

Ultra-rush immunotherapy with polymerized extracts during COVID-19 pandemic: safety of restarting administrations without dose-adjustments

Mariana Bragança MD , José Luís Plácido MD , Luís Amaral MD

PII: S1081-1206(22)00127-2
DOI: <https://doi.org/10.1016/j.anai.2022.02.014>
Reference: ANAI 3862



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 23 November 2021
Revised date: 15 February 2022
Accepted date: 15 February 2022

Please cite this article as: Mariana Bragança MD , José Luís Plácido MD , Luís Amaral MD , Ultra-rush immunotherapy with polymerized extracts during COVID-19 pandemic: safety of restarting administrations without dose-adjustments, *Annals of Allergy, Asthma Immunology* (2022), doi: <https://doi.org/10.1016/j.anai.2022.02.014>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Ultra-rush immunotherapy with polymerized extracts during COVID-19 pandemic: safety of restarting administrations without dose-adjustments

Mariana Bragança, MD^a, José Luís Plácido, MD^a, Luís Amaral, MD^a

^a Serviço de Imunoalergologia, Centro Hospitalar Universitário de São João, Porto, Portugal

Corresponding Author:

Mariana Bragança, MD

Serviço de Imunoalergologia, Centro Hospitalar Universitário de São João, Porto, Portugal

Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal

Telephone: +351 22 551 2100

Fax: +351 220 919 073

E-mail: m_lbraganca@hotmail.com

Conflicts of interest: none.

Funding Source: none.

Keywords: COVID-19; safety; subcutaneous immunotherapy

Abbreviations

AIT: allergen-specific immunotherapy

HDM: house dust mite

SCIT: subcutaneous immunotherapy

SLIT: sublingual immunotherapy

WHO: World Health Organization

Word count: 1000

Figures: none.

Tables: one.

Allergen-specific immunotherapy (AIT) is the only therapy that can change the natural history of allergic diseases and it has been established as an effective treatment in immediate-type allergic reactions and associated diseases such as asthma and rhinoconjunctivitis. This applies to both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). SCIT is safe and mostly well tolerated. However, patients are required to attend a medical facility with trained staff and proper equipment to manage potential reactions.¹

In our department nearly 4500 SCIT injections are carried out annually. Polymerized extracts are used in more than 99% of our patients. These extracts result from polymerization of allergens into high molecular weight molecules using glutaraldehyde as a cross-linking agent, reducing allergenicity while retaining immunogenicity. Differences from unmodified extracts are shown in table 1.² An ultra-rush protocol is routinely used in the build-up phase of SCIT which consists of the administration of 0.2- and 0.3-ml doses in alternate arms with a 30-minute interval reaching the maintenance dose of 0.5 ml on the first day. Thereafter, this dose is administered monthly. In our experience, this is an effective, practical and safe schedule to follow. Previous studies using ultra-rush

AIT with polymerized extracts described local and mild systemic reactions in 11% and 1% of patients, respectively.^{3,4}

The SARS-CoV-2 pandemic had a significant impact in our clinical practice. In Portugal, the national state of emergency was declared and lockdown measures were imposed in March 2020, soon after the World Health Organization (WHO) declared COVID-19 as a pandemic. As a result, our regular clinical activity was suspended until May. Patients in maintenance phase of aeroallergens SCIT were encouraged to keep the scheduled doses at their primary care facilities. However, due to an overload of COVID-19 related tasks, a significant percentage of patients were forced to delay SCIT administration.⁵ With the reestablishment of regular clinical activity after the lockdown, these patients were invited to resume their treatments without dose adjustment, after a three-month interruption. The rationale was to reduce the time of surveillance after injections in order to avoid overcrowding the waiting room during a pandemic phase, as government restrictions were still in place to limit patient flow in health care facilities. This also allowed for a higher number of SCIT restarts per day.

A retrospective analysis of demographic and clinical data of patients receiving maintenance SCIT with aeroallergens, who missed doses due to COVID-19 restrictions and restarted their treatment at our center between May and July 2020, was performed to assess the safety of reinitiating aeroallergen SCIT without dose adjustments. Patients with systemic reactions in previous administrations were not included in this analysis. They were submitted to an ultra-rush protocol. The adverse reactions reported were classified as local

reaction, local large reaction (defined as pruritus and/or erythema >2.5 cm at the site of injection) and systemic reactions.⁶

A total of 273 patients were scheduled, but only 241 restarted SCIT. The mean age (SD) was 23 ± 14 years and 53.5% were male. The diagnosis of allergic rhinitis was present in 97.5% patients, of which 45.1% and 12.9% had concomitant conjunctivitis and atopic dermatitis, respectively. Asthma was present in 36.8% of patients. Most patients were polysensitized (66%) with a mean of 3.6 ± 1.9 positive allergens per patient. All patients were under SCIT with polymerized aeroallergen extracts, 51.0% to house dust mite (HDM) and 58.1% of these with more than one allergen, 24.1% to pollens and of these 26.2% also with more than one; 24.1% to a mix of HDM and pollens, and 0.8% to a mix of HDM and cat. The mean number of days overdue was 65 ± 14 days, ranging from 23 to 146 days, and the mean duration of treatment before the missed dose was 98.9 ± 4.4 weeks.

Five patients had local reactions. None of the patients had large local or systemic reactions and all continued SCIT.

To be effective, SCIT should be continued for at least three years, requiring regular visits to a health care facility, as systemic reactions may occur.⁶ In early 2020, due to the COVID-19 pandemic, clinical practice adjustments were made in many Allergy Departments because most health care staff were redirected to COVID-19 related activities, or even to ensure the safety of both patients and health care workers. Additionally, patient adherence to SCIT decreased due to caution and fears of public spaces and hospitals.⁷ As a result, many patients interrupted their aeroallergen SCIT or increased the administration intervals with a potential decline in efficacy.⁸ Therefore,

whenever possible, treatment was restarted taking into consideration the risk-benefit analysis.⁹

Scientific literature is scarce and divergent regarding restarting SCIT after missed doses. Safety is a major concern when patients have gaps in immunotherapy administration, and most adjust the dose according to the time interval since the last injection. Protocols from several centers were analyzed and in cases of > 35 days since last dose (i.e., > 7 days overdue), the dose was reduced.⁸ Data from our center suggests that restarting SCIT with polymerized aeroallergen extracts in patients in maintenance phase without previous systemic reactions is safe without the need for dose adjustment, including a wide interval, to a maximum of 146 days.

It is noteworthy that none of the patients treated with SCIT for pollens had adverse reactions during the pollen season, questioning the necessity for seasonal dose adjustment. However, the restarts were done between May and July, and all adult and adolescent patients were compelled to use face mask, including outdoors during this period, which limits contact with pollen allergens.

In conclusion, there is no standard adjustment protocol for missed doses during aeroallergen SCIT, and most allergists adjust doses according to the time interval since the last injection. Our results suggest that is safe to restart SCIT with polymerized aeroallergen extracts during maintenance phase without the need for dose adjustment in those without a previous systemic reaction. Randomized clinical trials and other prospective data are needed to support this hypothesis, as this is an empiric observation with modified extracts from a single center.

REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63 Suppl 86:8-160.
2. Grammer LC, Shaughnessy MA, Patterson R. Modified forms of allergen immunotherapy. *J Allergy Clin Immunol*. 1985;76(2 Pt 2):397-401.
3. Morais-Almeida M, Arede C, Sampaio G, Borrego LM. Ultrarush schedule of subcutaneous immunotherapy with modified allergen extracts is safe in paediatric age. *Asia Pac Allergy*. 2016;6(1):35-42.
4. Santos N, Pereira AM, Silva R, Torres da Costa J, Placido JL. Characterisation of systemic reactions to subcutaneous immunotherapy with airborne allergens and classification according to WAO 2010. *Allergol Immunopathol (Madr)*. 2015;43(1):25-31.
5. Carneiro-Leao L, Amaral L, Coimbra A, Placido JL. Real-life experience of an allergy and clinical immunology department in a Portuguese reference COVID-19 hospital. *J Allergy Clin Immunol Pract*. 2020;8(10):3671-2.
6. James C, Bernstein DI. Allergen immunotherapy: an updated review of safety. *Curr Opin Allergy Clin Immunol*. 2017;17(1):55-9.
7. Yegit OO, Demir S, Unal D, Olgac M, Terzioglu K, Eyice Karabacak D, et al. Adherence to subcutaneous immunotherapy with aeroallergens in real-life practice during the COVID-19 pandemic. *Allergy*. 2021.
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;125(5):505-6 e2.

9. Klimek L, Pfaar O, Worm M, Bergmann KC, Bieber T, Buhl R, et al.

Allergen immunotherapy in the current COVID-19 pandemic: A position paper of

AeDA, ARIA, EAACI, DGAKI and GPA: Position paper of the German ARIA

Group(A) in cooperation with the Austrian ARIA Group(B), the Swiss ARIA

Group(C), German Society for Applied Allergology (AEDA)(D), German Society

for Allergology and Clinical Immunology (DGAKI)(E), Society for Pediatric

Allergology (GPA)(F) in cooperation with AG Clinical Immunology, Allergology

and Environmental Medicine of the DGHNO-KHC(G) and the European

Academy of Allergy and Clinical Immunology (EAACI)(H). Allergol Select.

2020;4:44-52.

Table 1. - Characteristics of native and modified extracts.

	Native extracts	Modified extracts (Allergoids)
Molecular Weight	Low	High
IgE-binding capacity	Reduced	Lower*
Allergenicity	High	Significantly Reduced*
Immunogenicity	Significant	Maintained*
Build-up period	Weeks	Day(s)
Safety	Risk of SR	Lower rate of SR*
Standardization	Difficult	Possible

Abbreviations: SR: systemic reactions.

Note: *Comparing to native extracts.

Journal Pre-proof