

Safety and Effectiveness of a Single Multiallergen Subcutaneous Immunotherapy in Polyallergic Patients

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Keywords

Allergic asthma · Polyallergic · Polysensitization · Multiple allergen immunotherapy · Undiluted mixtures

Abstract

Background: As the number of allergic sensitizations increases the severity of allergic respiratory diseases worsens. Multiple monoallergen immunotherapy can be accompanied by poor treatment adherence and high costs, single multiallergen immunotherapy needs to prove efficacy whilst maintaining a good safety profile. **Methods:** Observational, retrospective, multicenter study using a 2-pollen single undiluted multiallergen subcutaneous immunotherapy (SCIT) in routine clinical practice in Spain. Patients with rhinoconjunctivitis, with/without controlled asthma, sensitized to grass, olive, Parietaria, Cupressus, plane tree and/or

Salsola pollen were included. Primary and secondary clinical efficacy endpoints were quality of life (mini Rhinitis Quality of Life Questionnaire (miniRQLQ)) and visual analogue scale (VAS) respectively. All adverse events were documented.

Results: Ten centers included 97 patients, median age 32 years. SCIT treatment included combinations of grass mix with olive, Parietaria, Cupressus, plane tree or Salsola or olive with Parietaria, Cupressus or Salsola. The mean duration of SCIT was 1.8 years with a high treatment adherence (73%). Significant improvement in quality of life, nasal and ocular symptoms, activity limitations and practical problems ($p < 0.0001$) and other symptoms ($p = 0.024$) was observed. Most patients did not develop asthma-like symptoms and a significant improvement of all allergic symptom severity was

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perceived. VAS showed a significant improvement in rhinoconjunctivitis and asthma by patients and physicians. Twenty-nine patients experienced adverse reactions, 25 had local and 6 had systemic reactions. **Conclusions:** Single undiluted multiallergen SCIT treatment of two different pollens is efficacious and safe in both children and adults, showing that it is a suitable option for the treatment of polyallergic patients.

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Introduction

Polysensitization to nontaxonomically related pollens occur in the majority of allergic patients in Spain and rest of the Mediterranean areas. In many of those patients, different pollens elicit allergic symptoms, therefore, treating physicians need to efficiently tackle polyallergy [1, 2]. Allergen immunotherapy remains to date the only disease-modifying treatment for IgE-mediated respiratory allergies. Multiple monoallergen immunotherapy might be efficacious, but it can be accompanied by poor treatment adherence and high costs. In polyallergic patients, allergen mixtures can be considered if supported by clinical evidence [3, 4].

Depigmented-polymerized allergen extracts adsorbed onto aluminum hydroxide have demonstrated clinical efficacy in several studies conducted with different allergens and in polysensitized patients while keeping a good safety profile [5–7]. Depigoid® DUO pollen mixture (2,000 DPP/mL) is a single undiluted multiallergen depigmented-polymerized allergen extract indicated for polyallergic patients.

Material and Methods

We conducted a real-life, retrospective, multicenter study to evaluate the safety and effectiveness of a single undiluted multiallergen subcutaneous immunotherapy (SCIT) in polyallergic patients. Children, adolescents, and adults (ages 8–72) with allergic rhinoconjunctivitis and/or asthma (Table 1) due to grasses, *Olea europaea*, *Parietaria judaica*, *Cupressus arizonica*, *Platanus acerifolia*, and/or *Salsola kali* treated with a single multiallergen (Depigoid® DUO 2,000 DPP/mL pollen combination) SCIT for a minimum period of 12 months, within routine clinical practice, were included. Polyallergy was determined by clinical history, positive SPT (wheal ≥ 3 mm), and/or positive-specific IgE (≥ 0.75 kU/L) to more than one allergen listed above. In 37 patients (38.1%), molecular diagnosis was performed, as this was routine clinical practice, molecular diagnosis was only performed when SPT or specific IgE could not confirm the type of polysensitization. In all cases, the *rush* build-up phase consisted in the administrations of 0.2

Table 1. Baseline characteristics

Gender (male), n (%)	55 (56.7)
Age (median, IQR)	32 years (22, 48)
ICM (median, IQR), kg/m ²	24.4 (22.3, 27.3)
Time since diagnosis (median, IQR)	2.7 years (2.4, 3.6)
Severity of the rhinoconjunctivitis, n (%)	
Mild	2 (2.1)
Moderate	74 (76.2)
Severe	21 (21.6)
Concomitant asthma, n (%)	47 (48.5)
Controlled asthma	47 (48.5)
Allergen sensitization (SPT), n (% of patients in which it was performed)	
Grass pollen	9 (17.3)
Olive pollen	11 (18.6)
<i>Parietaria judaica</i> pollen	3 (12)
<i>Cupressus arizonica</i> pollen	2 (6.7)
<i>Platanus acerifolia</i> pollen	1 (4.3)
SPT, skin prick test.	

+ 0.3 mL with 30-min interval, followed by a monthly maintenance phase of 0.5 mL, in a perennial schedule. Time interval from “first patient first injection” and “last patient last injection” went from Feb 2016 to March 2018. Patients had to have initiated SCIT at least 5 months prior to start of pollen season, median SCIT treatment time was 1.8 years (range 1.5, 2.2 years).

This study was conducted in 10 centers in Spain (Hospital de Sant Joan de Déu, Manresa; Hospital Universitario de Fuenlabrada; Hospital General Universitario de Valencia; Hospital Rafael Méndez, Lorca; Hospital Universitario San Cecilio, Granada; Hospital Universitario Príncipe de Asturias, Alcalá de Henares; Hospital Universitario Infanta Sofía, San Sebastián de los Reyes; Clínica Atenea, Valencia; Hospital Royo Villanova, Zaragoza and Hospital Reina Sofía, Tudela), in areas with high pollen load, with the approval of the corresponding Ethics Committee and previous consent from the participants. The primary objective was to evaluate treatment effectiveness using the abbreviated disease-specific rhinoconjunctivitis quality-of-life questionnaire (miniRQLQ) [8] with a Minimal Clinically Important Difference of 0.5 [8]. Secondary outcomes were changes in perceived quality of life and asthma control test measured with a visual analogue scale of 10 mm, description of demographic, clinical (presence of symptoms and severity using a Likert scale) measured at baseline and within pollen season and safety characteristics of the treatment. Adverse events were recorded and graded according to EAACI 2006 grading system [9].

Results

One hundred twenty-eight patients received at least one dose of Depigoid® DUO and were included in the safety analyses. Reasons for withdrawal were no diagnosis

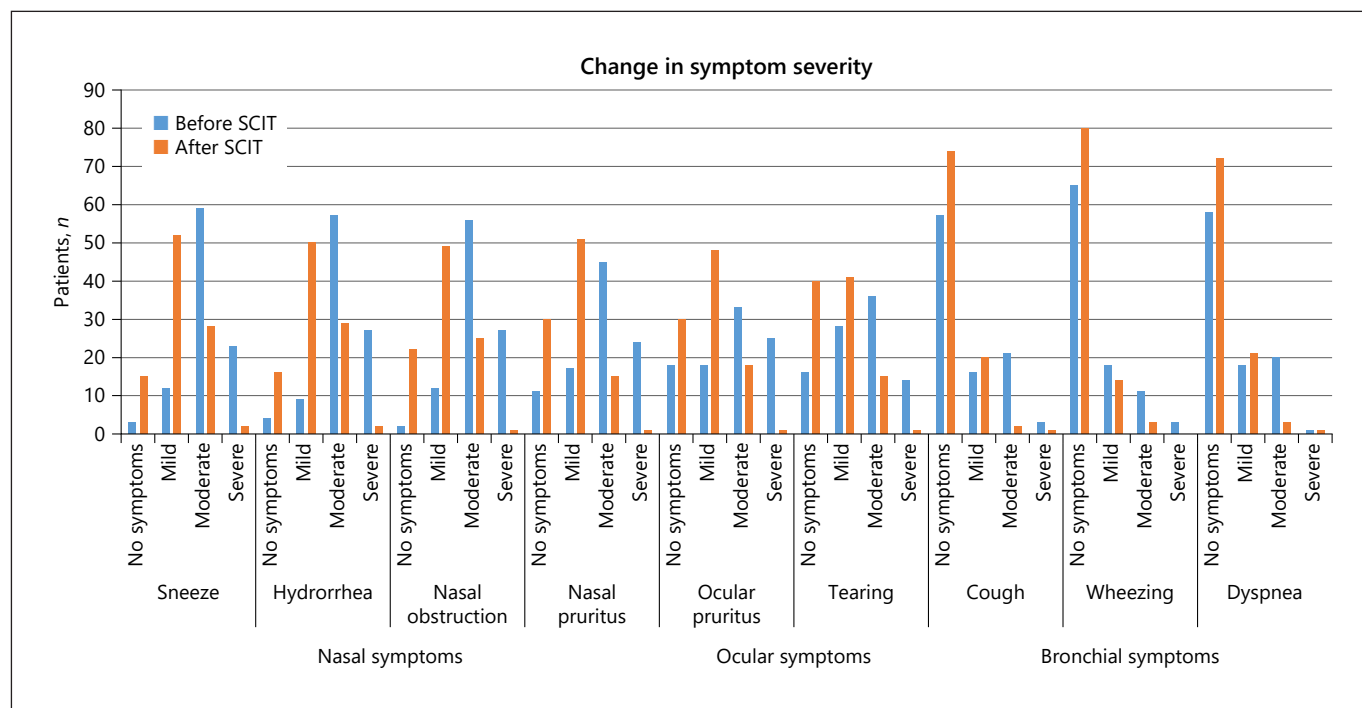


Fig. 1. Number of patients with mild, moderate, severe or without nasal, ocular, and bronchial symptoms before and 12 months after SCIT. SCIT, subcutaneous immunotherapy treatment.

Table 2. Effectiveness of the treatment

	Pre-Depigoid® DUO	Post-Depigoid® DUO	Difference	p value*
miniRQLQ median (IQR)				
Total score	2.9 (2.0, 3.6)	1.4 (0.6, 2.6)	-1.1 (-2.1, -0.1)	<0.0001
Nasal symptoms	4.0 (3.0, 5.0)	2.0 (1.0, 3.3)	-1.3 (-2.7, 0.0)	<0.0001
Ocular symptoms	2.7 (1.0, 3.7)	1.0 (0.3, 2.0)	-1.3 (-2.3, 0.0)	<0.0001
Other symptoms	1.7 (0.7, 2.7)	1.0 (0.0, 2.7)	-0.3 (-1.3, 0.7)	0.0243
Practical problems	4.0 (3.0, 5.0)	1.5 (1.0, 3.5)	-1.5 (-3.5, 0.0)	<0.0001
Activities	2.7 (2.0, 3.7)	1.0 (0.3, 2.7)	-1.0 (-2.0, 0.0)	<0.0001
Perception of disease (VAS) Doctor's perspective median (IQR)				
Rhinoconjunctivitis	3.4 (2.2, 5.7)	7.6 (5.7, 9.2)	3.7 (1.0, 5.2)	<0.0001
Asthma	5.8 (2.7, 7.6)	8.6 (7.1, 9.5)	2.1 (0.5, 4.9)	<0.0001
Perception of disease (VAS) Patient's perspective median (IQR)				
Rhinoconjunctivitis	3.1 (1.8, 5.2)	7.5 (5.2, 9.0)	3.6 (0.5, 6.1)	<0.0001
Asthma	5.4 (2.7, 7.5)	8.1 (7.0, 9.1)	1.9 (0.3, 5.2)	<0.0001

VAS, visual analogue scale; miniRQLQ, mini Rhinitis Quality of Life Questionnaire. * Wilcoxon test.

of rhinoconjunctivitis or asthma, not received treatment for a minimum of 12 months, not meeting inclusion criteria, no data for main variable, uncontrolled asthma, and/or started SCIT after study approval. Data from 97 patients were obtained for the primary objective. The most common allergen combination was GrassMix/*Olea*

europaea (38%), followed by GrassMix/*Cupressus arizonica* (14.4%) and *Olea europaea/Salsola kali* (12.40%). Other allergen combinations used were GrassMix/*Salsola kali* (10.3%) GrassMix/*Parietaria judaica* (8.2%), *Olea europaea/Cupressus arizonica* (8.2%), *Olea europaea/Parietaria judaica* (5.2%), and GrassesMix/*Platanus acerifo-*

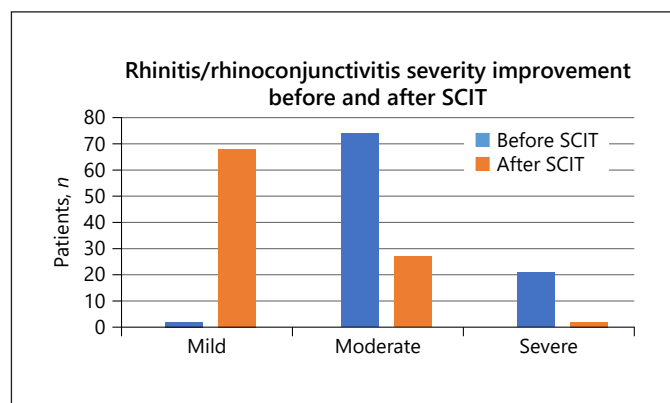


Fig. 2. Improvement in number of patients with mild, moderate, or severe rhinitis/rhinoconjunctivitis before and after SCIT. SCIT, subcutaneous immunotherapy treatment.

Table 3. Asthma severity classification before and after SCIT

Asthma classification prior to SCIT, n (%)	
Intermittent asthma	14 (29.8)
Mild persistent asthma	11 (23.4)
Moderate persistent asthma	16 (34.0)
Occasional episodic asthma	4 (8.5)
Frequent episodic asthma	2 (4.3)
Asthma classification after SCIT, n (%)	
Intermittent asthma	29 (61.7)
Mild persistent asthma	10 (21.3)
Moderate persistent asthma	7 (14.9)
Severe persistent asthma	1 (2.1)

SCIT, subcutaneous immunotherapy treatment.

lia (3.1%). Fifty-five patients were male (56.7%) and median age was 32 years (range 22, 48). Median time since diagnosis was 2.7 years (range 2.4, 3.6). At baseline, patients experience a significant burden of disease with 75.3 and 22.7% of patients denoting moderate or severe rhinoconjunctivitis, respectively, and 47 patients (48.5%) had concomitant asthma (Table 1). Within the adult population, 15 (37.5%) had moderate persistent asthma, 11 (27.5%) had mild persistent asthma and 14 (35%) had intermittent asthma according to GEMA (Guía Española en el Manejo del Asma) guideline [10]. Within the pediatric population, one (14.3%) had moderate persistent asthma, 2 (28.6%) had frequent episodic asthma and 4 (57.1%) had occasional episodic asthma according to GEMA guideline [10]. Median value of FEV₁% (adjusted for age, height, and weight) before treatment was 92.9% (range 82% and 105%). Twenty-seven patients (27.8%) were sensitized to Phl p 1, 20 (20.6%) were sensitized to Phl p 5, 3

(3.1%) to Phl p 7, 6 (6.2%) to Phl p 12, 22 (22.7%) to Ole e 1, 4 (4.1%) to Par j 2, 4 (4.1%) to Cup s 1, and 7 (7.2%) to Sal k 1. Eighty-four patients (86.6%) required concomitant medication of which 24 (28.6%) were taking oral antihistamines for a median time of 2 months, 24 (28.6%) were taking short-acting β_2 for a median time of less than a month (range 0, 0.2 years), 3 (3.6%) required inhaled steroids for a median time of less than a month. Seventy-two (74%) patients required other concomitant medication such as leukotriene receptor antagonists, piperazine derivatives, and other antiallergic agents.

Results for change in quality of life showed a clinically significant improvement, median decrease 1.1 points (IQR 2.1, 0.1; p value <0.0001) in the miniRQLQ total score compared to baseline. Similarly, clinically significant improvements were observed in all dimensions of the questionnaire: “nasal symptoms” 1.3 (IQR 2.7, 0.0; p < 0.0001), “ocular symptoms” 1.3 (IQR 2.3, 0.0; p < 0.0001), “activities” 1.0 (IQR 2.0, 0.0; p < 0.0001), “practical problems” 1.5 (IQR 3.5, 0.0; p < 0.0001), and “other symptoms” 0.3 (IQR 1.3, 0.7; p = 0.024) improved significantly (Table 2).

After 12 months of treatment a significant reduction in nasal (p = 0.0013), ocular (p < 0.0001), and respiratory symptoms (p = 0.0017) was observed with a complete resolution of symptoms in 5.2, 21.6, and 14.5% of patients with nasal, ocular, and respiratory symptoms, respectively. Most patients experienced an improvement in symptom severity with nasal (sneezing 63.4, hydroporrhea 61.7, obstruction 65.3, and pruritus 76.1%), ocular (itching 91.8 and tearing 78.1%), and respiratory symptoms (cough 87, wheezing 82.4, and dyspnea 84%) being predominantly mild after 12 months of treatment with Depigoid® DUO. Presence of severe symptoms was reduced in 91.3, 92.6, 96.3, 95.8, 96, 92.9, 66.7, and 100% of patients with severe sneezing, hydroporrhea, nasal obstruction, nasal pruritus, ocular itching, tearing, cough, and wheezing, respectively, before treatment (shown in Fig. 1). Depigoid® DUO treated patients perceived an improvement in quality of life with a median visual analogue scale increase of 3.6 points (IQR 0.5, 6.1; p < 0.0001) for rhinoconjunctivitis and 1.9 points (IQR 0.3, 5.2; p < 0.0001) for asthma. Similar results were obtained for physician perceived change in quality of life (Table 2). Seventy-nine percent of patients perceived their asthma as well controlled and 21% as partially controlled before SCIT while 96% perceived it as well controlled and only 4% as partially controlled 12 months after SCIT. Rhinoconjunctivitis (p < 0.0001) and asthma severity significantly improved after treatment with Depigoid® DUO (Fig. 2; Table 3).

Treatment adherence was high, 71 out of 97 patients (73.2%) continued with SCIT 12 months after treatment initiation. Two patients discontinued the treatment due to an adverse event, none of them related to the treatment with Depigoid® DUO.

The treatment was safe and well tolerated. One hundred twenty-eight patients received 2,569 doses of Depigoid® DUO throughout the study. Twenty-nine patients experienced an adverse reaction, none of them severe or unexpected. Most of them (25) were local reactions, and 6 were systemic reactions. Five of the systemic reactions were grade I (one urticaria and 4 mild asthma with rhinoconjunctivitis) and one grade II reaction that presented with asthma. None of these adverse reaction lead to treatment discontinuation.

Conclusion

Depigoid® DUO has shown in this real-life study, with a very good treatment adherence, to improve the disease related and perceived quality of life, decrease the severity of nasal, ocular, and bronchial symptoms or their complete resolution, while maintaining a very good safety profile. The main limitation of this study is the lack of control arm (either by symptomatic treated group or placebo controlled); however, the objective was to show effectiveness within routine clinical practice and show improvement inpatient compared to baseline, therefore, a retrospective study is suitable to answer this question. Studies with a single undiluted multiallergen SCIT are scarce despite increasing rates of polysensitization in Eu-

rope. Depigoid® DUO has shown to be safe and efficacious and is a suitable option for the treatment of polyallergic patients.

Statement of Ethics

All patients, parents, or legal guardians signed the informed consent. The study protocol was approved by the institute's committee on human research from Hospital Universitario de Fuenlabrada.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All coauthors made substantial contributions to the conception and design of the work; they also reviewed and interpreted the data obtained. All coauthors critically reviewed the data and final manuscript for publication.

Availability of Data and Material

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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