HSPI The Open Access Publisher

JCAVI JOURNAL OF CHILD, ADULT VACCINES AND IMMUNOLOGY
ISSN 2994-2586

Brief Communication

Impact of coronavirus pandemic on safety and time of administration of subcutaneous immunotherapy among pediatric patients

Ana Margarida Mesquita*, Ricardo Moço Coutinho, José Luís Plácido and Alice Coimbra

MD, Allergy and Clinical Immunology Department, University Hospital Center of São João, EPE, Porto, Portugal

Abstract

Introduction: Allergen immunotherapy is the only targeted therapy that can modify the natural course of allergic diseases. In pediatric patients, SCIT with aeroallergens is an effective treatment and should be considered as a preventive strategy in the treatment of allergic diseases, even though one of the major concerns about it is its safety. The main purposes of this study were to assess the safety of SCIT ultra-rush schedules with polymerized extracts in a pediatric population and to determine the impact of the COVID-19 pandemic on the safety and time of administration of subcutaneous immunotherapy among pediatric patients.

Methods: A retrospective medical records review of patients under 18 years of age undergoing SCIT was made and re-scheduling due to restrictions imposed by the COVID-19 pandemic was recorded.

Results: A total of 192 pediatric patients were included. Fifty-nine (31%) had local reactions and systemic reactions were not reported. In March 2020, the first case of COVID-19 was diagnosed in Portugal and all non-urgent appointments and procedures were postponed. In our group of pediatric patients, 43 (22%) were referred to primary care, 38 (20%) stopped AIT definitively and 111 (58%) maintained administrations in the hospital. Only 2 (2%) of them had reactions upon reinitiation.

Conclusion: In this study, the ultra-rush protocol using polymerized extracts was safe in pediatric patients. Although the effectiveness of AIT may be compromised due to prolonged suspension of the treatment, it is important to note that despite longer interruptions, administrations may continue without compromising safety, maintaining shorter visits and a lower number of injections.

More Information

***Address for Correspondence:** Ana Margarida Mesquita, MD, Allergy and Clinical Immunology Department, University Hospital Center of São João, EPE, Porto, Portugal,
Email: mesquita.amb@gmail.com

Submitted: August 19, 2022
Approved: September 01, 2022
Published: September 02, 2022

How to cite this article: Mesquita AM, Coutinho RM, Plácido JL, Coimbra A. Impact of coronavirus pandemic on safety and time of administration of subcutaneous immunotherapy among pediatric patients. J Child Adult Vaccines Immunol. 2022; 6: 001-004.

DOI: 10.29328/journal.jcavi.1001008

Keywords: Coronavirus; Safety; Time of administration; Subcutaneous immunotherapy; Pediatric patients

Introduction

Allergen Immunotherapy (AIT) is the only targeted therapy that can modify the natural course of allergic diseases and has recognized benefits in asthma, rhino-conjunctivitis, and food and venom allergies [1]. AIT can be administered either by subcutaneous (SCIT) or sublingual (SLIT) route for three to five years [2].

In pediatric patients, SCIT with aeroallergens is an effective treatment and should be considered as a preventive strategy in the treatment of allergic diseases [3].

One major concern about SCIT is its safety. The most common reactions with SCIT are local ones at the injection site and may include redness, pruritus, or edema. Systemic reactions such as asthma, angioedema, generalized urticaria, or anaphylaxis have been reported in 2% of all SCIT patients [1]. In children, systemic reactions are very uncommon but are more frequent with SCIT than with SLIT [4]. Still, it is widely accepted that SCIT in pediatric age is safe and well tolerated, but adequate precautions are mandatory. Patients are required to attend a medical center with trained staff and proper conditions to manage severe allergic reactions.

Different schedules of SCIT administrations, namely the classic, cluster, or accelerated (rush or ultra-rush), can be

chosen. The obvious advantages of accelerated schedules are a reduction in the number of injections and the time needed to achieve the maintenance phase, decreasing the number of appointments to a medical center, and reducing the costs for both the patients and the institutions. These protocols may even improve compliance to SCIT, since the fear of needles, particularly among younger children, is an important issue that can be addressed by reducing the number of administrations. However, concerns about the safety and effectiveness of these schedules have been reported. Rush or ultra-rush schedules are not commonly used in pediatric populations and data on their effectiveness and safety in these patients is scarce [5].

Polymerized allergen extracts, which are submitted to chemical procedures to reduce allergenicity, have proven to be effective and safe, and are of particular interest for use in accelerated SCIT protocols [6,7].

In our center, patients with clinical symptoms suggesting asthma or rhinitis are checked for aeroallergen sensitization using skin prick tests. When needed, specific IgE measurements or component resolved diagnosis is also used to better understand sensitization patterns and help in allergen choice for immunotherapy. In our department SCIT with aeroallergens is only done with polymerized allergen extracts and it is largely used in both adults and children. Ultra-rush protocols have been routinely used for years for initiating SCIT in adults and, in our experience, they are effective, practical and safe.

In Portugal, the first case of COVID-19 (an infectious viral disease with global proportions) was reported in March 2020. In the same month, a national state of emergency was declared and lockdown measures were imposed. Our Allergy Department, based at a university hospital (Centro Hospitalar Universitário de São João) that was the COVID-19 reference for the north of Portugal, also had to adopt several measures to cope with this new challenge. All non-urgent activity was suspended and outpatient appointments were mainly converted to phone consultations. Initiations in allergen immunotherapy were postponed and maintenance protocols were either suspended or transferred to primary care centers at their regular schedule. For this reason, some patients ended up either stopping immunotherapy or interrupting administrations for several weeks, until it was possible to return to in-hospital administrations.

The main purposes of this study were to assess the safety of SCIT ultra-rush schedules with polymerized extracts in a pediatric population and to determine the impact of the COVID-19 pandemic on the safety of increasing the time period between administrations.

Methods

A retrospective medical records review of patients under 18 years of age, undergoing SCIT with any aeroallergen between September 2019 and September 2020, was made in an Allergy and Clinical Immunology Department, in Centro Hospitalar Universitário de São João. Data on age, gender, allergic diseases, allergen extracts, and manufacturer were collected. Information about rescheduling due to restrictions imposed by the COVID-19 pandemic was also obtained, but only the patients that maintained administrations in the hospital were included, due to the absence of following up-information from the patients that continued SCIT in primary care centers. Since all of these procedures were part of basic daily clinical practice and we only did a medical records review, ethical approval was not required. All clinical information and identification details were only accessible to the authors when collecting data to maximize confidentiality. All the patients signed informed consent before the start of SCIT administration.

All patients aged 18 years and over, and under sublingual immunotherapy were excluded.

The ultra-rush regimen consisted in administrating 0.2 + 0.3 mL with a 30-minute interval in alternate arms, reaching the maintenance dose of 0.5 ml on the first day. No pre-medication was prescribed. The polymerized extracts used were from different pharmaceutical companies (Diater®, Hal allergy®, Inmunotek®, Leti®, Roxall®, and Stallergenes®). The extracts were chosen by the Allergist according to the results of skin prick tests, specific IgE and in some particular cases, molecular components.

SCIT was administered by trained personnel under medical supervision in our department. Patients remained for at least 30 minutes following each administration and they were evaluated for pain, edema, or pruritus at the injection site and for systemic reactions. Local reactions were measured using the largest diameter observed.

The adverse reactions were classified as immediate or late and local or systemic. Local reactions under 5 cm in diameter were not considered relevant and treatment was not deemed necessary. For larger reactions, depending on their extent, treatment with the application of cold compresses and/or oral antihistamines was prescribed. Systemic reactions were managed according to the EAACI recommendations [4]. The safety of immunotherapy was defined as the absence of adverse reactions, the time of immunotherapy was considered the duration of ongoing treatment with SCIT, and the delay time was calculated in patients who had to delay administrations in months, between the last on-schedule administration and the following delayed one.

IBM SPSS Statistics for Windows, Version 27.0, was used to perform statistical analysis, mostly descriptive, and the chi-square test was used for comparisons. Results were considered statistically significant for a p - value less than 0.05.

Results

A total of 192 pediatric patients were included, 99 (52%) males with a mean age of 10 (standard deviation ± 3) years. The median time of SCIT was 17 (interquartile range 25) months. Concerning atopic diseases, 62 (32%) had rhinoconjunctivitis, 55 (29%) rhinitis, 6 (3%) asthma, 2 (1%) conjunctivitis, 1 (0.5%) atopic dermatitis, and 66 (34.5%) had a combination of at least two of these (32 rhinoconjunctivitis and asthma, 29 rhinitides and asthma, 4 rhinoconjunctivitis and atopic dermatitis and 1 had asthma and atopic dermatitis).

AIT with house dust mites (HDM) was prescribed in 104 (54%) patients, with pollens (grasses, *Parietaria*, *Olea, Plantago*, *Betula*, *Platanus*) in 56 (29%), with mixtures of HDM and pollens in 31 (16%) and with *Alternaria* in 1 (1%). Polymerized allergen extracts were used in all patients.

Regarding AIT extracts, a mixture of *Dermatophagoides pteronyssinus* (*Dp*) and *Lepidoglyphus destructor* (*Ld*) was the most used in the HDM allergic patients (49, 26%), followed by *Dp* (40, 21%). In the pollen allergic patients, a mix of grasses were the most prescribed extract (45, 23%). Some patients were undergoing SCIT with mixtures of HDM and pollens: *Dp* and grasses in 21 (11%) and a mixture of *Dp*, *Ld,* and grasses in 9 (5%) patients.

Fifty-nine (31%) had local reactions: erythema, pruritis and/or edema at the injection site. Of these, 27 had reactions after the initial administrations, 49 in the subsequent ones and 17 in both phases. The extracts used for SCIT in the group with local reactions were HDM in 23 (39%), pollens in 19 (32%), and mixtures of HDM and pollens in 17 (29%). Systemic reactions were not reported. Treatment included local measures and/or oral antihistamines. The subsequent doses were divided for administration in both arms into 8 patients. Dose reduction was never required and all patients maintained the 0.5 mL dose during the maintenance phase. The sample characterization is summarized in Table 1.

Table 1: Personal data of pediatric patients (*n* = 192).

Sex - *n* (%)	Male	99 (52%)
	Female	93 (48%)
Mean age (years ± SD)		10 ± 3
Median time of SCIT – months (IQR)		17 (25)
Atopic disease – n (%)	Rhinoconjunctivitis	62 (32%)
	Rhinitis	55 (29%)
	Asthma	6 (3%)
	Conjunctivitis	2 (1%)
	Atopic dermatitis	1 (< 1%)
	Rhinoconjunctivitis + asthma	32 (17%)
	Rhinitis + asthma	29 (15%)
	Rhinoconjunctivitis + atopic dermatitis	4 (2%)
	Asthma + atopic dermatitis	1 (< 1%)
AIT choice – n (%)	HDM	104 (54%)
	Pollens	56 (29%)
	Mixture of the above	31 (16%)
	Alternaria	1 (< 1%)
Adverse reactions – n (%)	Local	59 (31%)
	Initial administration	27 (14%)
	Subsequent administration	49 (26%)
	Systemic	0

n: number; %: percentage; SD: Standard Deviation; SCIT: Subcutaneous Immunotherapy; IQR: Interquartile Range; AIT: Aeroallergen Immunotherapy.

In March 2020, the first case of COVID-19 was diagnosed in Portugal, and a state of emergency was declared on March 13. All non-urgent appointments and procedures were postponed. AIT administration was not an exception and, therefore, it was suspended for at least 2 months. In our group of pediatric patients, 43 (22%) were referred to primary care centers and continued AIT administration without any delay and 38 (20%) stopped AIT definitively because of fear of hospital visits or medical indications.

A total of 111 (58%) patients maintained administrations in the hospital and therefore had to delay them. Of these, AIT with house dust mites (HDM) was performed in 62 (56%) patients, pollens in 28 (25%) and mixtures of HDM and pollens in 21 (19%). The mean delay time of the AIT administrations was 3 (±1) months, 93 (84%) reinitiated with the total dose (0.5 mL) and 18 (16%) with a divided dose, one in each arm. One patient suspended AIT for 10 months, restarted with a divided dose and adverse reactions were not reported.

In this group of 111 patients, only 2 (2%) had reactions at the time of the reinitiation: a 9-year-old boy underwent 20 months of AIT with HDM (*Dp + Ld*) with previous local reactions during the maintenance doses and restarted AIT 4 months later with the total dose; a 10-year-old boy who had completed 4 months of AIT with mixtures of HDM and pollens (*grasses + Dp),* divided the dose for both arms because of local reactions at the initial and maintenance phases and restarted AIT 3 months later also with a divided dose.

Thirty-nine patients undergoing AIT with pollens restarted it with the full dose in one arm. Adverse reactions were not reported, even though the administrations were delayed between 2 and 5 months and were re-initiated during the spring.

No statistically significant associations were found between local reactions and allergic disease or allergen sensitization.

Discussion

In this group of pediatric patients, systemic reactions were not reported and less than one-third had local reactions. These were easily managed and dose reductions were not necessary to continue allergen immunotherapy.

In this study, the ultra-rush protocol using polymerized extracts was safe in allergic patients of pediatric age, with the advantage of the maintenance dose being reached on the first day of treatment.

There is no consensus about which dose adjustment strategy is necessary after a delay in AIT administration, and it is unclear whether some patients may tolerate longer gaps, particularly in the pediatric population [8]. In our department, after a delay of more than 2 months, both in adults and in children, it was general practice to divide the full dose for both arms without dose adjustments. The COVID-19 pandemic did not change this. The median time of interruption of AIT was 3 months and only 2% reported reactions upon reinitiating.

These findings suggest that restarting SCIT with a divided dose after a pause in administrations is safe, but we can not recommend this practice based only on our results. Furthermore, clinicians should always be aware of potential adverse reactions, even though these seem to be uncommon.

The authors point out the fact that the sample was composed of patients from only one center as a limitation of the study. It should be also mentioned that, as with any retrospective review of data, there could be possible flaws in the records interfering with the results another limitation is that sample size and power analysis was not performed.

Conclusion

Although the effectiveness of AIT may be compromised due to prolonged suspension of the treatment, it is important to note that despite longer interruptions, administrations may continue without compromising the safety, maintaining shorter visits and a lower number of injections.

Nonetheless, more studies with more patients are necessary to confirm our results regarding the reasonable delay for restarting AIT while maintaining its effectiveness and safety.

It is also important to emphasize that AIT administration should always be carried out in an appropriate clinical setting with trained staff capable of recognizing and managing reactions.

Author's contribution

Ana Margarida Mesquita - Conceptualization, study design, data analysis, drafting and final writing;

Ricardo Moço Coutinho - Data analysis, drafting and final writing;

Jose Luis Plácido - Revision and supervision;

References

1. Alice Coimbra - Revision and supervision.Alvaro-Lozano M, Akdis CA, Akdis M, Alviani C, Angier E, Arasi S, Arzt-Gradwohl L, Barber D, Bazire R, Cavkaytar O, Comberiati P, Dramburg S, Durham SR, Eifan AO, Forchert L, Halken S, Kirtland M, Kucuksezer UC, Layhadi JA, Matricardi PM, Muraro A, Ozdemir C, Pajno GB, Pfaar O, Potapova E, Riggioni C, Roberts G, Rodríguez Del Río P, Shamji MH, Sturm GJ, Vazquez-Ortiz M. EAACI Allergen Immunotherapy User's Guide. Pediatr Allergy Immunol. 2020 May;31 Suppl 25(Suppl 25):1-101. doi: 10.1111/pai.13189. PMID: 32436290; PMCID: PMC7317851.
2. Jutel M, Kosowska A, Smolinska S. Allergen Immunotherapy: Past, Present, and Future. Allergy Asthma Immunol Res. 2016 May;8(3):191-7. doi: 10.4168/aair.2016.8.3.191. PMID: 26922928; PMCID: PMC4773206.
3. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, Ryan D, Agache I, Ansotegui IJ, Arasi S, Du Toit G, Fernandez-Rivas M, Geerth van Wijk R, Jutel M, Kleine-Tebbe J, Lau S, Matricardi PM, Pajno GB, Papadopoulos NG, Penagos M, Santos AF, Sturm GJ, Timmermans F, van Ree R, Varga EM, Wahn U, Kristiansen M, Dhami S, Sheikh A, Muraro A. EAACI guidelines on allergen immunotherapy: Prevention of allergy. Pediatr Allergy Immunol. 2017 Dec;28(8):728-745. doi: 10.1111/pai.12807. Epub 2017 Oct 27. PMID: 28902467.
4. Alvaro-Lozano M, Akdis CA, Akdis M, Alviani C, Angier E, Arasi S, Arzt-Gradwohl L, Barber D, Bazire R, Cavkaytar O, Comberiati P, Dramburg S, Durham SR, Eifan AO, Forchert L, Halken S, Kirtland M, Kucuksezer UC, Layhadi JA, Matricardi PM, Muraro A, Ozdemir C, Pajno GB, Pfaar O, Potapova E, Riggioni C, Roberts G, Rodríguez Del Río P, Shamji MH, Sturm GJ, Vazquez-Ortiz M. EAACI Allergen Immunotherapy User's Guide. Pediatr Allergy Immunol. 2020 May;31 Suppl 25(Suppl 25):1-101. doi: 10.1111/pai.13189. PMID: 32436290; PMCID: PMC7317851.
5. Morais-Almeida M, Arêde C, Sampaio G, Borrego LM. Ultrarush schedule of subcutaneous immunotherapy with modified allergen extracts is safe in paediatric age. Asia Pac Allergy. 2016 Jan;6(1):35-42. doi: 10.5415/apallergy.2016.6.1.35. Epub 2016 Jan 27. PMID: 26844218; PMCID: PMC4731479.
6. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, Friedrichs F, Fuchs T, Hamelmann E, Hartwig-Bade D, Hering T, Huttegger I, Jung K, Klimek L, Kopp MV, Merk H, Rabe U, Saloga J, Schmid-Grendelmeier P, Schuster A, Schwerk N, Sitter H, Umpfenbach U, Wedi B, Wöhrl S, Worm M, Kleine-Tebbe J, Kaul S, Schwalfenberg A. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int. 2014;23(8):282-319. doi: 10.1007/s40629-014-0032-2. PMID: 26120539; PMCID: PMC4479478.
7. Carneiro-Leão L, Amaral L, Coimbra A, Plácido JL. Real-life experience of an allergy and clinical immunology department in a Portuguese reference COVID-19 hospital. J Allergy Clin Immunol Pract. 2020 Nov-Dec;8(10):3671-3672. doi: 10.1016/j.jaip.2020.08.042. Epub 2020 Sep 2. PMID: 32890757; PMCID: PMC7467073.
8. Larenas-Linnemann DE, Epstein T, Ponda P, Bernstein D, Williams P, Creticos P. Gaps in allergen immunotherapy administration and subcutaneous allergen immunotherapy dose adjustment schedules: Need for prospective data. Ann Allergy Asthma Immunol. 2020 Nov;125(5):505-506.e2. doi: 10.1016/j.anai.2020.07.015. Epub 2020 Jul 18. PMID: 32693206; PMCID: PMC7368643.