ABSTRACT

This is a retrospective analysis of the clinical evolution of 14 patients diagnosed with allergic rhinoconjunctivitis (AR) and/or allergic asthma (AA) caused by *Alternaria alternata*, who were attended by the allergology service of Vega Baja Hospital of Orihuela (Alicante, Spain). The purpose was to assess the clinical impact and safety of 1-year of subcutaneous immunotherapy with a polymerized molecular allergoid of Alt a 1. Impact of the treatment on allergic diseases (mean number AR/AA episodes and ARIA/GINA classifications), changes in symptoms and prescribed medication, change in the global subjective clinical status of patients and satisfaction with the treatment were also evaluated. Adverse reactions were also recorded and analysed. After 1-year of treatment, fewer AR and AA episodes ($p < 0.05$) and improvements in ARIA/GINA classifications were observed. Significant improvements of symptoms ($p < 0.05$) and a resulting general reduction of the medication prescribed was also detected. Improvements in the global subjective clinical status and good satisfaction rates were observed. Only 1 patient presented a local and not clinically relevant adverse reaction. The treatment showed promising effects with a significant improvement in the clinical status of all patients with a good safety profile.

Keywords: Clinical evaluation, Subcutaneous immunotherapy (SCIT), *Alternaria alternata*, Allergic Rhinoconjunctivitis (AR), Allergic Asthma (AA).

Impact statement: 1-year of SCIT with a polymerized allergoid of Alt a 1 appears to have induced clinical benefits in 14 patients with allergic rhinoconjunctivitis and/or allergic asthma caused by *Alternaria alternata*.

List of abbreviations

AA: Allergic Asthma

AR: Allergic Rhinoconjunctivitis

ARIA: Allergic Rhinitis and its Impact on Asthma

ASIT: Allergen-specific Immunotherapy

CSMS: Combined Symptom and Medication Score

GINA: Global Initiative for Asthma

H1A: H_1 antagonist

LR: Local Reaction

NA: Non-Allergic

QoL: Quality of life

SCIT: Subcutaneous Immunotherapy

sIgE: Specific IgE

SR: Systemic Reaction

VAS: Visual Analogue Score

Introduction

Fungal allergy comprises a worldwide issue considering that fungi are characterized by growing in almost any type of environment and that exposure to these organisms can cause IgE-mediated disorders such as AR, AA and atopic dermatitis (1). Although these diseases do not usually threat patients´ lives, they can result in considerable morbidity (2, 3) and cause a significant deterioration in patients' quality of life (QoL) (4, 5).

On this matter, *Alternaria* species are considered the most important genus regarding fungal allergy, being *Alternaria alternata* the maximum exponent. Surveys performed on several European countries revealed that sensitization rate reaches 11.9% (6), with other surveys conducted in the USA providing similar results (7).

Allergen-specific Immunotherapy (ASIT) with *A. alternata* extracts has proved to have a great clinical potential (8, 9, 10, 11, 12). However, only two studies (11, 12) have been performed with treatments based on Alt 1, the most relevant allergen of *A. alternata* instead of the complete allergen extract. Furthermore, since the strategy in the preceding studies with isolated Alt a 1 was to administer the allergen in its native form, it would be of interest to assess if administration of chemically modified Alt a 1 is able to enhance the clinical benefits. This is a retrospective analysis of the clinical evolution of 14 patients with AR and/or AA caused by *A. alternata* who were treated with a polymerized molecular allergoid of Alt a 1 for at least 1-year.

Material and Methods

This retrospective analysis was focused on the clinical evolution of 14 patients treated with Modigoid® Alt a 1 who attended the subsequent 1-year visit at the allergology service of Vega Baja Hospital of Orihuela (Alicante). Subcutaneous immunotherapy (SCIT) was initiated between December 2019 and June 2020, out of the period in which *A. alternata* spores reach their highest rates in the region. Patients were reassessed 1-year after the initiation of treatment according to routine clinical practice.

All the clinical interventions of this study were conducted in accordance with the ethical standards established in the Declaration of Helsinki of 1946.

Selection of cases

Patients diagnosed of AR and/or AA due to *A. alternata* sensitization, for whom SCIT with Modigoid® Alt a 1 was prescribed in a routine clinical practice, were considered for analysis. *A. alternata* allergy was confirmed by a clinical history related to the exposure to *A. alternata*, a positive Prick test result (≥ 3 mm), and a specific IgE value ≥ class 2 (≥0.70 kU/L) by ImmunoCAP IgE assay. The prescription of treatment was decided following EAACI recommendations for the use of SCIT with aeroallergens. The analysis was conducted in all the patients attending the reassessment visit regardless of the final clinical impact of the treatment. None of the patients treated with Modigoid failed to attend the 1-year visit. No intervention either diagnostic or added follow-up was applied to patients, other than the usual clinical practice.

Study treatment

Patients received SCIT with purified polymerized Alt a 1 (Modigoid® Alt a 1, ROXALL Medicina España S.A., Zamudio, Spain). This vaccine has been shown to have a

hypoallergenic effect (13). Treatment schedule comprised a rush build-up of 0.2 mL (0.8 µg of Alt a 1) + 0.3 mL (1.2 µg of Alt a 1) separated by 15-minutes. Afterwards, patients received a maintenance dose of 0.5 mL (2 µg of Alt a 1) with an interval of 1-month till the end of the treatment. The treatment duration is intended for 3 years.

Outcomes measures:

a) Impact on AR and AA:

Mean number of AR and AA episodes requiring medical advice suffered within the last year before treatment initiation and during the 1-year treatment were compared. In addition, frequency (intermittent or persistent) and intensity (mild or moderate/severe) of AR according to ARIA guidelines (14) and intensity (mild, moderate or severe) of AA according to GINA guidelines (15) before and after 1-year were compared. As part of the common clinical practice, patients with asthma were classified according to frequency and severity of symptoms and not to the level of treatment required to control the disease.

b) Symptoms and prescribed rescue medication:

Symptoms related with AR or AA (rhinorrhoea, sneezing, congestion, itching, eye symptoms, dyspnoea, wheezing and cough) were assessed according to a 4-point Likert scale (0 = without symptoms, 1 = mild symptom, without interference with daily activities, 2 = moderate symptom, slight interference with daily activities and 3 = severe symptom, great interference with daily activities) in both baseline and 1-year visits and mean scores compared. Assessment was carried out considering the day of more severe symptoms in the last two months prior to the corresponding visit.

Additionally, impact of the treatment on prescribed rescue medication (dose and/or potency of medication) was also compared.

c) Specific IgE levels:

Serum specific IgE levels (kU/L) against *A. alternata* complete extract before and 1-year after the treatment (quantified by ImmunoCAP - Thermo Fisher Scientific/Phadia) were compared.

d) Satisfaction with the treatment:

Satisfaction with the treatment was rated by patients using a Visual Analogue Scale (VAS) ranging from 0 to 10, being 10 the highest degree of imaginable satisfaction, and 0 the lowest degree of satisfaction that may exist.

e) Global subjective clinical status:

Evolution of the global subjective clinical status of patients was assessed from both patients´ and physician´s perspective by a Likert Scale (much worse, worse, equal, better or much better).

f) Safety:

Any adverse reaction occurred during the treatment was analysed. Local reactions (LR) were classified according to the time of onset (immediate or delayed) and diameter. Systemic reactions (SR) were graded according to the WAO grading system.

Statistical analysis

For comparison of quantitative variables, a non-parametric test (Wilcoxon signed rank test) for paired data (basal and 1-year) was used. No statistical test was used for comparison of the categorical variables. A bilateral statistical significance level of 0.05 was applied. The entire analysis was carried out with the support of the statistical package SPSS version 26.

Results

Patients' baseline information

Patients' mean age was 26.2 years (range 16-42), being 8 men and 6 women. Twelve out of 14 patients were diagnosed with AR (6 with concomitant AA). Two patients were diagnosed only with AA. Two patients also had other associated allergic pathologies. Only 3 patients were monosensitized to *A. alternata*. Additionally, 3 patients had received previous immunotherapy for the treatment of *A. alternata* allergy (1 case), mites allergy (1 case) and other mould allergy (1 case).

Impact on AR and AA

Average number of annual AR and AA episodes requiring medical advice decreased from 2.85 (SD=1.57) to 0.85 (SD=0.80) (relative reduction of 70.2%) and from 3 (SD=1.69) to 0.75 (SD=0.46) (relative reduction of 75%), respectively, comparing baseline and 1-year visits ($p < 0.05$, Wilcoxon test). Among 12 patients suffering from AR, 11 experienced an improvement in their AR classification (ARIA) after 1-year; 7 patients improved from persistent to intermittent AR, 4 of them shifting from moderate/severe to mild AR and 3 remaining with mild AR. Furthermore, 3 patients improved from intermittent and mild AR to not having symptoms while one patient suffering from intermittent and moderate/severe AR decreased to intermittent but mild AR. Two patients did not improve their ARIA status. Additionally, among 8 patients with AA at baseline, 6 patients underwent an improvement in their GINA classification: one patient suffering from moderate asthma experienced a disappearance of symptoms and 5 remaining patients reported an attenuation of symptoms, from severe to mild asthma (2 patients) and from moderate to mild asthma (3 patients). On the contrary, 2 patients did not experience any variation in their AA classification.

Symptoms and prescribed rescue medication:

Significant improvement was observed after 1-year in all the symptoms assessed (rhinorrhoea, sneezes, congestion, itching, eye symptoms, dyspnoea, wheezing and cough), evidencing a decrease in each mean symptom-scoring ($p < 0.05$, Wilcoxon test) (Table 1). For rhinorrhoea, sneezes, itching, eye symptoms, dyspnoea and cough, mean relative decreases ranged from 50% to 83%. Congestion and wheezing reached a 100% relative decrease (total disappearance).

A general improvement in the prescribed rescue medication was also observed. Percentage of patients improving the dose/or potency of oral H1A antihistamines, topical H1A antihistamines, topical (intranasal or inhaled) corticoids, bronchodilators and other type of medication were 92%, 50%, 100%, 62.5% and 50% for each type of medication, respectively.

Specific IgE levels

A significant increase in mean specific IgE (sIgE) levels against *A. alternata* whole extract was evidenced after 1-year, from 17.56 kU/L (SD = 15.26) to 28.75 kU/L (SD=21.67) ($p < 0.05$, Wilcoxon test). Statistical comparison of sIgE levels was feasible in 13 patients (n = 13)).

Satisfaction with the treatment:

After 1-year, mean value of satisfaction with Modigoid treatment was 8.86 (SD=0.77). All patients rated their satisfaction between 8 and 10 (Figure 1a).

Global subjective clinical status:

Regarding the evolution of patients´ global subjective clinical status after 1-year of treatment (Figure 1 b), all patients reported a better or much better clinical status. This data coincided almost completely with the subjective clinical status reported by the physician.

Safety:

Only 1 patient (Patient 10) experienced a LR not clinically relevant (immediate oedema of less than 5 cm at the injection site). The reaction was resolved without requiring any treatment within 5-hours. No SR was recorded.

Discussion

ASIT with isolated Alt a 1 represents a novel and very encouraging therapeutic approach in treatment of allergic diseases caused by A. *alternata*. Results observed in this analysis suggest that 1-year of SCIT with a molecular allergoid of Alt a 1 has an impact on the global subjective clinical status of the patients revealed by an improvement in the 14 patients diagnosed with AR and/or AA. A relative reduction of 70.2% and 75% in average number of annual AR and AA episodes, respectively, were observed. The decrease was consistent with changes in the type and/or intensity of AR (ARIA classification) and AA (GINA classification), evidencing a clinical improvement in 11 out of 12 patients diagnosed with AR and in 6 out of 8 patients with AA.

Likewise, it seems that the treatment had a positive impact in the symptoms associated as mean relative decrease of symptom-scoring ranged between 50% and 100% for all symptoms. Improvements in symptoms related to AA may be of considerable interest for future clinical approaches considering the high prevalence of asthma among patients

sensitized to *A. alternata.* (16). Additionally, clinical improvements were accompanied by a global reduction of the dose/potency of prescribed rescue medication.

All these results are consistent with the results obtained in the study conducted by Tabar *et al.* in 2019 (12). In this study, combined symptom and medication score (CSMS) after 1-year of SCIT with native Alt a 1 was significantly lower in the high-dose group (0.37 µg of Alt a 1) comparing with placebo group, with no significant differences between low-dose (0.2 µg of Alt a 1) and placebo group. Considering the clinical benefits observed in this case analysis using a dose of 2 µg of polymerized Alt a 1, the study reinforces the fact that clinical benefits of SCIT with Alt a 1 appear to be dose dependent and further studies should consider this aspect.

Although there were general improvements in all the variables assessed, few deviations were also observed since several patients kept either the same ARIA or GINA classification. Obviously, considering that ARIA and GINA classifications represent useful but generic tools for diagnose, the lack of changes in this classification does not necessarily imply an absence of clinical improvement. Results of patients have to be correlated together with the evolution observed in the rest of the endpoints.

Changes in sIgE reported in this retrospective analysis seem to coincide with those usually found in AIT trials. In fact, the effect of AIT is usually an increase in sIgE at the beginning of therapy, especially using aluminium derived adjuvants, followed by a gradual decrease (17, 18). Thus it seems plausible that, as reported, serum IgE against *A. alternata* remain higher than the baseline IgE after 1- year of treatment with Alt a 1.

SCIT with polymerized Alt a 1 showed good safety results in all patients. Only one patient experienced a LR that could likely to be triggered by a discontinuation of the treatment during some months (associated to COVID pandemic). In any case, LR was not clinically

relevant. These good results may be associated with the lower IgE binding capacity of the allergoid but should be confirmed in further studies. Safety results could also have been positively influenced by the medication taken by patients when they started the SCIT, a common practice in most of patients prescribed with immunotherapy.

Another important issue is the impact of *Alternaria* spores or other allergen sources from the environment on study outcomes. On this matter, considering the fluctuation of spore levels in the study region within 2019, 2020 and 2021, similar or even higher outdoor concentrations were observed in the months prior to the 1-year assessment compared with the months prior to baseline (19). Therefore, the benefits observed appear to be mainly associated with the 1-year treatment and at least not greatly influenced by *Alternaria* spores in the environment. In the same way, all patients included in this analysis were subjects in whom symptoms were mainly related with *A. alternata* exposure. Thus, in polysensitized patients, other types of allergen sources should have not significantly influenced study outcomes.

Focusing on the doses of Alt a 1 administered in previous studies (maximum dose of 0.37 µg), this case analysis showed that polymerization of the allergen allows for administering higher doses with no safety concerns in our experience. In addition, the treatment could be given with a rush schedule reaching the maintenance dose in a single day, implying an induction phase considerably shorter than ones of the preceding studies with Alt a 1 ranging between four and five weeks (11, 12).

Considering the limitations (such as sample size or selection criteria) associated with this case analysis based on the common clinical practice, both the clinical impact and the safety results should be confirmed by future controlled studies. Moreover, patients analysed should be considered for future reassessments in order to determine the long-term effect (at least 3 years and up) of the treatment. In any case, despite these limitations,

SCIT with a molecular allergoid of Alt a 1 seems to be a highly effective therapeutic approach for *A. alternata*-allergic patients and further studies should determine in depth the potential health effects of this therapy.

Conclusions

This case analysis of 14 patients suffering from AR and/or AA caused by *A. alternata* showed that SCIT with a molecular allergoid of Alt a 1 appears to induce clinical notable benefits in these patients. The study suggests that this type of treatment seems to induce significant improvements in the symptoms related to AR and AA and in the amount of medication required to treat these two diseases. The treatment also showed very good safety results.

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Conflict of interest:

The author of this case analysis declares the absence of any types of conflict of interests with the study.

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This study was a compilation of cases of patients who were treated following the usual clinical practice.

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FIGURE LEGENDS:

Figure 1:

Title: Patients´ satisfaction with the treatment and evolution of the global subjective clinical status after 1-year of SCIT with a polymerized molecular allergoid of Alt a 1

Legend: **a.** Patients´-rated satisfaction values with 1-year of SCIT with a polymerized molecular allergoid of Alt a 1. VAS ranges from 0 to 10, being 10 the highest degree of imaginable satisfaction and 0 the lowest degree of satisfaction that may exist. **b.** Global subjective clinical status after 1-year of SCIT with a polymerized molecular allergoid of Alt a 1 compared with baseline (Likert Scale values: much worse, worse, equal, better or much better). The evolution of the clinical status was reported from both patients´ and physician´s perspective.

Note: n (%): (% calculated with n = 14). SCIT: Subcutaneous Immunotherapy; VAS: Visual Analogue Scale.

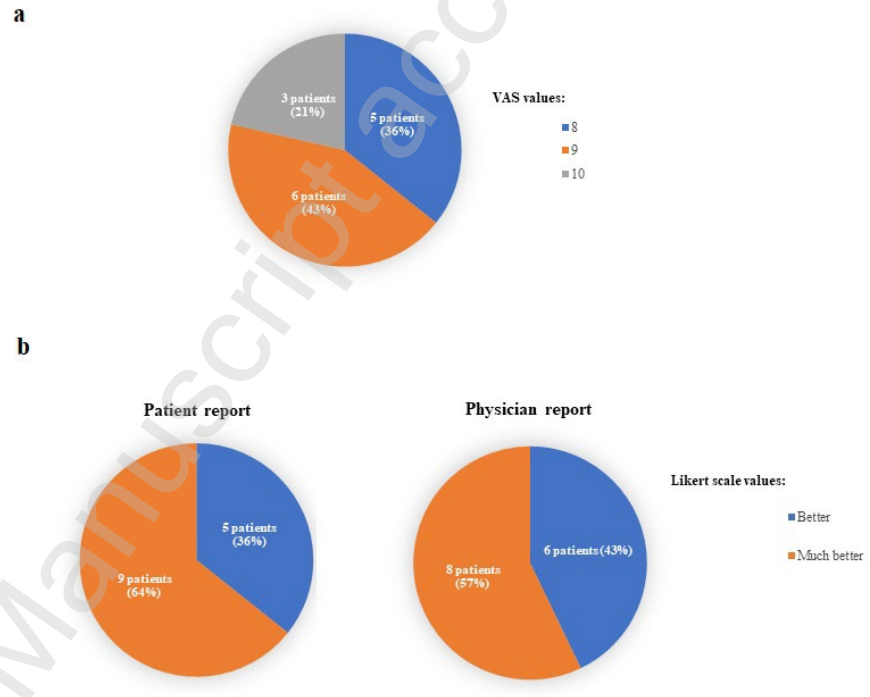

Table I: Evolution of patients´ symptom-scores after 1-year of SCIT with a polymerized molecular allergoid of Alt a 1

Symptom	Baseline visit	1-year visit	Absolute change between visits[1]	Relative change between visits (%)[2]	P[3]
Rhinorrhoea					
Mean (SD)	1.57 (0.85)	0.64 (0.63)	1.36 (0.75)	65.48 (36.08)	< 0.05
95% CI	(1.08 - 2.06)	(0.28 - 1.01)	(0.93 - 1.79)	(44.65 - 86.31)	
Median	2.00	1.00	1.50	58.35	
Sneezes					
Mean (SD)	1.43 (0.76)	0.36 (0.50)	1.07 (0.83)	83.33 (24.62)	< 0.05
95% CI	(0.99 - 1.87)	(0.07 - 0.64)	(0.59 - 1.55)	(67.69 - 98.98)	
Median	2.00	0.00	1.00	100.00	
Congestion					
Mean (SD)	0.79 (0.89)	0.00 (0.00)	0.79 (0.89)	100 (0.00)	< 0.05
95% CI	(0.27 - 1.30)	(0.00 - 0.00)	(0.27 - 1.30)	(100 - 100)	
Median	1.00	0.00	1.00	100.00	
Itching					
Mean (SD)	1.29 (0.73)	0.50 (0.52)	0.79 (0.58)	62.5 (0.58)	< 0.05
95% CI	(0.87 - 1.71)	(0.20 - 0.80)	(0.45 - 1.12)	(38.55 - 86.45)	
Median	1.00	0.50	1.00	50.00	
Eye symptoms					
Mean (SD)	0.57 (0.65)	0.14 (0.36)	0.43 (0.51)	78.57 (39.34)	< 0.05
95% CI	(0.20 - 0.94)	(-0.07 - 0.35)	(0.13 - 0.73)	(42.19 - 114.95)	
Median	0.50	0.00	0.00	100.00	
Dyspnoea					
Mean (SD)	1.14 (1.17)	0.43 (0.51)	0.71 (0.82)	60.42 (32.04)	< 0.05
95% CI	(0.47 - 1.82)	(0.13 - 0.73)	(0.24 - 1.19)	(33.63 - 87.21)	
Median	1.00	0.00	0.50	58.33	
Wheezing					
Mean (SD)	0.93 (0.92)	0.00 (0.00)	0.93 (0.92)	100 (0.00)	< 0.05
95% CI	(0.40 - 1.46)	(0.00 - 0.00)	(0.40 - 1.46)	(100 - 100)	
Median	1.00	0.00	1.00	100.00	
Cough					
Mean (SD)	1.07 (1.07)	0.36 (0.50)	0.71 (0.91)	58.33 (41.79)	< 0.05
95% CI	(0.45 - 1.69)	(0.07 - 0.64)	(0.19 - 1.24)	(23.40 - 93.27)	
Median	1.00	0.00	0.00	58.33	

Note. Symptom-scale ranges between 0 and 3 (0 = without symptoms. 1 = mild symptom. 2 = moderate symptom and 3 = severe symptom). [1] Absolute change between visits: (value of baseline visit - value of ~~one~~ 1-year visit).[2] Relative change between visits: (value of baseline visit - value of ~~one~~ 1-year visit)/value of baseline visit) *100. Percentages

greater than 0 indicate a decrease in the symptom-scale value after the treatment. This value could be calculated only in patients with baseline visit value > 0. Patient 14 increased its symptom-scale value for sneezes from 0 to 1.[3] Wilcoxon test. SCIT: Subcutaneous Immunotherapy SD: standard deviation; CI: confidence interval.