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RESEARCH ARTICLE

Evaluation of the safety of dose escalation period of subcutaneous specific allergic immunotherapy in patients with rhino-conjunctivitis or allergic asthma previously vaccinated against SARS-CoV-2

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Abstract

BACKGROUND: More than 90% of the Spanish population has been vaccinated against the SARS-CoV-2 virus in our setting. The administration of this vaccine is not contraindicated in allergic subjects; however, it is unknown whether any precaution should be taken when initiating subcutaneous allergen immunotherapy after this vaccination. The objective of the study was to analyze the safety of subcutaneous allergen immunotherapy during the dose escalation phase in subjects sensitized to pollens or mites previously vaccinated against SARS-CoV-2.

METHODS: An observational study with retrospective data collection from protocolled patients' medical records was designed. Outpatients older than 12 years with diagnosis of pollen or house dust mite allergic rhinitis with or without bronchial allergic asthma were selected who had completed the subcutaneous immunotherapy dose escalation phase. A complete SARS-CoV-2 vaccination was required for the inclusion.

RESULTS: Three hundred and seventy-nine patients were included by 53 investigators. The mean age was 31 years old and 55,9% female. Time from last SARS-Cov-2 vaccination dose to subcutaneous immunotherapy initiation was 4.1 months (95%CI 3.8-4.4). subcutaneous immunotherapy with a pollen allergoid was administered to 135 patients (35.6%) with a total of 739 injections, while subcutaneous immunotherapy using a house dust mite allergoid was administered to 244 patients (64.4%) with a total of 1311 doses. During the dose escalation phase with the pollen allergoid, 45 patients (33.3%) suffered 93 local adverse reactions (12.6% of injections), while 17 patients (12.6%) experienced 17 systemic allergic reactions (2.3% of injections) of them 14 were World Allergy Organization Grade 1 and 3 of Grade 2. During the dose escalation phase with the house dust mite allergoid, 55 patients (22.5%) reported 133 local adverse reactions (10.1% of injections), and 7 patients (2.9%) showed 7 World Allergy Organization Grade 1 systemic reactions (0.5% of injections). No systemic reactions Grade 3 or higher were reported.

CONCLUSIONS: The well-known safety profile of the subcutaneous allergen immunotherapy using pollen or house dust mite allergoids has not been changed after the SARS-CoV-2 vaccine administration. No relevant differences in the incidence of local or systemic allergic reactions during the dose escalation phase were identified, so it is considered that the patient's safety has not been compromised to initiate this treatment after the SARS-CoV-2 vaccine administration.

KEYWORDS: Allergen immunotherapy; subcutaneous immunotherapy; dose escalation; pollen; house dust mites; safety; COVID-19; SARS-CoV-2 vaccine.

INTRODUCTION

Vaccination against SARS-CoV-2 has been achieved in different proportions of the population worldwide. In the environment in which this study was carried out (Spain), 41,310,204 people had received at least one dose, representing more than 90% of the population. At the time of the study, 60.4% of the administered doses in Spain corresponded to original Comirnaty, 21.78% to original Spikevax, 8.8% to Vaxzevria, 7.1% to bivalent Comirnaty (original/omicron BA. 4-5), 1.8% to Jcovden and 0.2% to bivalent Spikevax (origin/omicron BA.1).[1]

According to the information described in the summary of product characteristics of the vaccines currently available against SARS-CoV-2, their use is not generally contraindicated in people with any type of allergic disease except in those people who have presented an allergic reaction with a previous dose of any of the vaccines or suspected of being allergic to any of their excipients.

At this point, it is known that the most frequently described reactions after the administration of SARS-CoV-2 vaccines, which appear in 1/10 people, are mild and consist mainly of pain at the injection site, fatigue, fever and muscle pain. Globally, allergic reactions are rare, occurring in approximately 1/100,000 vaccines.[1]

In reference to the currently available clinical evidence, the fact of receiving concomitant allergen immunotherapy treatment should not be a contraindication for the administration of the vaccine against COVID-19. Usually, with other types of vaccine such as the flu vaccine, it is advisable to separate the administration of both treatments by a week. As the administration of vaccines against COVID-19 can cause both immediate and delayed local reactions, it is recommended to administer allergen immunotherapy in the contralateral arm.[2]

At the present time, we do not have information on whether the already established safety profile of subcutaneous allergen immunotherapy (SCIT) for a specific allergen extract may have been modified by the effect of previous vaccination against the SARS-CoV-2 virus. Allergologists expressed they concern in this matter, as their clinical impression was an increase of adverse reactions. This situation was that we wished to investigate in this study.

Subcutaneous immunotherapy begins with the gradual administration of increasing doses of an allergen extract to an allergic subject. This is administered over a weekly dosing dose escalation phase, until the optimal maintenance dose is reached which then will be monthly administered for a minimum of three years. The therapeutic objective is to reduce the patient's symptoms and need of antiallergic/antiasthmatic medication when exposed to the causative allergen.[3] During the dose escalation phase of SCIT, the maximum dose reached should be individualized as the highest tolerated dose. In general, most adverse reactions are observed, particularly after the first doses.[4,5] For this reason, SCIT injections must be administered under the control of a trained health professional, and the patient must remain under observation for

at least 30 minutes after the administration of each dose.

This study intends to explore whether the proportion of patients and the number of adverse reactions observed during the dose escalation phase of SCIT may be different from that described for the specific allergen extract in the situation prior to vaccination against the SARS-CoV-2 virus.

As each manufacturing company uses different biological standardization processes, and that the procedures for quantifying the concentration of major allergens existing in each of the therapeutic extracts are also different, the clinical safety results published in relation to specific therapeutic extracts cannot be extrapolated in a general way to all commercial products. This project explored the safety profile of the dose escalation period of SCIT. In patients who had already received a full course of vaccination against COVID-19, information on the safety profile observed was collected to compare it with the data described in the pre-COVID-19 era.

METHODS

Study design and setting

An observational exploratory study was designed with collection of retrospective aggregated information from medical records. The study was approved by the Ethics Committee of the Hospital Universitario Puerta de Hierro (Majadahonda, Madrid, Spain) on July 28th, 2022 (minutes 15/2022). The study was conducted in line with ethical principles of the Declaration of Helsinki.

The study was completed in 53 Spanish public and private allergy departments from July to October of 2022. SCIT was initiated before the data collection for the study, so the patients were selected retrospective and consecutively from those fulfilling eligibility criteria. All patients who received at least one dose of SCIT were included in the study.

Study objectives

The primary objective of this study was to analyze the safety of SCIT during the dose escalation phase in subjects sensitized to pollens or mites previously vaccinated against SARS-CoV-2.

Eligibility criteria

The eligibility criteria were the following: a) Out-patients older than 12 years; b) Diagnosis of rhino-conjunctivitis with or without bronchial asthma of allergic etiology; c) Hypersensitivity to pollen or mites determined by skin prick test and / or allergen-specific positive IgE; d) Patients who had completed the dose escalation phase of SCIT with the pollen allergoids Allergovit® or the house dust mite allergoid Acaroid® (both manufactured by Allergopharma GmbH & Co. KG, Reinbek, Germany); e) Patients who had received the full schedule of vaccination against SARS-CoV-2.

Due to the retrospective and aggregated data study, collecting secondary data form the patient's clinical records, the obtention of the patient's informed consent was waived.

Data sources and measurement

Information was collected referred to patient age and gender and the main allergic diagnosis (rhino-conjunctivitis, allergic asthma or both conditions).

All the patients were vaccinated against SARS-CoV-2 with available products. Time from last dose of SARS-CoV-2 vaccination to the initiation of SCIT and the brand name of the vaccine received was collected.

Allergovit® and Acaroid® are hypoallergenic depot formulations indicated for the treatment of IgE-mediated allergic rhinitis/rhinoconjunctivitis and/or bronchial asthma secondary to pollen or mites hypersensitivity respectively. The hypoallergenicity of the formulation allows to administer higher allergen maintenance doses within the upper range of the interval recommended by the World Health Organization in order to ensure maximal efficacy.[6]

Data about the SCIT doses schedule for the dose escalation phase was recorded. The patients were scheduled to initiate the SCIT with these products at the most appropriate schedule as per usual clinical practice. Information about the doses schedule for the dose escalation phase was collected. Usually, the SCIT dose is administered weekly, with increasing doses of the allergenic extract up to the individual maintenance dose or the maximum dose of 600 Therapeutic Units (TU). The composition and schedules of each product is described in Table 1. The patients stayed at least 30 minutes after each SCIT dose in the clinic to observe the appearance of any adverse reaction. The number of doses administered during the dose escalation period was also registered.

For the description of the main objective, the patient's adverse reactions to SCIT appearing during the dose escalation period were registered, specifying whether the reaction was early (appearing within the first 30 minutes after injection) or delayed (appearing later than 30 minutes after injection), and the type of adverse reaction (local or systemic). Early local reactions were considered if the largest diameter of the local reaction was greater than 5 cm in adult and 3 cm in children, while the diameter of delayed local reactions had to be larger than 10 cm in adults and 7 cm in children. The severity of the systemic allergic adverse reactions was graded based on the criteria and recommendations of the World Allergy Organisation (WAO) currently classified into 5 grades (1-5), where Grade 1 corresponds to the least severe and Grade 5 to the most severe.[7]

Sample size

No formal sample size was estimated for this exploratory study.

Statistical methods

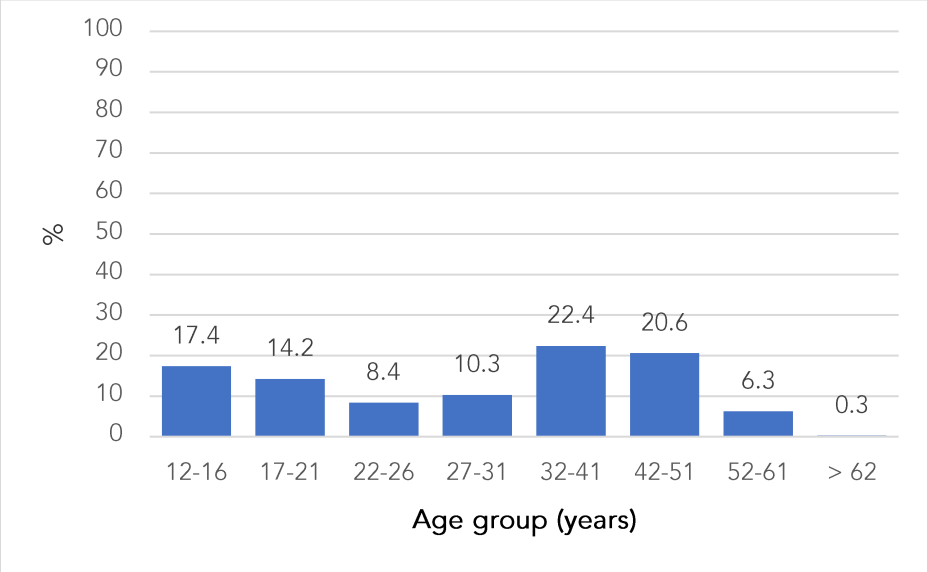
A descriptive analysis was completed displaying frequencies and percentages and exact 95% Confidence interval for the qualitative variables and the usual values for qualitative variables (mean, standard deviation, minimum and maximum, and 95% confidence interval). The software used for the statistical analysis was SPSS 27.0 (IBM Corp., Armonk, NY, USA). Type I error was established at a two-sided 0.05 level.

RESULTS

Information about 379 patients was collected by 53 Spanish investigators. A total of 212 patients (55.9%) were women and 167 men

(44.1%) with a mean age of 31 years. Figure 1 shows the proportion of patients by age group.

Figure 1. Distribution of patients by age group



The clinical manifestation of the allergic disease was only rhino-conjunctivitis in 199 patients (52.5%), only allergic asthma in 11 patients (2.9%) and both conditions in 169 patients (44.6%).

A total of 79 patients (20.8%) had suffered from a COVID-19 infection, which occurred, a mean of 7.5 months (95%CI 5.8-9.1) before the SARS-CoV-2 vaccine was administered. 266 patients (70.2%) received Comirnaty® (BioNTech/Pfizer), 84 patients (22.2%) were vaccinated with Spikevax® (Moderna), 28 patients (7.4%) with Vaxzevria® (Astra Zeneca), and 6 patients (1.6%) with COVID-19 Jcovden® (Janssen).

Time from last dose of SARS-CoV-2 vaccination to the initiation of SCIT was a mean of 4.1 months (95%CI 3.8-4.4).

Data for a total of 379 patients were evaluated, 135 patients (35.6%) had been treated with the pollen allergoid, and 244 patients (64.4%) had received the house dust mite allergoid. The doses schedules administered by each product are displayed in Table 1.

A total of 739 injections of the pollen allergoid and 1311 injections of the house dust mites allergoid were administered.

Table 1. Dose schedules for dose escalation during subcutaneous immunotherapy (SCIT).

Subcutaneous immunotherapy product	Allergen preparations	Doses schedules for dose escalation: Therapeutic Units (TU) per injection and per week (/)	Number of treated patients (%)
Pollen allergoids	*Grass pollen, cereals, birch, alder, artemisa, plantago ovata, hazel, olea europaea*	Standard regimen (Strength A and B): 100/200/400/800/1500/3000/6000	49 (36.3)
		Accelerated regimen (Strength A and B): 200/600/2000/6000	58 (43)
		One strength regimen (Strength B): 1000/3000/6000	9 (6.7)
		Other regimens	19 (14)
House dust mites allergoids	*Dermatophagoides farinae, dermatophagoides pteronyssinus*	Standard regimen (Strength A and B): 100/200/400/600/1000/2000/4000/6000	52 (21.3)
		Cluster regimen (Strength A and B): 300+300/1000+2000/3000+3000	105 (43)
		Other regimens	87 (35.7)

Safety results

During pollen SCIT, 20 patients of 135 (14.8%) suffered from 50 local early reactions, while 25 patients of 135 (18.5%) experienced 43 delayed local reactions. Total number of patients with local adverse reaction was 45 (33.3%). Systemic allergic reactions occurred in 17 patients of 135 (12.6%), 14 of these reactions were classified as WAO Grade 1, whereas 3 reactions were of WAO Grade 2. No systemic allergic reactions with WAO Grade 3 or higher were reported. No patients needed to be discontinued from SCIT due to an adverse reaction. The number of local and systemic reactions during the dose escalation phase, detailed by number of SCIT injections are summarized in Table 2.

Table 2. Adverse reactions during dose escalation with the pollen allergoid

	Local reaction			Systemic reaction
	Early local reaction	Delayed local reaction	**Total local reaction**	**Total systemic reaction**
Patients experiencing at least one adverse reaction, N (%)	20 (14.8%)	25 (18.5%)	**45 (33.3%)**	**17 (12.6%)**
Injections causing adverse reactions, n (%)	50 (6.8%)	43 (5.8%)	93 (12.6%)	17 (2.3%)

N (%): number of patients with at least one adverse reaction in percentage compared to all patients receiving pollen SCIT (135 patients); n (%): number of injections causing adverse reactions in percentage compared to the total number of injections (739 injections).

During house dust mite SCIT, 24 patients of 244 (9.8%) suffered from 61 early local reactions, while 31 patients of 244 (12.7%) experienced 72 delayed local reactions. The number of patients with local reactions was 55 (22.5%) Systemic allergic reactions occurred in 7 patients of 244 (2.9%), all these reactions were classified as WAO Grade 1 reactions. Two patients (0.8%) discontinued SCIT due to systemic allergic reactions. The number of local and systemic reactions during the dose escalation phase, detailed by number of SCIT injections are summarized in Table 3.

Table 3. Adverse reactions during dose escalation with the house dust mite allergoid.

	Local reaction			Systemic reaction
	Early local reaction	Delayed local reaction	Total local reaction	Total systemic reaction
Patients experiencing at least one adverse reaction, N (%)	24 (9.8%)	31 (12.7%)	55 (22.5%)	7 (2.9%)
Injections causing adverse reactions, n (%)	61 (4.7%)	72 (5.5%)	133 (10.2%)	7 (0.5%)

N (%): number of patients with at least one adverse reaction in percentage compared to all patients receiving pollen SCIT (244 patients); n (%): number of injections causing adverse reactions in percentage compared to the total number of injections (1,311 injections).

DISCUSSION

This retrospective study investigated the safety profile during the dose escalation phase of SCIT using pollen or house dust mite allergoids in patients who had completed a full course of vaccination against COVID-19 approximately 4 months before. During dose escalation, the pollen allergoids induced at least one local adverse reaction in 33.3% of patients while 12.6% of the patients developed systemic allergic reactions. When dose escalation was performed with the house dust mite allergoid, 22.5% of patients suffered from local reactions while 2.9% of patients experienced systemic allergic reactions. With both allergoids, no systemic allergic reaction of WAO Grade 3 or higher was reported.

Several randomized controlled trials have been performed with the grass or birch pollen allergoid by the same manufacturer in recent years investigating safety of different accelerated dose escalation regimens.[8-11] Two trials compared safety and tolerability of the accelerated dose escalation scheme with 4 injections of strength A and B with that of the standard regimen with 7 injections of strength A and B for the grass and birch pollen allergoids in adults.[8,9] Local reactions appeared in up to 55.4% of patients while systemic reactions affected up to 10.7% of patients. No systemic allergic reaction of WAO grade 3 or higher and no serious adverse reactions occurred in these trials. For the grass pollen allergoid, a One Strength

dose escalation regimen using only strength B was compared with the Standard dose escalation scheme in two randomized controlled trials including adults, adolescents, and children. Local reactions were reported in up to 53.5% of patients and systemic allergic reactions in up to 5.8% of patients while no systemic allergic reaction of WAO grade 3 or higher occurred. In these both trials, 3 patients experienced serious adverse reactions, but all were expected for the product.[10,11]

Safety of SCIT with the house dust mite allergoid in several randomized controlled trials was summarized by Klimek et al. Up to 33.6% patients developed local reactions while systemic allergic reactions were observed for up to 11.2% of patients. Serious adverse events were reported for 0.4% of patients, however none of these were unexpected for the product.[12] But these trials were performed for up to two years so that adverse events both during dose escalation and maintenance phase were evaluated in contrast to the trials with the pollen allergoids mentioned above and the retrospective analysis on hand. Since more adverse events occur during the dose escalation than the maintenance phase the results are only limited comparable.[13]

In general, the number of adverse reactions reported in clinical trials is higher than in daily life since patients are obviously stronger monitored especially when safety is the primary endpoint. In those trials patients were observed for up to 120 minutes after each SCIT injection and they were instructed to document any presumably adverse reaction appearing even later than 24 hours after injection which were reviewed in the next visit.[8-11] In contrast, in the daily practice patients stay in the physicians' practices for 30 minutes as recommended e.g. by the European allergen immunotherapy guideline.[14] This is reflected by a retrospective study in Italy that investigated the accelerated dose escalation regimen of the pollen allergoid. Local reactions occurred in 9.0% of patients while no systemic allergic reaction was observed. The authors assumed that some delayed local reactions may have been missed.[15]

Currently, many publications support the evidence of the efficacy and safety of SCIT for the treatment of IgE-mediated respiratory diseases, demonstrated by randomized clinical trials, and meta-analyses.[16-20] In them, many factors have been described to be related to the incidence of adverse reactions: the SCIT product selected, due to the different standardization processes; the type of SCIT, native extract or allergoid; the concentration of the allergen; the dose administered in each injection; the type of allergen, where pollen produce higher incidence of adverse events than mites[21];if the SCIT contains only one allergen or it is multiple; the number of sequential doses and the time between doses; most local and systemic reactions appear with the first SCIT doses. But also, patient's characteristics could derive in higher risk of adverse reactions. Recognized risk factors for systemic reactions include uncontrolled asthma at the time of administration of injections, dosing errors, a

prior history of injection-related systemic allergic reactions and administration of injections during peak allergy seasons.[21-23]

With the introduction of the COVID-19 vaccines questions have arisen whether there may be interferences between AIT and COVID-19 vaccination. Multiple statements and position papers dealt with this aspect and outlined recommendations.[24-28] An expert panel of the European Academy of Allergy and Clinical Immunology (EAACI) published a position paper on the administration of COVID-19 vaccines in allergic or asthmatic patients receiving AIT. The panel evaluated the immunological mechanism of COVID-19 infection, of COVID-19 vaccination and of AIT and, also considered the data published for other infectious vaccines administered during ongoing AIT. Based on this knowledge they concluded that "the immunological mechanisms of AIT and COVID-19 vaccines do not seem to interfere as both primarily target the immune system in a specific, non-overlapping manner". Therefore, the panel recommended to administer COVID-19 vaccines at the interval of 7 days from SCIT preparations to definitely assign potential side effect of each one.[28]

Web-based surveys in Germany and Italy were designed to evaluate the impact of COVID-19 on allergic diseases and patients under AIT from the physician's perspective during the COVID-19 pandemic.[29-30] The Italian survey was completed by 66 physicians and more than 80% of them did not have the impression that AIT influenced the severity of COVID-19. 93% continued ongoing AIT and about the half prescribed new AIT during the COVID-19 pandemic.[30] The Germany survey, initiated by the German Society for Allergology and Clinical Immunology (DGAKI), was responded by 345 physicians. 70% of them stated that they regularly initiated SCIT while 85% continued SCIT with aeroallergen preparations during the maintenance phase as usual. Concerning safety and tolerability, there was no evidence for a higher incidence of adverse events in patients without current symptoms of COVID-19 infection during the COVID-19 pandemic.[29] Accordingly, both surveys showed that the physicians administered and initiated SCIT nearly unchanged during the COVID-19 pandemic. Nevertheless, the German survey did not indicate a higher incidence of adverse events. This is in accordance with the retrospective results presented in the analysis on hand.

We have not found differences in the incidence of local or systemic adverse reactions in SCIT after the SARS-CoV-2 vaccination. Therefore, the results indicate that the allergoids are safe in patients who have received a full SARS-CoV-2 vaccination.

The study had the limitations inherent to retrospective data collection studies. It was not possible to stratify the analysis by commercial SARS-CoV-2 vaccine, nor by age, gender or clinical symptoms, due to the aggregation of the data. In view of the high proportion of SARS-CoV-2 vaccinated subjects in Spain, it was not possible to design a comparative study of vaccinated versus not vaccinated subjects.

The possibility exists that the case histories may not have documented enough information on the appearance of adverse reactions to SCIT, thereby limiting their description. The documented frequency may have been lower than real data. This is particularly possible about the description of local adverse reactions. The reporting of systemic adverse reactions was probably more concordant with the clinical real-world situation, in this sense we observed that the well-known safety profile was not affected.

CONCLUSIONS

The well-known safety profile of a SCIT using pollen or house dust mite allergoids has not been changed after the SARS-CoV-2 vaccine administration. No relevant differences in the incidence of local or systemic allergic reactions during the dose escalation phase were identified, so it is considered that the patient's safety has not been compromised to initiate SCIT after the SARS-CoV-2 vaccine administration.

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Conflict of Interest Statement

Nataly Cancelliere consultant for Allergopharma Spain, S.L.U. Begoña Soler-López was contracted by Allergopharma Spain, S.L.U. for the design, monitoring, statistical analysis and publications management. Remaining authors declare no conflict of interest.

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