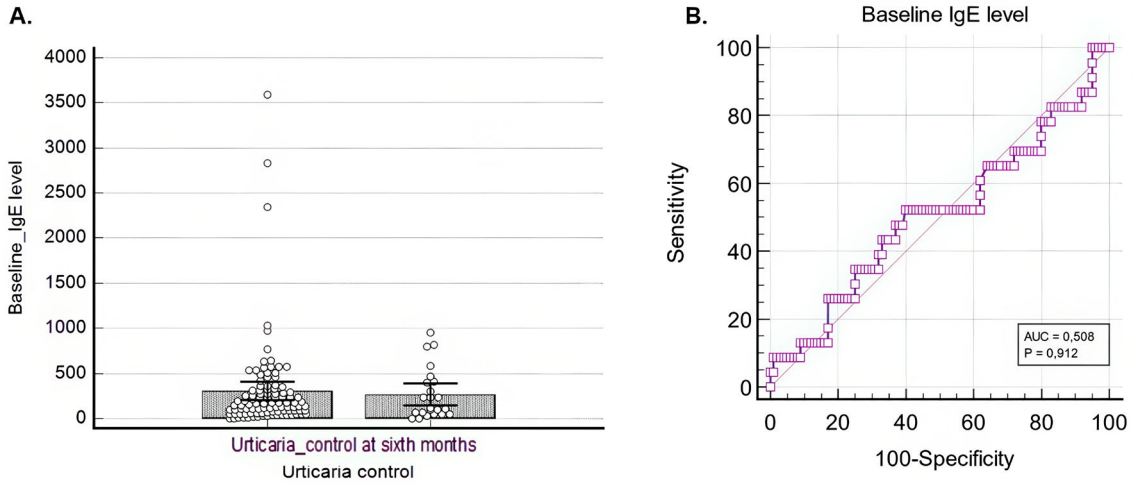


Table II *- Variables associated with uncontrolled urticaria in the sixth month of treatment, multivariable analysis.*

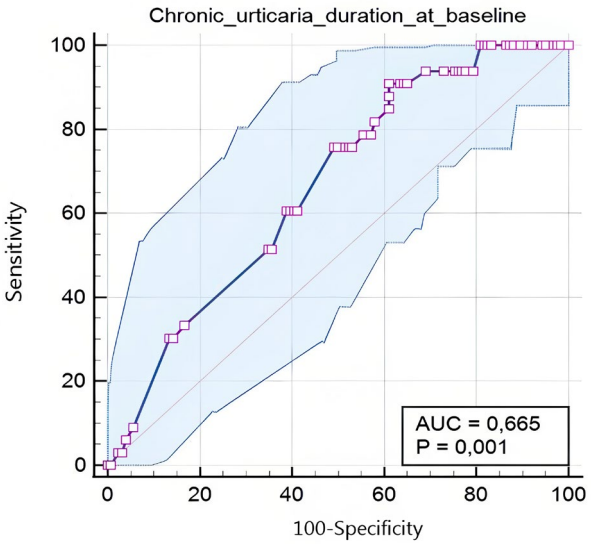
	OR	95%CI		P-value
Chronic urticaria duration at baseline, months	0.986	0.974	0.999	**0.03**
Regular antihistamine use during omalizumab treatment	3.095	1.036	9.247	**0.04**
Systemic corticosteroids use due to urticaria attack in the last six months	1.228	0.452	3.340	0.69
D-dimer level, mg/dl	1.191	0.629	2.255	0.60

used to inferstatistical significance. ROC analysis was done to assess baseline IgE level and CU duration at baseline as predictors of uncontrolled urticaria.

Results

Throughout the study period, 11 (6%) patients were lost to follow-up as they did not attend their appointments. Therefore, a total of 159 patients were enrolled in the study (**figure 1**). The mean age of the patients was 44 ± 14 years, and 100 (63%) of them were female (**table I**). All patients received standard-dose omalizumab for six months. In the sixth month of omalizumab, urticaria was under control in 126 (80%) patients. The median of baseline IgE level was similar in controlled and uncontrolled patients (**figure 2**, **table II**) (p = 0.73). Sensitization to inhalant allergens was higher in the uncontrolled group. Baseline median D-dimer level, and regular antihistamine use during omalizumab treatment were significantly higher in the uncontrolled group. The other characteristics such as female gender, presence of angioedema, baseline eosinophil counts and blood basophil

Figure 3 *- The ROC analysis for predictors of urticaria control score based on chronic urticaria duration at baseline.*



counts, ANA positivity, IgG-anti-TPO positivity, and comorbidities were similar in both groups (**table I**).

CU duration at baseline was significantly shorter in the uncontrolled group (**table I**). ROC analysis revealed that CU duration at baseline was related to urticaria control in the sixth month (AUC 0.665, 95%CI [0.586-0.738]). If the cutoff is selected as fifty-three months, estimated sensitivity and specificity is 90.91% (75.7-98.1) and 38.89% (30.3-48.0), respectively. If the cutoff for baseline urticaria duration was selected as eighteen months, estimated sensitivity and specificity was 60.61% (42.1-77.1) and 61.11% (52-69.7), respectively (**figure 3**). While this AUC suggests limited predictive strength, it highlights that chronic urticaria duration alone may not strongly predict control outcomes. However, this factor could still contribute valuable context within a comprehensive clinical assessment when considered alongside additional clinical variables.

In multivariable regression analysis model, independent risk factors for uncontrolled urticaria in the sixth month were CU duration at baseline and regular antihistamine use under omalizumab therapy (Nagelkerke R^2 = 0.214, **table II**).

Discussion and conclusions

The results of our study show that the control of urticaria in patients receiving omalizumab for six months is not related to baseline IgE level. CU duration at baseline and regular antihistamine use throughout 6 months are independently related to the control of urticaria.

Balp *et al.* pointed out that the cumulative proportion of patients undergoing remission within year 1 ranged from 21% to 47%, while at year 5, it was reported as 34% and 45%. There is some uncertainty about defining remission in urticaria (13). The differences in the rates arise from the uncertainty of the concept of remission in urticaria. While some authors define the absence of urticaria without treatment in the last 3 months as remission, some others consider it as patients reporting the absence of urticaria based on responses on self-reported questionnaires (13-15). Urticaria was under control at the sixth month in 80% of the patients in our study, but this treatment response may decrease when omalizumab injection intervals are extended, the dose is reduced, or treatment is discontinued. On the other hand, a significant proportion of these patients may also be in spontaneous remission and omalizumab may not have contributed to remission in these patients (16). As noted in the study by Marcus *et al.*, some patients with CU can achieve remission by the sixth month even without treatment, suggesting that the optimal evaluation period for treatment response in those who do respond may be extended to this time point (17). Consequently, the choice to assess treatment response at 12 weeks in some studies may have resulted in certain patients who would respond between the third and sixth months being classified as non-responders (18-20). We did not evaluate the treatment process after the sixth month of omalizumab.

CU duration at baseline and regular antihistamine use throughout 6 months of therapy are independently related to the control of urticaria. Unlike our cohort, Chen *et al.* described a tendency of longer disease duration in non-responders (21). In the study conducted by Chen *et al.*, a smaller sample size was included (138 patients in total), with 25% of patients presenting with only CIndU and an additional 13% having CSU accompanied by CIndU, which is higher than in our cohort. Treatment response was evaluated at the 12th week, with a response rate of 70%, which was lower than in our study. Additionally, 27% of these patients used methotrexate or cyclosporine in addition to omalizumab. The similarity in CU duration at baseline between responders and non-responders may be attributable to the duration of other treatments received before omalizumab initiation, potentially explaining the similar disease duration found, in contrast to our patients. Other studies did not support the relation between CU duration at baseline and treatment response (18, 22). However, in the studies by Cakmak *et al.* and Yang *et al.*, fewer patients were included (130 each), with a significantly higher proportion of CIndU cases compared to our study (20% and 17%, respectively). In both studies, the higher prevalence of CIndU patients – 20% and 17%, respectively – likely influenced the relationship between CU duration at baseline and disease control, as the treatment response rates for these patients were lower compared to those with only CSU. In the study by Ertas *et al.* involving 93 patients with CSU, the relationship between IgE levels and response to omalizumab was investigated. The non-responder rate was found to be 14%, and CU duration at baseline was higher in non-responders compared to responders (19). However, these patients discontinued omalizumab and were monitored for relapse over a 52-week period. In the multicenter, retrospective study by Marzano *et al.*, which included 470 patients comparing responders and non-responders to omalizumab, no significant differences were found in CU duration at baseline; however, treatment response was evaluated at the 12th week. Furthermore, the patients in their study were older (median age 49 *vs* 44) and had shorter CU duration at baseline (20 months *vs* 24 months) compared to our cohort (20). As expected, the rate of regular antihistamine use during omalizumab treatment was higher in uncontrolled patients. EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines recommend daily use of sgAHs to prevent the occurrence of wheals and angioedema, rather than on demand (5). Although it is not in accordance with the guidelines, some of our controlled patients (45%) do not comply with the recommendation and used antihistamines on demand.

Similar to our study, Ghazanfar e*t al.* evaluated 117 patients and showed no association between baseline IgE level and control of

urticaria at third month of omalizumab. Moreover, non-responders had a shorter urticaria duration. Unlike our study, 10% of the patients had received immunosuppressive drugs (azathioprine, methotrexate or cyclosporine) for urticaria before omalizumab (23). In a retrospective study, including 71 patient-year experience, while 57% of individuals showed a complete response within the first week, 80% had a complete response during follow-up. In this study, the omalizumab dose and/or intervals were changed after remission, and no correlation was found between urticaria control and baseline IgE level (24). Contrary to our study, Cakmak *et al*. found an association between low baseline IgE level and uncontrolled urticaria in the sixth month of omalizumab, but responders had a higher atopy (73% *vs* 4%) rate and, therefore, higher baseline IgE levels than our cohort (39% *vs* 13%) (22). In fact, there are some differences in the literature regarding threshold values for low IgE, defined as levels below 15.2 to 43 IU/mL (9, 25-27). In the study by Marzano *et al.*, a threshold value of 100 kUA/L was used for high IgE levels, while no clear cutoff was specified for low IgE levels. Additionally, the average IgE level among non-responders was found to be 42.1, which is above the accepted limit for low IgE according to some publications, while below the threshold in others (9, 25-27). Some studies showed an association between low IgE level and unresponsiveness to omalizumab (7, 27-29). Asero *et al.*, in their study of 86 patients with CSU and low IgE levels, categorized patients into subgroups based on baseline IgE levels as follows: Group A, total IgE levels 1-9 IU/mL (n = 28); Group B, IgE 10-19 IU/mL (n = 24); Group C, IgE 20-29 IU/mL (n = 22); and Group D, IgE 30-39 IU/mL (n = 12) (29). Group A had the highest proportion of non-responders to omalizumab at month 4 (64.3%; $p < 0.001$ *vs* subgroups B-D) and the lowest proportion of rapid responders (21.4%; $p < 0.005$ *vs* subgroups B-D). This study indicated that in patients with CSU, a lower IgE value, particularly those with levels below 10 IU/mL, may more effectively predict non-responders to omalizumab compared to the conventional cutoff of 40 IU/mL. Additionally, despite 46% of the patients having atopic status, they comprised 42% of the group with IgE levels below 40 IU/mL. The discrepancy may be due to the atopic status, the rates of chronic urticaria subtypes in the study populations, and different cutoffs of low IgE level. Yang *et al*. found higher baseline IgE level was associated with early response to omalizumab (263.0 *vs* 140.0 IU/mL). However, duration of the treatment was limited to one month (18).

Previously, a higher D-dimer level was defined as a predictor of uncontrolled urticaria after omalizumab treatment (30). In our cohort, baseline D-dimer level was higher in uncontrolled group, however D-dimer level was not found to be a predictor in multivariable analysis. Furthermore, in the study by Asero *et al.*, CSU patients with low IgE levels were included, and these low IgE values were divided into subgroups (29). However, no differences were found between any subgroup in terms of elevated D-dimer and urticaria control.

It was reported that autoimmunity might be a predictive factor for unresponsiveness to omalizumab therapy (21, 31, 32). However, baseline ANA and anti-TPO values were similar between groups in our study. In total, 13% and 15% of patients in the controlled and uncontrolled groups had high anti-TPO titers at baseline. The importance of this result lies in the indication that patients may respond well to omalizumab treatment even if they have positive anti-TPO titers.

This study has several limitations. It was designed retrospectively. Additionally, due to the uneven distribution of the cohort, it was not possible to categorize patients into chronic inducible urticaria and chronic spontaneous urticaria groups for urticaria control assessment. Our results can be re-evaluated with a larger cohort, but our findings are important. Further researches are needed to investigate the mechanism by which the response to omalizumab is weaker in patients with a shorter duration of urticaria at baseline.

In conclusion, the control of urticaria is not associated with baseline IgE level but with CU duration at baseline. In addition, the baseline IgE level does not seem to be determinative for predicting treatment outcomes with omalizumab.

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Contributions

GT, MD: conceptualization, data curation, formal analysis, investigation, methodology, validation, writing – original draft, writing – review & editing. ED, MD: conceptualization, data curation, validation, writing – review & editing. GK, MD: data curation, formal analysis, investigation, methodology, validation, writing – original draft, writing – review & editing. AFK, MD: conceptualization, data curation, methodology, validation, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Rita Limão[1], Rita Brás[1], Elisa Pedro[1], Susana L. Silva[1,2,3], Anabela Lopes[1,2]

Dupilumab in patients with atopic dermatitis – assessing treatment response, clinical features and potential biomarkers in real-life

[1]Department of Immunoallergology, Unidade Local de Saúde Santa Maria, Lisbon, Portugal
[2]Clínica Universitária de Imunoalergologia, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal
[3]Instituto de Medicina Molecular João Lobo Antunes, Faculty of Medicine, Universidade de Lisboa, Lisbon, Portugal

Key words

Atopic dermatitis; dupilumab; IgE; LDH; Th2.

Corresponding author
Rita Limão
Department of Immunoallergology
Centro Hospitalar Universitário Lisboa Norte
Avenida Professor Egas Moniz
1649-028 Lisbon, Portugal
ORCID: 0000-0002-7228-1097
E-mail: ritalimaooliveira@gmail.com

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Impact statement

Dupilumab proved to be effective in Th2-high AD. Sustained reduction in total IgE and aeroallergens specific IgE during 52 weeks of treatment may have long-term benefits and deserves further research.

Summary

Background. *The clinical and pathophysiological heterogeneity of atopic dermatitis (AD) endophenotypes is associated with wide diversity in response to therapy. The aim of this study was to evaluate the response to dupilumab in a group of AD patients and identify clinical/immunological features associated with different patterns of response.* ***Methods****. A retrospective observational study was performed, including 30 adults with AD who completed 12 months treatment with dupilumab, in a Portuguese Immunoallergology Department. Demographic, clinical, and immunological data were analyzed, including total serum IgE, sensitization to aeroallergens, peripheral eosinophilia and inflammatory biomarkers (sedimentation rate, C-reactive protein and lactate dehydrogenase-LDH). Patients who achieved EASI-75/EASI≤7, SCORAD-75/SCORAD≤24, NRS-pruritus≤4 or DLQI≤5 at 6 months of treatment were considered responders and those that achieved all these goals at 16 weeks were considered super-responders.* ***Results****. Clinical evaluation revealed a significant reduction in median SCORAD, EASI, DLQI, NRS-pruritus and NRS-sleep over 12 months on dupilumab ($p < 0.01$), in parallel with decrease in serum Th2 pathway biomarkers and LDH. All patients responded to dupilumab, and 26.7% were super-responders, supporting that dupilumab is highly effective in moderate to severe Th2-high AD.* ***Conclusions****. In this cohort, none of the evaluated biomarkers at baseline were associated with a better/earlier clinical response to dupilumab. Dupilumab treatment for 52 weeks resulted in a significant and sustained reduction in blood levels of total IgE and allergen-specific IgE to aeroallergens. The potential long-term clinical benefit of these effects, even after discontinuing dupilumab therapy in patients with AD, should be explored to a greater extent.*

Introduction

Atopic dermatitis (AD) is the most common inflammatory skin disease. It is clinically characterized by intensely pruritic papulovesicular skin lesions that progress to scaling, depigmentation or hyperpigmentation and subsequent lichenification. AD pathophysiology is complex, involving genetic and environmental factors and it is based on a dysfunction of innate and adaptive immunity with predominantly Th2 inflammation, although it is currently recognized that Th1, Th17 and Th22 pathways also contribute to its pathogenesis (1).

Classically, AD has been classified into intrinsic and extrinsic based on total serum IgE levels and/or existence of allergic sensitization. However, this classification is too simple to

comprise the different phenotypes of the disease. Different AD phenotypes have been recognized based on clinical characteristics, namely severity and chronicity of the disease, age at onset, ethnicity, race, genetic background and presence of comorbidities (2, 3). The AD endotypes can also be differentiated based on their molecular and cellular characteristics (4, 5). This heterogeneity of AD endophenotypes is associated with diverse responses to treatment.

In recent years, the main therapeutic strategies, in addition to repairing the skin barrier or influencing the microbiome, target the suppression of the Th2 inflammation pathways. A major scientific and clinical breakthrough came with dupilumab, a fully human monoclonal antibody that targets the alpha subunit of the IL-4 receptor, thereby inhibiting IL-4/IL-13 signaling, key cytokines in inflammatory Th2 diseases, like AD (6).

Clinical trials and real-life studies with dupilumab have demonstrated significant improvement in both severity scores and quality of life indexes in patients with moderate to severe AD (7). However, a subset of patients who do not respond to dupilumab has been reported; these patients may benefit from other therapeutic targets to control inflammation (1).

It is therefore necessary to characterize inflammatory and immunological endotypes of AD due to their significant implications in the stratification of disease phenotypes and for the development of targeted therapies within the scope of precision medicine, increasing the probability of achieving disease control in all patients.

In this study, we investigated the evolution of serum inflammatory biomarkers and pattern of sensitization in a group of Portuguese patients with severe AD and their association with clinical response over 52 weeks of treatment with dupilumab.

Materials and methods

Study design, population and ethical considerations

We performed a retrospective cohort study enrolling 30 patients with severe AD followed up at a Portuguese Immunoallergology Department. Criteria for initiating treatment with dupilumab included: clinical diagnosis of AD based on the Hanifin and Rajka criteria (8); moderate to severe disease with EASI (Eczema Area and Severity Index) > 21 and/or SCORAD (SCORing Atopic Dermatitis) > 50; uncontrolled disease despite topical therapy with corticosteroids and calcineurin inhibitors, requiring the use of systemic immunosuppressive therapy or no indication. Pregnant or breastfeeding women were excluded.

Patients over 18 years of age who completed 52 weeks with dupilumab at an initial dose of 600 mg followed by 300 mg administered every other week were included in the study. This study was conducted in accordance with ethical standards established in the Declaration of Helsinki of 1946 (9).

Demographic, clinical and analytical data collection

Demographic and clinical data were retrieved and collected from clinical databases, including age, gender, previous history of atopy as defined by the World Allergy Organization (10), onset of AD, duration of illness, atopic comorbidities and previous use of systemic therapies for AD. Objective clinical findings were assessed according to the EASI and SCORAD severity scores. The assessment of subjective symptoms was based on NRS (Numerical Rating Scale) for pruritus and sleep, and on the DLQI (Dermatological Life Quality of Life Index) quality of life scale.

Inflammatory and immunological biomarkers were analyzed, including blood eosinophil counts, sedimentation rate (SR), C-reactive protein (CRP), lactate dehydrogenase (LDH), total IgE and specific IgE (sIgE) to aeroallergens according to positive skin prick tests (wheal ≥ 3mm compared with the negative control) (11).

Clinical evaluation and measurement of biomarkers in peripheral blood were performed before dupilumab (T0), at 6 (T6) and 12 months of treatment (T12).

Patients who reached EASI-75/EASI ≤ 7 or SCORAD-75/SCORAD ≤ 24 or NRS-pruritus ≤ 4 or DLQI ≤ 5 after 6 months with dupilumab were considered responders. Patients who achieved all of these goals at 16 weeks were considered super-responders (12, 13). The association between patients' clinical and inflammatory/immunological parameters at baseline and their clinical response to dupilumab was also analyzed.

Statistical analysis

Statistical analysis was performed using the IBM-SPSS software package (version 25.0). Descriptive parameters such as means and standard deviations for normally distributed continuous data, frequencies, and percentages for categorical data, were calculated. Parametric quantitative data were presented as the mean and standard deviation. Non-parametric quantitative data were presented as a median (interquartile range). Categorical data were reported as a percentage showing the proportion of positive results. Normal distribution was confirmed using Shapiro-Wilk test or skewness and kurtosis. The t-independent test or Mann Whitney test were used to compare parametric and non-parametric variables between groups (responders *vs* super-responders), respectively, and the paired-T or Wilcox tests to assess the evolution of biomarkers severity indexes and quality of life scores during treatment with dupilumab. Differences were considered statistically significant if $p < 0.05$.

Results

Clinical features and baseline AD severity and biomarkers

Thirty Caucasian patients were included. Their mean age was 35.7±12.4 years (minimum 17; maximum 61) and 56.7% were

***Table I** - Demographic and clinical characterization of study population.*

Variables	
Female, n (%)	17 (56.7)
Age, mean ± SD [minimum-maximum], years	35.7 ± 12.4 [17-61]
Age at diagnosis of AD, mean ± SD [minimum-maximum], years	7.4 ± 10.3 [1-40]
Duration of AD, median; IQR [minimum-maximum], years	28; 16.5 [4-47.5]
Other atopic diseases, n (%)	
Allergic rhinitis	30 (100)
Allergic asthma	21 (70)
Allergic conjunctivitis	12 (40)
IgE mediated food allergy	7 (23)
Allergic sensitization*, n (%)	
Mites	30 (100)
Pollens	23 (77)
Epithelia	14 (47)
Previous use os systemic therapies for AD, n (%)	
Cyclosporin A	27 (90)
Methotrexate	3 (10)
Azathioprine	5 (17)
Corticosteroids	29 (97)
Omalizumab	12 (40)

AD: atopic dermatitis; IQR: interquartile range; SD: standard deviation; *positive skin prick test (mean wheal diameter ≥ 3 mm compared to negative control).

female. The median duration of AD was 28 years (IQR 16.5; minimum 4; maximum 47.5).

Clinical features of the population evaluated are detailed in **table I**. All patients had other associated atopic diseases and identified allergic sensitization to aeroallergens. Most patients had undergone other systemic therapies for AD in the past, mainly cyclosporin (n = 27) and corticosteroids (n = 29) (**table I**).

All patients had moderate to severe AD prior to initiation of dupilumab, with median SCORAD and EASI values of 74.2 and 29.7, respectively. Regarding self-reported scores for NRS-pruritus and NRS-sleep, their median scores were 7. Patients reported a significant negative impact on quality of life due to AD, with a median DLQI of 19 prior to dupilumab (**table II**).

Median total serum IgE and circulating eosinophil counts at baseline was 4064 U/mL (minimum 423 U/mL, maximum 28489 U/mL) and 370/L (minimum 60/L, maximum 2020/L), respectively (**table II**). There were no differences between responders and super-responders in relation to baseline total IgE, circulating eosinophil counts, SR, CRP or LDH.

Clinical response to dupilumab

Overall, there was a significant reduction in EASI, SCORAD, NRS-pruritus, NRS-sleep, and DLQI over 12 months of dupilumab ($p < 0.001$) (**table II**). Notably, this improvement was already significant upon 6 months treatment for all scores evaluated ($p < 0.05$) (**figure 1**).

All patients reached EASI-75/EASI ≤ 7, or SCORAD-75/SCORAD ≤ 24 or NRS-pruritus ≤ 4 or DLQI ≤ 5 after 6 months of dupilumab and were therefore considered responders. A subgroup of 8 patients (26.7%) achieved all these goals at 16 weeks and were classified as super-responders.

***Figure 1** - Evolution of atopic dermatitis severity indexes during treatment with dupilumab.*

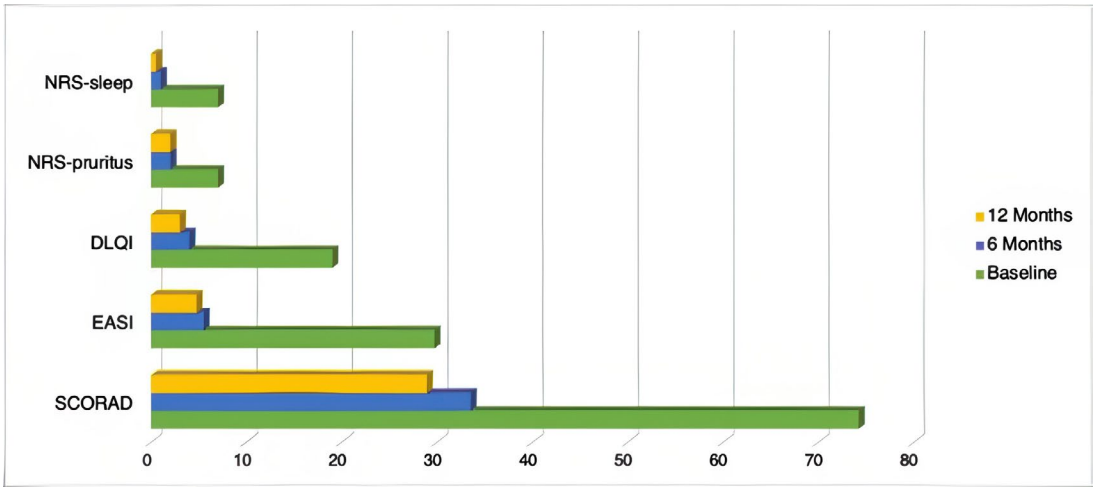


Table II *- Evolution of AD severity indexes and biomarkers during treatment with dupilumab.*

	Baseline	12 months	P-value
AD Severity indexes, median [minimum-maximum]			
SCORAD	74.2 [41.5-103.1]	28.9 [6.4-44.9]	< 0.001
EASI	29.7 [11.8-65.4]	4.8 [0.3-16.9]	< 0.001
DLQI	19 [4-29]	3 [0-8]	< 0.001
NRS-pruritus	7 [3-10]	2 [0-8]	< 0.001
NRS-sleep	7 [0-7]	1 [0-10]	< 0.001
Serum biomarkers, median [minimum-maximum]			
Total IgE (U/mL)	4,064 [423-28,489]	1,892 [133-7,549]	< 0.001
Eosinophil count (/L)	370 [60-2,020]	465 [90-1,840]	n/s
SR (mm)	12.5 [2-66]	12 [2-64]	n/s
CRP (mg/dL)	0.06 [0.03-0.38]	0.07 [0.02-3.42]	n/s
LDH (U/L)	215 [155-522]	177 [133-255]	0.002
sIgE *D. pteronyssinus* (kU/L) n = 27	101 [9.9-101]	77.5 [1.3-101]	< 0.001
sIgE *D. farinae* (kU/L) n = 22	94.5 [11.6-101]	55.1 [1.1-101]	< 0.001
sIgE *Lepido. destructor* (kU/L) n = 24	76 [0.6-101]	19.6 [0.4-101]	< 0.001
sIgE *Phleum pratense* (kU/L) n = 19	20.3 [0.5-101]	5.73 [0.34-77.5]	< 0.001
sIgE *Olea europaea* (kU/L) n = 7	24.6 [0.37-101]	3.95 [0-86.7]	0.018
sIgE *Parietaria judaica* (kU/L) n = 12	16.5 [0.6-70.2]	5.16 [0-55.5]	0.003
sIgE Cat epithelia (kU/L) n = 19	39.8 [6.9-101]	17 [0.8-89.2]	< 0.001
sIgE Dog epithelia (kU/L) n = 6	45 [23.5-97]	25.1 [6.22-35.2]	n/s

AD: atopic dermatitis; CRP: C-reactive protein; DLQI: dermatological life quality of life index; EASI: Eczema Area and Severity Index; IQR: interquartile range; LDH: lactate dehydrogenase; NRS: numerical rating scale; n/s: non-significant; SCORAD: SCORing atopic dermatitis; sIgE: specific IgE; SR: sedimentation rate.

Furthermore, at baseline, 4 patients were on cyclosporine (average dose 150 mg/day), and 15 patients were on systemic corticotherapy (average dose equivalent to prednisolone 12.3 mg/day). After 16 weeks treatment with dupilumab, only 1 patient remained on cyclosporine and another patient on oral prednisolone for disease control. At 6 and 12 months of dupilumab, no patient was on systemic immunosuppressive therapy.

Similarly, there were no differences between responders and super-responders regarding the clinical variables analyzed at baseline, namely regarding gender prevalence, age at AD diagnosis, length of AD or the presence of atopic comorbidities. Likewise, no differences were observed between the 2 groups regarding baseline disease severity classification according to the SCORAD and EASI severity scores or inflammatory and immunological biomarkers at baseline.

Within the group of responders at 6 months (n = 22), excluding the 8 super-responders, and looking at each target criteria used to define clinical response, 12 patients (54.5%) featured an EASI-75 or EASI ≤ 7, 10 (45.5%) featured a SCORAD-75 or SCORAD≤24, 18 (81.9%) patients reported NRS-pruritus ≤ 4 and 16 (72.7%) DLQI ≤ 5 at 6 months of treatment. Importantly, 9 patients were classified as responders only on the basis of sub-

Figure 2 *- Evolution of total serum IgE during treatment with dupilumab.*

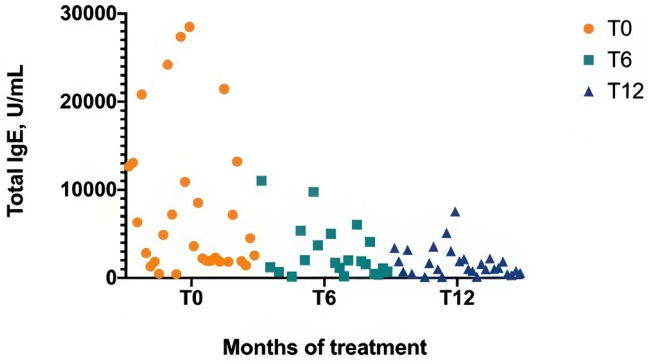
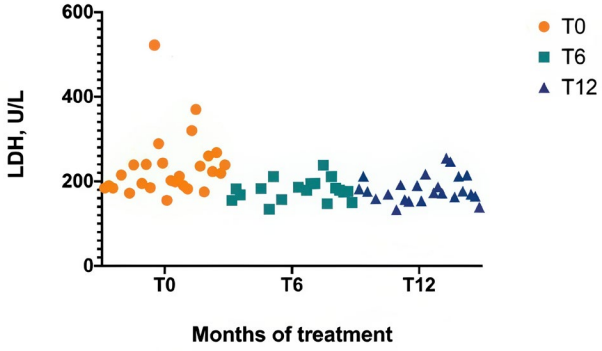


Figure 3 *- Evolution of LDH during treatment with dupilumab.*



jective and self-reported NRS-pruritus and/or DLQI quality of life scale not meeting defined criteria for clinical response in the EASI and SCORAD disease severity indexes, and 5 of them did not reach these criteria even at 52 weeks of dupilumab, despite statistically significant reductions in the median values of these disease severity indexes throughout the treatment.

This subgroup of 9 patients, that achieve symptomatic or quality of life goals but not in EASI or SCORAD response, featured significantly higher median EASI values at baseline (49.1 *vs* 25.8, p = 0.027). There were no other differences between this subgroup and the other responders regarding the clinical or laboratory variables analyzed at baseline.

Evolution of biomarkers during treatment with dupilumab

Median total serum IgE at baseline decreased significantly at 6 and 12 months of treatment (p < 0.001) (**figure 2**). Also, the median values of sIgE to mites, pollens and cat epithelium had a significant reduction over the 52 weeks of dupilumab (p < 0.001). In contrast, circulating eosinophil counts and sIgE to other aeroallergens evaluated, upon 12 months treatment did not differ significantly in relation to baseline (**table II**).

Regarding inflammation markers, there was a significant reduction in the median LDH at 12 months on dupilumab (p = 0.002), which was already observed after the first 6 months of treatment (**figure 3**). SR and CRP values did not vary significantly throughout the same period (**table II**).

The evolution of these parameters did not differ between the 2 groups, that is, there were no significant differences in the median values of the biomarkers at 6 and 12 months of dupilumab between responders and super-responders.

Dupilumab: associated ocular surface disease

A total of 13 patients (43.3%) developed dupilumab-associated ocular surface disease. The most frequent eye symptoms were conjunctival hyperemia (33.3%), pruritus (26.6) and dryness (16.7). Ocular surface disease developed after a mean of 19.4 weeks of dupilumab (SD 18.2; range 2-52). Most cases (84.6%) were managed with topical therapy, including corticosteroid, antihistamine, antibiotic and cyclosporine, and 2 patients required oral doxycycline. Dupilumab dosing interval was increased to 3 or 4 weeks in 4 patients, not affecting the good response to treatment, and 1 patient permanently discontinued dupilumab at 52 weeks because of severe keratitis, after attempted interval increased to control ocular disease. A personal history of allergic conjunctivitis was found to increase the risk of developing dupilumab-associated ocular surface disease (OR 4.33 [95%CI 0.93-20.24], p = 0.046). Baseline SCORAD was higher in patients that developed ocular surface disease (80.7 *vs* 68.5; p = 0.046). In addition, these patients featured higher median baseline eosinophils' count (595/µL *vs* 265/µL) (p = 0.043).

Discussion and conclusions

Dupilumab is available for treatment of patients with severe AD in Portugal since 2019. The present study reports the first data on the clinical outcome of dupilumab, addressing the clinical response and evolution of serum biomarkers over 52 weeks treatment with dupilumab in a group of 30 patients with moderate to severe AD under follow-up in a Portuguese immunoallergology department.

AD treatment should be guided according to severity and has been evolving towards precision/personalized medicine with the development of multiple immunological therapies, such as dupilumab. Clinical trials and real-life studies with dupilumab in AD patients have shown remarkable improvement in both severity and quality of life scores in moderate to severe AD (7).

In the present study, we also observed a significant reduction in EASI, SCORAD, NRS-pruritus, NRS-sleep, and DLQI throughout 1 year of treatment (**figure 1**), allowing in most patients clinically meaningful improvement of disease activity without the use of systemic immunosuppressive therapies.

The definition of clinical response to dupilumab has been evolving In 2020, in a study based on data from the multicenter registry of National Expertise Center for AD from Netherlands, the relevant clinical response was measured by an improvement ≥ 75% in the EASI or a reduction in NRS-pruritus score ≥ 4 points or reduction in the DLQI ≥ 4 points compared to the baseline value (12). This means that a clinical relevant response could be defined based on thresholds in one or more outcomes of the three major AD main domains-signs, symptoms and quality of life. In that study, patients were considered to be super-responders if they showed relevant clinical improvement in these 3 domains at week 16 of treatment (12). Recently, the optimal therapeutic goals to be achieved at 6 months have been defined for each specific domain, namely, EASI-75 or EASI ≤ 7, SCORAD-75 or SCORAD ≤ 24, total score of the NRS-pruritus ≤ 4, DLQI ≤ 5 and POEM (Patient Oriented Eczema Measure) ≤ 7 (13).

Taking this into account, the good response to dupilumab observed in our cohort is in agreement with an AD endophenotype, with predominantly Th2 inflammation, presence of allergic sensitization and with other associated atopic diseases (**table I**). In contrast, the lack of response to treatment with dupilumab would suggest other mechanisms, including impairment of the epidermal barrier, autoallergy or non-Th2 immunity underlying AD and different therapies aimed at acute-phase inflammation should be considered (1). In fact, this cohort does not appear to illustrate the diversity of AD endotypes due to patient selection bias. Discrepancy between the patients' subjective assessment and the physicians' objective evaluation of AD control has been discussed previously (14). We thus agree with the relevance of patient perception and self-reported assessment tools when assessing response to dupilumab treatment, namely DLQI, NRS-pruritus and NRS-sleep, since it is recognized that chronic pruritus and sleep deprivation secondary to AD have a significant negative impact on the quality of life and affect different aspects such as mood, sexual activity, social interaction, work and academic activity (15, 16). In our study, 9 patients were classified as responders, solely on the basis of subjective and self-reported NRS-pruritus and/or DLQI quality of life scale, while not meeting defined criteria for clinical response in the EASI and/or SCORAD disease severity scores. These patients had a significantly higher baseline EASI compared to the remaining responders, which may suggest that patients with more severe baseline disease may have a slower response to dupilumab, as improvement in pruritus usually precedes objective improvement in AD (17).

Recent studies have shown that dupilumab significantly reduced the levels of Th2 serum biomarkers in AD patients, in agreement with its mechanism of action (12, 18, 19, 20). Also in our study, we found that the median levels of total IgE, sIgE to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Lepidoglyphus Destructor*, *Phleum pratense* and cat epithelia significantly decreased at 6 and 12 months of therapy with dupilumab, probably related to its mechanism, that affects the production of IgE by blocking IgE switching cytokines (IL-4 and IL-13) on B-cells, (21). The median sIgE to *Olea europaea, Parietaria judaica* and dog epithelia did not differ significantly in the same period, which is likely related with the smaller number of patients sensitized to these aeroallergens in this sample (**table II**).

Of note, the median total IgE before the start of dupilumab was 4,064 U/mL, and 43.3% of patients (n = 13) had values above 5,000 U/mL and 30% (n = 9) above 10,000 U/mL (**figure 1**). It is known that patients with AD often have high levels of total IgE and that more severe disease have been associated with higher levels of this biomarker (22).

We observed a significant reduction in serum LDH during treatment with dupilumab, which has already been reported in previous studies (19). As LDH is a ubiquitous intracellular enzyme, serum LDH raises by cell breakdown in almost any tissue, including the skin. Therefore, LDH can be used as a marker for tissue damage in AD, but it is extremely nonspecific (23). Although some studies have indicated that higher baseline serum LDH levels are associated with a worst response to dupilumab in AD, we did not confirm this observation in our cohort (19, 24).

Presently, there are no validated inflammatory or immunological biomarkers that can predict good or bad response to this treatment in AD patients. In the present study, there were no differences between responders and super-responders in relation to the inflammatory and immunological biomarkers analyzed at baseline, including total IgE, circulating eosinophil counts, SR, CRP and LDH.

Regarding the safety profile, dupilumab treatment is generally well tolerated, but a substantial number of patients develop ocular surface disease (over 30% in some "real world" settings), of which most are mild-to-moderate. Topical treatment with anti-inflammatory eyedrops is often sufficient, without need to discontinue treatment (25). In our study, personal history of allergic conjunctivitis, higher baseline AD severity and higher eosinophil blood count before treatment were associated with increased dupilumab-associated ocular surface disease, as reported in clinical trials and real-life studies (26-28). Several mechanisms have been proposed for the development of this entity, namely eosinophilia after dupilumab treatment with increase in downstream activity of OX40 ligand and inhibition of IL-13 and indirect decreased production of mucin in the goblet cells of the conjunctiva. Recently, the occurrence of ocular adverse events during dupilumab therapy was also associated with a significant increase of IL-33 tear fluid levels and it has been identified a subset of memory Th2 cells that preferentially produce IL-33, related to severe itch with neuro-reconstruction in the inflammatory conjunctiva (29, 30). These mechanisms may explain the higher incidence of dupilumab-associated ocular surface disease reported in this group of patients (43.3%), all of them with a predominantly Th2 inflammation.

Despite the relatively small sample size and retrospective methodology, we highlight the relevance of our results, as the first study reporting a cohort of Portuguese patients treated with dupilumab, focusing on important aspects such as the evolution of total IgE and specific IgE to relevant allergens.

Our results reinforce previous data reporting the efficiency of dupilumab in AD, with a significant clinical improvement with reduction in EASI, SCORAD, NRS-pruritus, NRS-sleep and DLQI, in parallel with decrease in serum Th2 pathway biomarkers and LDH.

In our cohort, from a Department of Immunoallergology, 100% of patients were responders, 26.7% super-responders, supporting the high efficacy of dupilumab in moderate to severe Th2-high AD. A subgroup of 9 patients, with a significantly higher baseline EASI compared to the remaining responders, were classified as responders only on the basis of subjective scores, suggesting that patients with more severe initial may respond more slowly to dupilumab – which will be interesting to detail over a longer period. None of the evaluated biomarkers were associated with a better/earlier clinical response to dupilumab.

In our real-life study, dupilumab treatment for 52 weeks resulted in a significant and sustained reduction in blood levels of total serum IgE and allergen-specific IgE to mites, pollens and cat epithelium in moderate to severe AD. The potential long-term clinical benefit of these concomitant immunomodulatory effects in patients with AD, eventually maintained after increasing dose interval or discontinuing dupilumab therapy, should be deeply explored over an extended period.

Fundings

None.

Contributions

RL, SLS, AL: conceptualization, writing – original draft. RB, EP: data collection. RL, RB, SLS, AL: methodology, formal analysis.

Conflict of interests

The authors declare that they have no conflict of interests.

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LETTER TO THE EDITOR

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Marina Mauro[1], Donatella Bignardi[2], Ilaria Baiardini[3], Patrizia Bonadonna[4], Maria Chiara Braschi[5], Francesca Emiliani[6], Laura Guerra[2], Serena Liberati[7], Francesco Olivieri[4], Valerio Pravettoni[8], Donatella Preziosi[1], Erminia Ridolo[9], Federica Rivolta[8], Matteo Martini[5,10], Maria Beatrice Bilò[5,10]

Health-related quality of life in Hymenoptera venom allergy: validation of the Italian version of the vespid allergy quality of life questionnaire (VQLQ-i)

[1]Allergy Unit, Division of Pulmonology, S. Anna Hospital, ASST-Lariana, Como, Italy
[2]Allergology Unit, IRCCS San Martino Polyclinic Hospital, Genoa, Italy
[3]University of Genoa, DiMI, Genoa, Italy
[4]Allergy Unit and Asthma Center, Verona University Hospital, Verona, Italy
[5]Allergy Unit, Department of Internal Medicine, University Hospital delle Marche, Ancona, Italy
[6]Allergy Unit, AUSL della Romagna, Faenza, Italy
[7]Allergy Unit, Ospedale Infermi di Rimini, Rimini, Italy
[8]Department of Internal Medicine, IRCCS Cà Granda Foundation, Maggiore Policlinico Hospital, Milan, Italy
[9]Allergy and Immunology, University of Parma, Parma, Italy
[10]Department of Clinical and Molecular Sciences, Marche Polytechnic University, Ancona, Italy

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Corresponding author
Matteo Martini
Department of Clinical and Molecular Sciences
Polytechnic University of Marche;
Allergy Unit
University Hospital AOU delle Marche
Via Conca 71
60126 Torrette di Ancona, Ancona, Italy
ORCID: 0000-0001-9873-9695
E-mail: matteo.martini.med@gmail.com

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To the Editor,

Hymenoptera venom allergy (HVA), characterized by hypersensitivity reactions to stings from insects such as bees and wasps, poses a significant health concern worldwide. Besides the pathophysiological aspects of HVA, there is a growing recognition of its significant impact on Health-Related Quality of Life (HRQoL), comparable to other chronic conditions including allergic diseases

(1, 2). In addition to generic questionnaires, the Vespid Quality of Life Questionnaire (VQLQ) has been developed as a disease-specific instrument to assess the multidimensional impact of HVA on HRQoL (3), and it has been already validated in several languages (3-9).

The objective of this multicenter, cohort, single-nation study is the cross-cultural validation of the VQLQ in Italian language (VQLQ-i) in patients allergic to Yellow Jacket (YJ).

Seven Italian allergy centers consecutively recruited adult patients with HVA to YJ, diagnosed after systemic reactions, before and during Venom Immunotherapy (VIT), and without relevant psychiatric comorbidities. Psychometric testing for cross-cultural validation was performed according to the GAL2EN taskforce position paper (10), after translation from English to Italian language and *vice versa* by four independent translators and cognitive review performed on 10 Italian patients with HVA. The construct validity was verified with the correlation (Pearson's correlation, r) between total and single-item scores of VQLQ-i *versus* the Expectation of Outcome questionnaire (EoO). Cronbach's alpha coefficient was used to examine the internal consistency. The mean difference of VQLQ-i score between patients off-VIT and on-VIT was used to test the responsiveness (t-test). All the statistical analyses were performed with STATA v.18 (StataCorp LLC, Texas, USA). The study was approved by the Ethics Committees (210/2019) of the local sites, and written informed consents were obtained from patients.

A total of 127 patients (34 off VIT and 93 on VIT) were consecutively enrolled. Their characteristics are shown in **table I**. The mean age was 54.3 ± 12.6 years, and 70% were males. At least one re-sting was reported by 25% of the subjects, after VIT ini-

Table I – *Comparison of VQLQ validation studies in different languages.*

	Dutch VQLQ (3)*	**Dutch VQLQ (4)°**	**US English VQLQ (3)**	**Polish VQLQ (9)**	**German VQLQ (5)**	**Spanish HRQLHA (8)**	**Turkish VQLQ (6)§ (vespid)**	**Turkish VQLQ (6)§ (bee)**	**Portuguese VQLQ (7)**	**Italian VQLQ**
Patients	58 adults	74 adults	50 adults	78 adolescents	79 adults	116 adol, adults	65 adults	81 adults	49 adults	127 adults
Insect	YJ	YJ	YJ	YJ, bee	Wasp	YJ, Pol, bee	YJ	Bee	Wasp, bee	YJ
M I	12%	7%	6%	0%	16.5%	32%	8%	11%	14%	8%
M II	26%	28%	32%	10%	23%		39%	26%	16%	23%
M III	40%	29%	42%	63%	16.5%	68%	23%	30%	37%	23%
M IV	22%	36%	20%	30%	44%		31%	33%	33%	46%
VIT duration (y)	1- 3	1	n/r	2.6	n/r	3	3	3	n/r	2.3 ± 2.2
Mean VQLQ										
Off VIT	n/r	4.31	n/a	n/a	n/a	n/a	4.7 - 5.27	5.12 - 4.84	n/r	4.03 ± 1.55
On VIT	n/r	4.61	n/r	n/r	n/r	3.48	2.81 - 2.50	2.80	n/r	4.93 ± 1.20
α	0.96	n/r	0.88	0.91	0.95	0.95	0.97	0.96	0.85	0.97
r	**0.69**	**0.59 - 0.72**	**0.56**	n/r	**0.67**	0.5	**0.55 - 0.64**	**0.47 - 0.78**	**0.71 - 0.74**	**0.60**

α: Cronbach's alpha coefficient for internal consistency assessment; HRQLHA: Health-related Quality of Life Questionnaire for Hymenoptera Venom–Allergic Patients; M: Mueller score of severity of the index reaction; n/a: not applicable; n/r.: not reported; Pol: Polistes species; r: Pearson's or *Spearman* (*in italic*) correlation coefficient for construct validity between the mean scores of VQLQ and EoO (**in bold** if statistically significant: $p < 0.05$); US: United States; VIT: venom immunotherapy; VQLQ: Vespid Quality of Life Questionnaire; y: years; YJ: Yellow Jacket. *First Dutch validation study. °Randomized controlled study for cross-sectional and longitudinal Dutch validation; §Reversed VQLQ score compared with the other studies (*i.e.* the higher the VQLQ: the worst the HRQoL); Beekeepers are excluded from the analyses.

tiation, without any reaction. The final version of the VQLQ-i (**figure 1Suppl**) showed high internal consistency (Cronbach's alpha = 0.97), significant construct validity (r between mean scores of VQLQ-i and EoO = 0.60, 95%CI 0.48 - 0.69, $p < 0.001$), and significant responsiveness (VQLQ-i improvement after VIT initiation = +0.90, 95%CI 0.93-1.41, $p \leq 0.001$).

We translated the VQLQ to Italian language and validated the obtained questionnaire (VQLQ-i) with good levels of internal and external consistency. Our study is in line with the results and VQLQ scores of the other validation studies, when reported (**table I**) (3-6, 8), even if comparability with the single studies is hampered by the great heterogeneity of methods and populations. Specifically, some of them do not provide the obtained VQLQ score (*i.e.*, English (3), Polish (9), German (5), and Portuguese (7) VQLQ); the Spanish (8), Polish (9), and Portuguese (7) studies include bee-allergic patients and/or adolescents tool; the Turkish study (6) is not comparable due to the use of a reverse VQLQ score (*i.e.*, the higher the VQLQ, the worst the HRQoL). Furthermore, cultural differences might have an impact on the variance observed among results from different countries. Compared to the other validation studies of the VQLQ in adults with vespid venom allergy, our study enrolled the highest number of patients, with a well-represented range of reaction severity (from M1 to M4) and re-stung patients.

In conclusion, VQLQ is the only disease-specific tool to investigate the HRQoL in adult patients with YJ venom allergy that is currently validated across a significant number of countries and languages. This simple and quick tool can be easily implemented in clinical practice, and the Italian version is now available.

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Contributions

MarMau, MBB: conceptualization. MarMau: project administration. MarMau, DB, PB, MCB, FE, LG, SL, FO, VP, DP, ER, FR, MBB: investigation. IB, MatMar: methodology. MatMar: formal analysis. MarMau, IB, MatMar, MBB: writing - original draft. All authors: writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests related to the work.

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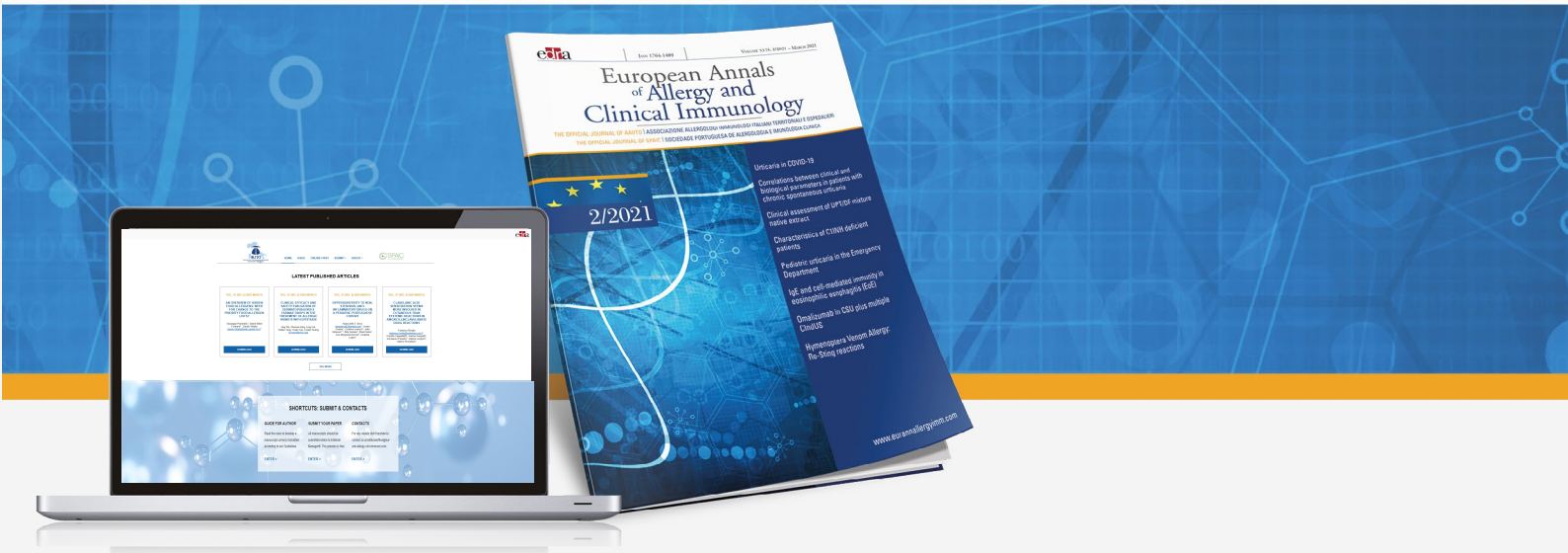

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