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EFFICACY AND SAFETY OF IMMUNOTHERAPY FOR ALLERGIC RHINITIS IN THE INDUCTION PHASE

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Abstract: Introduction. Allergen immunotherapy is an effective treatment for allergic rhinitis.**Aim:** to evaluate the efficacy and safety of subcutaneous immunotherapy during the induction phase according to the 2019 Mexican Immunotherapy Guide in patients with allergic rhinitis.**Material and methods:** analytical, prospective, quasi-experimental, longitudinal study in patients from 2 to 65 years of age with allergic rhinitis. Total Nasal Symptom Score and Portnoy were performed at the beginning and every two months, the data was analyzed with the IBM SPSS Statistics version 28 program. Summary and dispersion measures were used, comparing percentages by X2 and comparing means by variance ot Student test, considering a value of $p < 0.05$ as statistically significant. **Results:** 44 patients (22 women) were included, mean age 27.9 years. Mean symptom score before starting immunotherapy: 7.15, 4.04 at 2 months, 3.20 at 4 months and 2.77 at 6 months. Adverse effects occurred in 7.9% of the applications.**Conclusions:** The modifications stipulated for the induction phase in the 2019 Mexican Immunotherapy Guide are safe and effective in allergic rhinitis.
Keywords: efficacy, induction, subcutaneous immunotherapy, allergic rhinitis, safety.

INTRODUCTION

Allergic rhinitis (AR) is the most common cause of chronic rhinitis, affecting 10-20% of the population1 and is defined as an inflammatory process of the nasal mucosa, caused by allergens, typically mediated by IgE. It is characterized by the infiltrate of inflammatory cells in the mucosa and submucosa. This pathology is mediated by a type 1 hypersensitivity reaction. It has been observed that patients with allergic diseases present a deficiency of LsTreg. 2

To suspect RA in a patient, a clinical history compatible with allergic etiology

and one or more of the following signs and symptoms must be available: nasal congestion, rhinorrhea, nasal itching, sneezing, pale nasal mucosa, ocular hyperemia and epiphora, as well such as skin tests or specific serum IgE to determine the causative allergen and thus direct allergen immunotherapy (ATI)3-5

When the pharmacological treatment options for RA are not sufficient to improve symptoms, it is pertinent to use AIT,Since it is the only therapy that has been shown to modify the natural history of allergic pathologies, the evidence so far supports its use in: allergic asthma, hypersensitivity to hymenoptera venom and RA. 6

The approved routes of administration for this are the subcutaneous and sublingual routes, the former being recognized as the "gold standard". Its mechanism of action can be seen in figure 1.7, 8

The mechanisms through which AIT works differ if they are short-term or long-term and it is clinically translated when we observe a patient who received an incomplete regimen in the return of symptoms some time after his last dose. The clinical effect of SCIT can be measured with clinical parameters and with validated questionnaires such as the TNSS (Total Nasal Symptom Score), and assessment of adverse reactions derived from its use with the Portnoy scale.

Due to the recent publication of the Mexican Immunotherapy Guide in 2019 (GUIMIT 2019), it was decided to carry out this study with the objectives of evaluating the safety of AIT applied subcutaneously through the Portnoy scale, as well as the severity of symptoms through the TNSS in patients with a confirmed diagnosis of RA with sensitization to inhalant allergens.

MATERIAL AND METHODS

This is an analytical, prospective, quasi-experimental, longitudinal study in the Department of Allergy and Clinical Immunology of the Hospital Universitario de Puebla, in which people with RA recently diagnosed through in vivo (skin prick tests) or in vitro tests were included. (Allergy EUROLINE Inhalation Mexico_V2), in an age range of 2 to 65 years and who presented indications to start ITSC being accepted by the patient by signing an informed consent. Patients were studied in two periods, the first from October 2019 to March 2020 and the second from November 2020 to April 2021. Data were collected through the TNSS and Portnoy questionnaires bimonthly.

Patients included in the study were given SCIT and when necessary management was given with seawater (equivalent to 2.3% NaCI) 1 shot every 12 hours and fluticasone furoate nasal spray (27.5 µg/50 µl) 1 shot every 24 hours for the first 2 months. The sample size that was calculated as necessary for this study was 29 patients; however, 44 study subjects were included. Non-standardized extracts (w/v) were used in this work and the concentration and quantity guidelines of the extracts used were those stipulated in GUIMIT 2019.

Statistic analysis. The mean TNSS score, the rate of adverse events per number of patients and per number of applications were determined. At the end of the data collection from the questionnaires, summary and dispersion measures were used, comparing percentages by X2 (chi-square) and comparing means by Student's ot variance, considering the value of $p < 0.05$ as statistically significant. The collected data were analyzed using the computer statistical program (IBM SPSS Statistics version 28).**Ethical aspects.** The present research study was reviewed and authorized for its execution by the Research Ethics Committee of the ``hospital universitario de puebla``, it is guided by the regulations on Research in human beings derived from the General Health Law of

the United Mexican States, as well as by related international standards, such as the Declaration of Helsinki and its revisions, as well as the World Medical Association Guidelines for Good Clinical Practice.

RESULTS

A total of 44 patients were included in this study, of which 22 (50%) were female. The mean age was 27.9 years (SD 16.4). The average TNSS score found before the start of the ITSC was 7.15 (SD 3.58), at 2 months after its start it changed to 4.04 (SD 3.05), at 4 months it was 3.20 (SD 2.26) and at 6 months From 2.77 (SD 2.65) data that can be seen in Figure 2, when comparing the initial TNSS score with that of the last measurement made using the "t" test for paired samples, a t value of 7.6 was obtained with statistical significance. (p= <.001).

Other results that we found were those collected through the Portnoy scale, of a total of 176 applications, there were 14 adverse effects (7.9% during the dose increase phase); of these, twelve were local (6.8%) and two were grade 3 systemic (1.1%). Figure 3, when comparing the results of the initial and final Portnoy questionnaires using the "t" test for paired samples, a t value of 0.829 was obtained, but without statistical significance (p=.206). It was also determined that the rate of individuals who presented adverse reactions was 27% (12 of 44 participants) and of these 12, 5 were women (41.6%).

DISCUSSION

The decrease in allergic symptoms that we found in this study is similar to that reported by a study carried out at this same location using a scheme based on GUIMIT 2011.9 There are multiple studies that demonstrate the efficacy of AIT in reducing rhinitis tetrads, which is consistent with the application of the new guidelines. It must be noted that the tools used in other studies are not only clinical, some even use serum determinations such as total IgE, specific IgE, specific IgG4, 10 but there are also studies in which the "Total Nasal Symptom Score" is used for evaluation. of improvement over time. 11,12,9

The rate of adverse effects that we found attributable to AIT, assessed through the Portnoy scale, was lower for local reactions as published in GUIMIT 2019, where it is established that between 26 and 82% are observed. The rate of systemic adverse reactions depends on the country; In the US, a frequency of 0.3% was reported, in Europe 2.1%, in Germany 5.2% and specifically in Mexico 1.6%, the latter slightly higher than what we found in the present study.11

The discrepancy in local reactions may be due to the existence of different dose increase schemes with grouped, cluster, rapid (rush) and ultra-rapid (ultrarush) administration, as well as the standardized and non-standardized extracts used (p /v). On the other hand, the use of different scales to assess adverse effects also influences, for example, in the Portnoy scale there is no item for pain assessment, it is even known that the season of the year will be a factor that will modify the response to the ITA does temporarily correlate the application of a certain aeroallergen with its pollination.

In the study by Valle et al., using the same therapeutic extracts (Allergomex®) in the present study, they observed a rate of 9.03% for local reactions, without presenting systemic reactions. 9 This difference in terms of the presence of systemic reactions is probably due to differences in the populations, since in this study there were only patients with allergic rhinitis and in the other study asthma and allergic rhinitis.

REFERENCES

1. Small P, Keith PK, Kim H. **Allergic rhinitis**. Allergy Asthma Clin Immunol. 2018;14(2):32-41

2. Tyurin YA, Lissovskaya SA, Fassahov RS, Mustafin IG, Shamsutdinov AF, Shilova MA et al. **Cytokine Profile of Patients with Allergic Rhinitis Caused by Pollen, Mite, and Microbial Allergen Sensitization**. Journal of Immunology Research. 2017;2017:1-7

3. Dhami S, Nurmatov U, Arasi S, Khan T, Asaria M, Zaman H et al**. Allergen immunotherapy for allergic rhinoconjunctivitis: a systematic review and meta-analysis. Allergy**. 2017;72(11):1597-631.

4. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. **Allergen injection immunotherapy for seasonal allergic rhinitis (Review)**. *Cochrane Database* Syst Rev. 2007; 2007(1): 1-91.

5. Engeroff P, Caviezel F, Mueller D, Thoms F, Bachmann MF, Vogel M. **CD23 provides a noninflammatory pathway for IgE-allergen complexes**. J Allergy Clin Immunol. 2020;145(1):301-311

6. Larenas-Linnemann D, Rodríguez-Pérez N, Luna-Pech JA, Rodríguez-González M, Blandón-Vijil MV, Del-Río-Navarro BE et al. **Compromising between European and US allergen immunotherapy schools: Discussions from GUIMIT, the Mexican immunotherapy guidelines**. World Allergy Organ J. 2020;13(8):1-17.

7. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. **Standards for practical allergen-specific immunotherapy**. Allergy. 2006;61(82):1-20.

8. Senti G, Kündig T. **Novel delivery routes for allergy immunotherapy: intralymphatic, epicutaneous, and intradermal**. Immunol Allergy Clin North Am. 2016;36(1):25-37.

9. Valle-Rodríguez, F, López- García, A I, Rivero-Yeverino, D, Caballero-López, C G, Papaqui-Tapia, J S, Ruiz-Márquez, I P et al. **Eficacia y seguridad de inmunoterapia subcutánea para alérgenos inhalables en pacientes con alergia respiratoria**. Rev Alerg Mex. 2019;66(3):301-307.

10. Kopp MV, Bovermann X, Klimek L. **Accelerated Dose Escalation with Three Injections of an Aluminum Hydroxide-Adsorbed Allergoid Preparation of Six Grasses Is Safe for Patients with Moderate to Severe Allergic Rhinitis**. Int Arch Allergy Immunol. 2020;181(2):94-102.

11. Larenas-Linnemann D, Luna-Pech JA, Rodríguez-Pérez N, Rodríguez-González M, Arias-Cruz A, Blandón-Vijil MV et al. **Guía mexicana de inmunoterapia 2019**. Rev Alerg Mex. 2019; 66(1):1-105

12. Meltzer EO, Schatz M, Nathan R, Garris C, Stanford RH, Kosinski M**. Reliability, validity, and responsiveness of the Rhinitis Control Assessment Test in patients with rhinitis**. J Allergy Clin Immunol. 2013; 131(2):379-386

APPENDICES

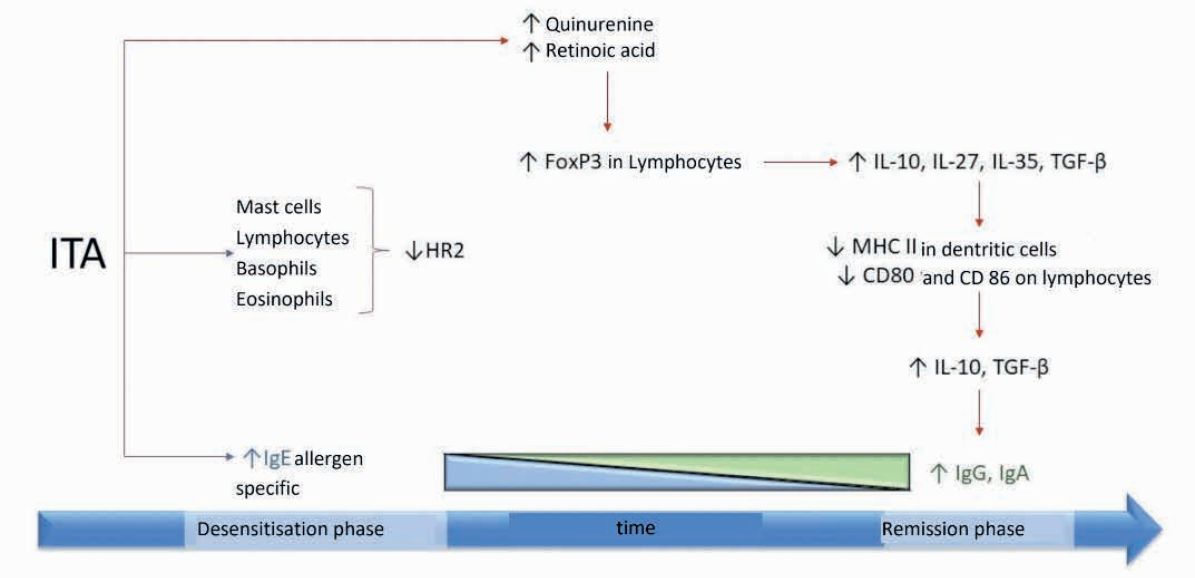

Figure 1. ITA mechanism of action. In the desensitization phase lThe reactivity of mast cells and basophils decreases from the administration of the first doses possibly due to an increase in inhibitory receptors type 2 for histamine (HR2) in mast cells, basophils, lymphocytes and eosinophils. Initially there is an increase in specific IgE for the allergen and then a gradual decrease, as well as a gradual increase in other immunoglobulin isotypes: IgG1, IgG4 and IgA, which function as blockers of the allergic response towards the allergen. In the Freferral requestfavors the production of kynurenine and retinoic acid that induce the expression of Foxp3 in LsT that helps the production of regulatory cytokines such as IL-10, transforming growth factor beta (TGF-β), IL-27 and IL-35), that induce changes especially in dendritic cells of the skin and mucous membranes, so that their histocompatibility molecules (MHC-II) decrease to present allergens, in such a way that the coactivating molecules (CD80, CD86) of T lymphocytes also decrease and so that they produce IL -10 and TGF-β, becoming tolerogenic or regulatory dendritic cells. The release of IL-10 and TGF-β serve to enhance the production of IgG and IgA blocking antibodies.

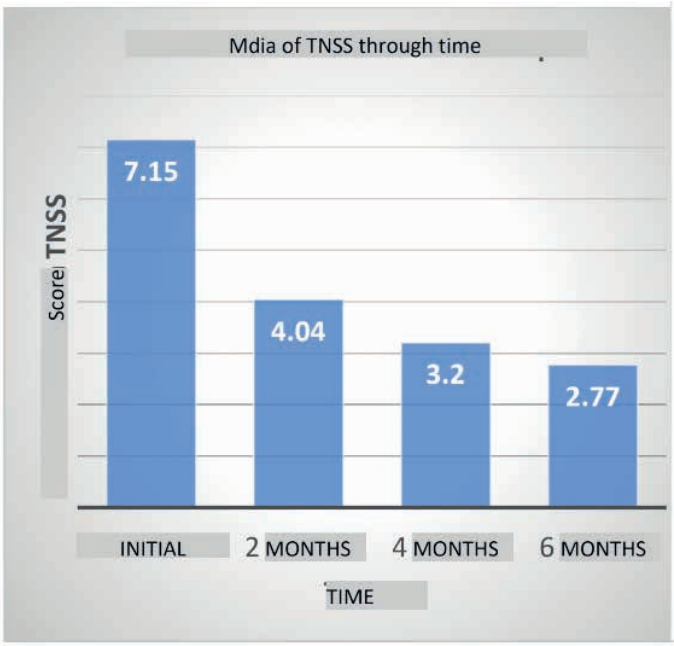

Figure 2. It is observed how the average score changed from the beginning of the dose increase phase to its end.

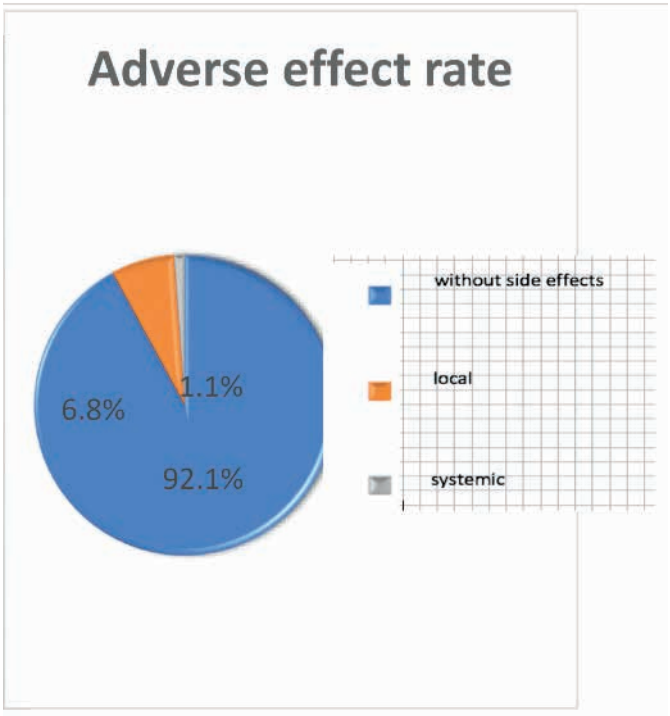

Figure 3. The rate of adverse effects is observed according to the number of applications of immunotherapy broken down as local, systemic and the percentage of patients who did not present adverse effects derived from its use.