OPEN ACCESS Freely available online

Journal of Vaccines & Vaccination

Short Communication

The Current State of Safety of Allergen Immunotherapy

Cristoforo Incorvaia[1*], Francesco Pucciarini[2], Bruena L. Gritti[3], Alessandro Barone[2], Erminia Ridolo[2]

[1]Cardiac/Pulmonary Rehabilitation, ASST Pini-CTO, Milan, Italy; [2]Medicine and Surgery Department, Allergy and Clinical Immunology, University of Parma, Parma, Italy; [3]School of Human Sciences, Gaetana Agnesi, Milan, Italy

ABSTRACT

Allergen Immunotherapy (AIT) is aimed at treating allergy by modifying the immunological response to allergens. However, administration of the causative allergen by Subcutaneous Immunotherapy (SCIT) to a sensitized patient may result in severe, and rarely fatal, systemic reactions. The identification of risk factors for anaphylaxis, especially concomitant uncontrolled asthma, has led to a significant reduction, but not yet elimination, in fatalities. The option of Sublingual Immunotherapy (SLIT) has been shown to be safer, with no fatalities reported thus far and including rare episodes of anaphylaxis, but the fact that the treatment is self-administered by the patient requires precautions and careful education.

Keywords: Subcutaneous immunotherapy; Sublingual immunotherapy; Safety; Severe systemic reactions; Fatalities

INTRODUCTION

The birth of Allergen Immunotherapy (AIT) dates back to 1910, when Noon tried to treat the grass pollen allergy by administering increasing doses of a pollen extract through subcutaneous route [1]. This treatment was purely empirical, given that the pathophysiological mechanisms of allergy were totally unknown, but it was able to reduce allergic symptoms. At the same time it was apparent that the injection of pollen extracts could cause systemic allergic reactions, including anaphylaxis. In the 1980s, when pathophysiological knowledge was significantly advanced and clinical efficacy had been demonstrated in numerous randomized placebo-controlled trials, the introduction of high biological potency products was associated with a series of fatal reactions that prompted careful reconsideration of the role of AIT [2,3]. The quest for safer methods led to the development of allergoids, which were aimed at reducing allergenicity while leaving immunogenicity unchanged. This was obtained by polymerizing the native allergens by using cross-linking agents, such as glutaraldehyde or formaldehyde, or with subsequently developed techniques such as formalinized alum-absorption and use of agents such as L-tyrosine or monophosphoryl lipid A as adjuvants [4] The other important step was the introduction, as alternative route to Subcutaneous Immunotherapy (SCIT), of Sublingual Immunotherapy (SLIT) which has been widely used in the last 30 years [5]. Both approaches resulted in satisfactory safety profiles, with no fatalities and rare anaphylactic reactions.

DISCUSSION

The progress of SCIT safety

A major advance has been the recognition of uncontrolled asthma when receiving the allergen injection as a critical factor for fatal and near fatal reactions [6]. Avoiding this risk resulted in a significant reduction in fatal reactions, but not their disappearance. A further risk factor is the administration of too high allergen doses. For example, comparing different dosages of the dust mite major allergen Der P 1, very different rates of Systemic Reactions (SRs) were observed, corresponding to 20% and 43% with the maintenance dose of 7 mcg and 21 mcg, respectively [7]. A recent review listed the factors enhancing the risk of anaphylactic reactions: they were previous SRs to SCIT, lack of dose reduction during the peak pollen season in patients with strong responses to skin tests, and physician's error in administering SCIT, such as mistaken patients identification and administration of wrong allergen extract. This makes recommendable that patient identification and verification the allergen extract to be administered is done by two different health workers and [8]. When risk factors for SRs are recognized, prevention by premedication would be feasible; however antihistamines prior to allergen injection have been shown to be effective in Hymenoptera venom immunotherapy [9], while there are no convincing data for respiratory allergy. Otherwise, there is evidence on the capacity to prevent SRs of the anti-IgE antibody omalizumab, as demonstrated by four randomized, placebo-controlled trials in patients with respiratory allergy [10], while a dose dependence of protection was reported for venom

Correspondence to: Cristoforo Incorvaia, Cardiac/Pulmonary Rehabilitation, ASST Pini-CTO, Milan, Italy, Email: cristoforo.incorvaia@gmail.com

Received: December 28, 2020; **Accepted:** January 13, 2021; **Published:** January 20, 2021

Citation: Incorvaia C, Pucciarini F, Gritti BL, Barone A, Ridolo E (2021) Estimation of Fatality Rate in Africa through the Behavior of COVID-19 in Italy Relevance to Age Profiles. J Vaccines Vaccin. S10: 004.

immunotherapy [11].

The SLIT safety, from liquid preparations to tablets

The first generation of SLIT products was based on liquid preparations from the most important allergen sources, including pollens, dust mites, molds, and animal epithelia, with variable allergen dosages according to different producers. When the safety of various preparations was analyzed, differently from SCIT, no dose dependence of adverse reactions (mostly consisting of local reactions at the site of contact with the allergen), was found [12]. Nevertheless, extremely high allergen doses were later reported to cause anaphylaxis, as reported in the case of a patients who, after three years of SLIT, had not taken doses for three weeks and then recovered all doses not taken previously in one solution [13]. The new generation of SLIT products in tablets was driven by the need to fulfill the requirements from regulatory agencies in terms of standardized quality [5]. These products ensure batch-to-batch reproducibility of allergenic potency and enable high quality standards. However, the superior allergenic potency was sometimes associated with anaphylactic reactions. The first report concerned two patients admitted to SLIT by one-grass pollen tablets (which starts directly with the maintenance dose) because of previous severe SRs to SCIT, who developed anaphylaxis at the first dose [14]. This event prompted the recommendation by the European Academy of Allergy and Clinical Immunology to avoid SLIT with no buildup phase in patients with previous severe SRs to SCIT [15]. Regarding the trials with dust mites, one measured in Index of Reactivity (IR) and the other in SQ (Standardized Quality), a dose dependence of adverse reactions was apparent, since among the different doses tested those most affected by reactions were the highest, i.e, 500 for the IR product [16] and 6 for the SQ product [17]. Treatment was stopped due to reactions in 11% and 2%, respectively. Also global analyses are available. Nolte et al. analyzed the safety data from 29 trials including one-grass pollen, ragweed pollen, and dust mite tablets. Despite no systemic reaction was classified as severe, epinephrine was administered 7 times with ragweed, 8 times with dust mite, and 10 times with one-grass SLIT tablets. Of note, epinephrine was also administered to 9 placebo-treated patients. The authors concluded that epinephrine use for adverse events to SLIT tablets, mostly occurring within the first week of treatment and not being severe, is uncommon [18]. In a meta-analysis of 65 randomized placebo controlled trials of SLIT in patients with allergic asthma, in which patients with previous reactions to AIT were not admitted, the authors concluded that "SLIT may be a safe option for people with well-controlled mild-to-moderate asthma and rhinitis who are likely to be at low risk of serious harm" [19].

CONCLUSION

The identification of risk factors for severe SRs led to a significant reduction in fatalities to SCIT, although complete prevention has not yet been achieved. SLIT, born with the aim of a higher safety, met this need, since no fatality has ever been reported. However, since the treatment is self-administered by the patient, it is essential that the first dose is received under medical supervision and that the patient receives all information to avoid dosing errors.

REFERENCES

1. Noon L. Discussion on vaccine therapy: Its treatment, value, and limitations. Proc R Soc Med. 1910;3:161–164.
2. CSM Update: Desensitising vaccines. Br Med J (Clin Res Ed). 1986;293(6552):948.
3. Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). J Allergy Clin Immunol. 1987;79(4):660-677.
4. Compalati E, Incorvaia C, Cavaliere C, Masieri S, Gargiulo A, Mistrello G, et al. The role of allergoids in allergen immunotherapy: From injective to sublingual route. Eur Ann Allergy Clin Immunol. 2020;52(5):195-204.
5. Passalacqua G, Bagnasco D, Canonica GW. 30 years of sublingual immunotherapy. Allergy. 2020;75(5):1107-1120.
6. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: National surveillance study on allergen immunotherapy (2008–2013). Ann Allergy Asthma Immunol. 2016;116(4):354-359.
7. Haugaard L, Dahl R, Jacobsen L. A controlled dose-response study of immunotherapy with standardized, partially purified extract of house dust mite: Clinical efficacy and side effects. J Allergy Clin Immunol. 1993;91(3):709-722.
8. Sánchez-Borges M, Bernstein DI, Calabria C. Subcutaneous immunotherapy safety: Incidence per surveys and risk factors. Immunol Allergy Clin North Am. 2020;40(1):25-39.
9. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilò MB, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. Allergy. 2018;73(4):744-764.
10. Shankar T, Petrov AA. Omalizumab and hypersensitivity reactions. Curr Opin Allergy Clin Immunol. 2013;13(1):19-24.
11. Boni E, Incorvaia C, Mauro M. Dose-dependence of protection from systemic reactions to venom immunotherapy by omalizumab. Clin Mol Allergy. 2016;14(1):1-4.
12. Gidaro GB, Marcucci F, Sensi L, Incorvaia C, Frati F, Ciprandi G. The safety of sublingual-swallow immunotherapy: An analysis of published studies. Clin Exp Allergy. 2005;35(5):565-571.
13. Blazowski L. Anaphylactic shock because of sublingual immunotherapy overdose during third year of maintenance dose. Allergy. 2007;63(3):374.
14. De Groot H. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. Allergy. 2009;64:963-964.
15. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI guidelines on allergen immunotherapy: Allergic rhinoconjunctivitis. Allergy. 2018;73(4):765-798.
16. Bergmann KC, Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. J Allergy Clin Immunol. 2014;133(6):1608-1614.
17. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: A randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2014;134(3):568-575.
18. Nolte H, Casale TB, Lockey RF, Fogh BS, Kaur A, Lu S, et al. Epinephrine use in clinical trials of sublingual immunotherapy tablets. J Allergy Clin Immunol Pract. 2017;5(1):84-89.
19. Fortescue R, Kew KM, Tsun Leung MS. Sublingual immunotherapy for asthma. Cochrane Database Syst Rev. 2020;9:CD011293.