Acta Biomed 2021; Vol. 92, N. 1: e2021037 DOI: 10.23750/abm.v92i1.9096

Original article

Evaluation of safety and tolerability of a rush up-dosing allergen-specific immunotherapy with grass pollen, birch, hazel, and alder allergoid in children with allergic rhinoconjunctivitis, with or without asthma

Giovanni Maria Traina[1], Alberto Martelli[2], Salvatore Barberi[3], Amelia Licari[4], Gianluigi Marseglia[4], Maria Angela Tosca[5], Giorgio Ciprandi[6]

[1]ASST-Melegnano-Martesana (Milan), Pediatrics and Neonatology Unit, Melzo e Cernusco sul Naviglio Hospital, Italy; [2]ASST-Rhodense (Milan), Pediatrics Unit, Garbagnate Milanese Hospital, Italy; [3]ASST-Rhodense (Milan), Pediatrics Unit, Rho Hospital, Italy; [4]Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [5]Allergy Center, Istituto G. Gaslini, Genoa, Italy; [6]Allergy Clinic, Casa di Cura Villa Montallegro, Genoa, Italy

Summary. *Background:* Usually, the number of injections required to achieve the maintenance dose in subcutaneous immunotherapy (SCIT) is relatively small for some of the currently used allergens, but this may still be uncomfortable for patients, thus compromising adherence and compliance. *Objective:* The purpose of this study was to evaluate the safety and tolerability of a dose acceleration of a conventional induction schedule using an allergoid extract of grass pollen, birch, hazel, and alder, needed to achieve the ideal maintenance dose. *Methods:* In this open-label study, 34 patients with allergic rhinoconjunctivitis, with or without asthma, were treated with SCIT using an allergoid for grass pollen or birch or mix trees with an increase in accelerated induction dose comprising only 3 injections, one per week, compared to a conventional induction pattern in five injections (once a week). Safety determination was assessed by evaluating local and systemic adverse events. Tolerability was evaluated by patients and physicians who performed the treatment. *Results:* No treatment-related adverse events were observed in any of the patients undergoing rush SCIT. No local reactions, no systemic reactions of any degree (WAO Grade) have been observed. Tolerability has always been rated as very good by both patients and physician. *Conclusions:* The induction phase, needed to achieve the monthly maintenance dose for a pollen extract, can be greatly accelerated, ensuring a tolerability comparable to that of the conventional schedule. (www.actabiomedica.it)

Key words: up-dosing, allergoid, safety, subcutaneous immunotherapy, tolerability

Introduction

In Europe, the most common cause of respiratory allergy is caused by the sensitizations to pollen allergens (1). For over 100 years, pollen allergy has been treated by subcutaneous immunotherapy (SCIT), gradually increasing allergen doses to an effective maintenance dose.

SCIT has now been shown, in numerous clinical studies and meta-analysis, to be effective both in allergic asthma (2) and in allergic rhinoconjunctivitis (3). Likewise all long-term treatments (4), adherence and compliance to SCIT are compromised by some factors. Certainly, one of the most important is related to the commodity needed to receive allergen administration, which not only binds the patients, and that

in the case of pediatric patients also commits the accompanying parents (5-7). The acceleration of the induction scheme of up-dosing (build-up) could allow that the patients achieve the maintenance dose faster, reducing significantly the disadvantages, and consistently increasing the adherence and the compliance to the treatment (8, 9). The shift from aqueous extracts to depot preparations, adsorbed to aluminum hydroxide or other adjuvants, allowed to significantly reduce the number of injections. Cluster and rush schedules were introduced to further accelerate dose build-up. However, these schemes carry an increased risk of adverse reactions, potentially severe (10-14). The development of chemically modified allergens, the so-called allergoids, achieved the combined goal of accelerating dose escalation and administering therapeutic doses with a reduced potential for side effects, while maintaining immunogenicity (11,12). Grass pollen, birch, hazel, and alder allergoids have been demonstrated to be effective and safe in previous studies in rapidly achieving maintenance dose (15,17,18). This accelerated build-up phase can reduce the inconvenience to parents and improve the attractiveness and adherence to SCIT.

The purpose of this study was to evaluate the safety and tolerability of up-dosing accelerated schedule for grass pollen and birch pollen allergoid, able to reach the maintenance dose in just three weeks.

Methods

This was an observational study, open-label, performed at a second-level pediatric allergology service, in children.

Inclusion criteria were: age between 8 and 17 years, both genders, diagnosis of allergic rhinoconjunctivitis, pollen allergy documented by positive skin prick test and/or serum specific IgE.

Exclusion criteria were: concomitant or past immunotherapy to other allergens, uncontrolled asthma, and diseases able to interfere the interpretation of results.

Test product

Purethal Grasses (Hal Allergy, Milan, Italy) is a mixture of grass pollens, and Purethal Tree is a mixture of birch, hazel, and alder pollens. Pollen allergens were chemically modified with phenol and adsorbed with aluminum hydroxide. Purethal is titled in units of 20.000 AUM/mL.

Treatment schedule

The patients were treated for 3 weeks in the induction phase and subsequently, after reaching the maintenance dose of 0.5 mL, they continued with this last dose every 4 weeks. Induction injections were administered weekly, gradually increasing the dose, provided that the previous dose was well tolerated. Induction injections were given weekly. Patients were given an initial dose of 0.1 mL the first week, equal to 2,000 AUM, a dose of 0.3 mL the second week, equal to 6,000 AUM, and a dose of 0.5 mL the third week, equivalent to 10,000 AUM. When the maximum dose was reached, a maintenance dose of 0.5 mL (10,000 AUM) was maintained every 4 weeks. After each administration the patients remained under observation for at least 40 minutes.

Criteria of evaluation

Adverse events (AEs) and serious adverse events (SAEs) were assessed by the investigators. The security endpoints were defined as follows:

- Mild: transient symptoms, no interference with the patient's daily activities;
- Moderate = marked symptoms, moderate interference with the patient's daily activities;
- Severe = significant interference with the patient's daily activities.

The incidence and intensity of systemic reactions after injections were evaluated according to the WAO classification. During the treatment phase, the variations of the vital life parameters were monitored (blood pressure, oxygen saturation, heart rate, and body temperature) before, during and after the treatment itself.

Ethical aspects

A written informed consent was signed by all the parents of the children. The IRB of the ASST-Rhodense approved the procedure.

Statistical analysis

The safety data were analyzed in a descriptive way. The sample size was calculated and was sufficient.

Results

Globally, 34 patients (18 males and 16 females, aged between 8 and 17 years) underwent to an up dosing protocol to achieve the ideal maintenance dose set in 0.5 mL month.

Clinical characteristics of patients, all with allergic rhinitis or allergic rhinitis and asthma due to allergy toward grass pollen, birch and mix trees, were homogeneous. Equally, their demographic and ethnic characteristics were homogeneous.

Adverse events

During the entire duration of the treatment, which involved up-dosing in 3 weeks, no adverse event of any kind, even mild, occurred. No swelling, erythema or itching at the injection site has been reported. Even at home, days after dosing, patients did not experience any side effects or adverse reactions.

Systemic reactions

No systemic adverse reactions (WAO Grade) occurred. Adrenaline has never been administered.

Tolerability

After treatment, the overall tolerability was assessed by investigators and patients separately. Investigators rated the treatment tolerability as "good" or "very good" for all 34 patients.

Discussion

This study showed that increasing the dose of an allergoid for subcutaneous allergen immunotherapy, such as grass pollens and tree mix (hazel, birch, and alder) pollens, can be performed in an accelerated way over three weeks, maintaining the same safety profile as the conventional scheme of six weeks. No increase in systemic or local adverse events, consequent to accelerated up-dosing, was observed. This accelerated up dosing scheme offers many advantages. It allows patients to achieve the recommended maintenance dose more quickly with consequent clinical benefits and the immunological responses of subcutaneous allergen immunotherapy itself (8,9,11,19,20). Moreover, concerning pediatric patients (5-17 years old), this speeded up scheme is able to meet the personal needs, work, study, and other activities, and this increases the therapeutic adherence and compliance to allergen immunotherapy (AIT). As previously expressed in several studies, the efficacy of AIT, administered by subcutaneous route, like all long-term treatments, can be compromised by poor adherence and/or compliance to therapeutic programs, even if less than the sublingual allergen immunotherapy. In this regard, it is interesting to note the results of a study comparing adherence to accelerated and conventional up-dosing schemes, where the majority of patients who have given up therapy belong to the traditional dose-increase scheme (9). Many studies have now evaluated the safety of the accelerated dose increase phases by reducing the number of injections or by adopting rush programs (multiple dose and increasing allergen doses every 15 to 60 minutes for a period ranging from one to three days until the maintenance dose is reached) or clusters (an intermediate form between conventional induction scheme and accelerated induction of dosing). With this latter scheme, called "cluster", two or three injections (increasing doses) are often administered to reach the maintenance dosage in four to eight weeks, unlike three or six months of the traditional scheme. Between these two, cluster schemes are characterized by a better risk/benefit ratio.

This study shows that an accelerated up-dosing scheme compared to the traditional one was well tolerated by pediatric patients, not increasing the frequency of local and systemic reactions, and was assessed very well by investigators, patients and parents.

Patients in treatment were kept under observation for the same time considered during traditional up-dosing schemes (20-26). The efficacy of the treatment demonstrated with a cumulative allergoid dose of 0,9 mL in three weeks, equal to 18,000 AUM re-

sulted in clinical benefit after pre-seasonal treatment of all treated patients as documented with monitoring of symptoms score and rescue medications. This reinforces the evidence that AIT efficacy depends on the maintenance dose (27).

Conclusions

The build-up dosing scheme of an extract of grass pollen or mix trees allergoid can be accelerated compared to the conventional one, from six to three weekly intervals, keeping the safety profiles and tolerability comparable. A not secondary objective of this scheme is, in our view, to attract more patients to SCIT, thus benefiting from its clinical and immunological effects.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Panzner P, Panzner P, Vachová M, Vítovcová P, Brodská P, Vlas T. A comprehensive analysis of middle-European molecular sensitization pro les to pollen allergens. Int Arch Allergy Immunol. 2014;164(1):74–82.
2. Abramson MJ, Puy RM, Weiner JM, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev. 2010;(8):Cd001186.
3. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev. 2007;(1):Cd001936.
4. Passalacqua G, Baiardini I, Senna G, Canonica GW. Adherence to pharmacological treatment and specific immunotherapy in allergic rhinitis. Clin Exp Allergy. 2013;43(1):22–8.
5. Cox LS, Hankin C, Lockey R. Allergy immunotherapy adherence and delivery route: location does not matter. J Allergy Clin Immunol Pract. 2014;2(2):156–60.
6. Reisacher WR, Visaya JM. Patient adherence to allergy immunotherapy. Curr Opin Otolaryngol Head Neck Surg. 2013;21(3):256–62.
7. D. Silva, A. Pereira, N. Santos, J. L. Plácido. Costs of treatment a ect compliance to speci c subcutaneous immunotherapy. Eur Ann Allergy Clin Immunol. 2014;46(2):87-94.
8. Calabria CW. Accelerated immunotherapy schedules. Curr Allergy Asthma Rep. 2013;13(4):389–98.
9. Cox L. Advantages and disadvantages of accelerated immunotherapy schedules. J Allergy Clin Immunol. 2008; 122(2):432–4.
10. Cardona R, Lopez E, Beltrán J, Sánchez J. Safety of immunotherapy in patients with rhinitis, asthma or atopic dermatitis using an ultrarush buildup. A retrospective study. Allergol Immunopathol (Madr). 2014;42(2):90–5.
11. Temiño VM, Wu P, Konig J, Fahrenholz JM. Safety of multiple aeroallergen rush immunotherapy using a modi ed schedule. Allergy Asthma Proc. 2013;34(3):255–60.
12. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI.AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, Year 3: what practices modify the risk of systemic reactions? Ann Allergy Asthma Immunol. 2013;110(4):274–278, 278.e1.
13. Maasch HJ, Marsh DG. Standardized extracts modified allergens–allergoids. Clin Rev Allergy. 1987;5(1):89–106.
14. Akdis CA, Blaser K. Regulation of specific immune responses by chemical and structural modifications of allergens. Int Arch Allergy Immunol. 2000;121(4):261–9.
15. Corrigan CJ, Kettner J, Doemer C, Cromwell O, Narkus A; Study Group. Efficacy and safety of preseasonal speci c immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. Allergy. 2005;60(6):801–7.
16. Rajakulasingam K. Early improvement of patients' condition during allergen speci c subcutaneous immunotherapy with a high-dose hypoallergenic 6-grass pollen preparation. Eur Ann Allergy Clin Immunol. 2012;44(3):128–34.
17. Brehler R, Klimek L, Pfaar O, Hauswald B, Worm M, Bieber T. Safety of a rush immunotherapy build-up schedule with depigmented polymerized allergen extracts. Allergy Asthma Proc. 2010;31(3):e31–8.
18. Pfaar O, Urry Z, Robinson DS, et al. A randomized placebo-controlled trial of rush preseasonal depigmented polymerized grass pollen immunotherapy. Allergy. 2012;67(2):272–9.
19. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31(1):143–78.
20. Brehler R, Kahlert H, Thum-Oltmer S. Hypoallergenic preparations in SCIT. Allergo J. 2010;19:477–84.
21. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: the world allergy organization subcutaneous immunotherapy systemic reaction grading system. J Allergy Clin Immunol. 2010;125(3):569–574, 574.e1-574.e7.
22. Likert R. A technique for the measurement of attitudes. Arch Psycol. 1932;22:1–55.
23. Tabar AI, Echechipía S, García BE, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus*. J Allergy Clin Immunol. 2005;116(1):109–18.
24. Linda Cox, Harold Nelson and Richard Lockey. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127(1 Suppl):S1–55.
25. Egert-Schmidt AM, Kolbe JM, Mussler S, Thum-Oltmer

S. Patients' compliance with different administration routes for allergen immunotherapy in Germany. Patient Prefer Adherence. 2014;8:1475–81.
26. Kiel MA, Röder E, Gerth van Wijk R, Al MJ, Hop WC, Rutten-van Mölken MP. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. J Allergy Clin Immunol. 2013;132(2):353–360.e2.
27. Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E; EAACI, Immunotherapy Task Force. Standards for practical allergen specific immunotherapy. Allergy. 2006;61(Suppl 82):1–20.

Received: 14 December 2019
Accepted: 11 February 2020
Correspondence:
Giorgio Ciprandi, MD
Via P. Boselli 5,
16146 Genoa, Italy
Tel. + 39 10 35338120
E-mail gio.cip@libero.it