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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Perspective

Gaps in allergen immunotherapy administration and subcutaneous allergen immunotherapy dose adjustment schedules

Need for prospective data

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Introduction

Many abrupt adjustments in the delivery of medical care became necessary owing to the unexpected emergence of the coronavirus disease 2019 pandemic in early 2020. To ensure social distancing and the concomitant requirements for personal protective equipment, practitioners have had to make a myriad of adjustments to continue providing subcutaneous allergen immunotherapy (SCIT). In many practices, SCIT was stopped or administration intervals have been increased, whereas other practices have transitioned some patients to the sublingual administration route.[1]

Although many locations have recently eased lockdown requirements, this led to a rise in cases in several states, resulting in further lockdowns. Thus, it might very well still take months before our daily routine shall come close to normal again. Learning from historical lessons, the H1N1 influenza "Spanish flu" pandemic lasted 15 months and killed 50 million people. It comprised the following 3 waves: the first (milder) one was in winter-spring 1918; the second wave, in September 1918, was disastrous and deadly, because it coincided with the massive troop gathering and transport of soldiers for World War I and an apparent aggressive mutation of the virus; and the last wave, beginning in 1919, had less severity. Finally, the virus resolved on the development of herd immunity, the ending of the war, and possibly a favorable mutation.

Although prevention of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is critical, it is also important that other health concerns are addressed to limit preventable emergencies. Maintaining good health appears to reduce the risk of severe COVID-19 disease. In the context of allergic diseases, SCIT has been reported to reduce symptoms and medication requirements in allergic rhinitis, conjunctivitis, and in patients with immunoglobulin E–dependent asthma, improving the quality of life. Moreover, a case could be made that patients with an allergy might experience some ancillary immunologic benefit in battling an infectious pathogen by being on an effective SCIT dose. Immunotherapy restores the function of dendritic cells and augments the number of active T_H1 cells, both enhance innate immunity, which could be important at the start of a SARS-COV-2 infection whose initial mechanism is innate immune suppression, a theory that might be interesting to explore.[2]

For SCIT to be effective, an optimal target monthly maintenance dose has to be administered. The extended spacing interval of injections, although acceptable from a safety point of view, may result in a diminution of therapeutic efficacy. Thus, as soon as the risk for

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SARS-CoV-2 transmission and infection can be reduced to levels considered safe by health authorities, it behooves the allergist to return to a maintenance immunotherapy schedule known to be effective.

At this moment, there are no data from controlled trials on dose adjustment after gaps in administration. The intention of this article is to review the limited data available and discuss what is needed to answer pressing questions related to resuming SCIT after gaps in therapy.

Published Data Related to Gaps in Subcutaneous Allergen Immunotherapy Administration

Dose Adjustment Schedules

In an online supplement to the Practice Parameters on Allergen Immunotherapy (third update), the authors propose a schedule on how to dose-adjust after a gap in SCIT administration. The schedule is based on the time elapsed since the missed dose.

Tangentially, the focused practice parameter update on sublingual immunotherapy recommends restarting the tablet for sublingual immunotherapy in-office after interruptions of more than 7 days. This is recommendable given anaphylaxis has been reported after the first tablet, be it rarely.[3]

The largest amount of data available comes from the collective experience of more than a thousand allergy specialists. An online survey of the American Academy of Allergy, Asthma, and Immunology (AAAAI) membership was conducted and reported in 2012.[4] Shortly afterward, almost 80% of responders reported dose-adjusting based on the date of the last administered dose. Most reduced the dose a certain number of steps back, others reduced a percentage, and a few reduced a certain volume. In the online supplement, we present dose adjustment schedules with one (Table e1) based on the most frequently used solutions according to the survey and others either used by large allergy practices (Table e2-e5) or proposed by the guidelines (Table e6 and e7).

Safety Reports Related to Gaps

The AAAAI and the American College of Allergy Asthma and Immunology Immunotherapy surveillance study started in 2008. Members submit data annually regarding SCIT-related systemic reactions and their severity. In the last update, the investigators gave a detailed description of a total of 7 fatal reactions since 2008 (1:9.1 million injection visits). Although not specifically queried for nonfatal reactions, there were no reports of fatal reactions occurring owing to a gap in therapy.[5] As discussed below, the issue of gaps in therapy will be more extensively queried in this year's upcoming surveillance survey.

Special Considerations

Allergen immunotherapy is still an art, and it might require extra precautions in patients who could be at higher risk for life-threatening systemic reactions. Patients with higher risk may include those with the following[5]: (1) history of anaphylaxis or mast cell disorder; (2) moderate to severe asthma; (3) high sensitization pattern or systemic reaction during skin prick testing; (4) systemic reactions to previous SCIT administration; and (5) patients receiving SCIT during peak pollen season for an allergen to which they are highly sensitized. Thus, the personal background of the patient should be taken into consideration when choosing a dose adjustment schedule after a gap in therapy; pediatric age could need extra caution.

Future

There is no consensus or firm evidence suggesting which dose adjustment strategy is superior after a gap in therapy. In addition, it is unclear whether some patients may tolerate longer gaps in therapy than previously allowed, both in terms of efficacy and safety. Understanding the consequences and developing optimal strategies for dose adjustment after gaps in therapy has become paramount during the COVID-19 pandemic. Thus, the AAAAI Immunotherapy, Allergen Standardization, and Allergy Diagnostics Committee are evaluating outcomes related to various dose adjustment strategies for gaps in therapy. A prospective, randomized single-center trial evaluating outcomes for 2 different dose adjustment schedules is underway. In addition, we are gathering data using the immunotherapy surveillance study. We would like to invite colleagues to join us and submit their data regarding gaps in therapy to the surveillance study (https://tinyurl.com/AITAnnualSurvey).

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2020.07.015.

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Supplementary Data

The below tables are some examples of different schedules for dose adjustment after gaps in subcutaneous allergen immunotherapy administration, developed by academia, large practices, and guidelines in an attempt to minimize the possibility of a systemic reaction. However, avoidance of a reaction cannot be guaranteed. The physician is further guided in the exact dose adjustment decision by clinical data such as the concentration of allergen being given, previous reaction history, and seasonality.

eTable 1
Empirical Dose Adjustment Schedule after Gaps in SCIT Administration Based on Mean Replies From the AAAAI Members' Survey (Aqueous Extracts)

All patients	
Intuitively, highly sensitive patients[a] might need special caution and more drastic dose reduction after gaps	
Dose increase phase	Dose adjustment actions to be taken
<2 wk since the last dose	Increase normally
≥2-3 wk	Repeat the last dose
≥3-4 wk	Reduce 1 dose
≥4-5 wk	Reduce 2 doses
90 d	Restart SCIT: from bottle 1, first dose
Maintenance phase	
<5 wk since the last dose	Apply normally
≥5-7 wk	Reduce by 25%
≥7-11 wk	Reduce 1 dose/Reduce by 45%
≥8-15 wk	Reduce 2 doses/Reduce by 55%
≥3-4 mo	Restart SCIT: from bottle 1, first dose

Abbreviations: AAAAI, American Academy of Allergy, Asthma, and Immunology; SCIT, subcutaneous allergen immunotherapy.
[a]Special caution might be needed for the following: (1) history of anaphylaxis or mast cell disorder; (2) moderate to severe asthma; (3) high sensitization pattern or systemic reaction during skin prick testing; (4) systemic reactions to previous SCIT administration; (5) patients receiving SCIT during peak pollen season for an allergen to which they are highly sensitized; and (6) pediatric patients.

eTable 2
Johns Hopkins Division of Allergy and Clinical Immunology Dose Adjustment Scenarios for Standard SCIT Dose Modifications Owing to Missed Injections

Scenario A: missed build-up visit. Based on time elapsed since the last dose.	
1-2 wk since the last dose	Continue schedule
2-3 wk (15-21 d)	Repeat the previous dose
3-5 wk (22-35 d)	Decrease by 1 dose
5-6 wk (36-42 d)	Decrease by 2 doses
>9 wk	Notify allergist for instructions
Scenario B: build-up schedule completed	
(Once final dose has been reached)	Repeat last dose in 2 wk then, Repeat last dose in 3 wk then, Repeat last dose in 4 wk then, Continue maintenance dose every 4 wk
Scenario C: missed maintenance visit	
4-6 wk (42 d) since the last dose	Continue schedule
6-7 wk (43-56 d)	Decrease by 1 dose
5-6 wk (57-63 d)	Decrease by 2 doses
>9 wk	Notify allergist for instructions

Abbreviation: SCIT, subcutaneous allergen immunotherapy.

eTable 3
Schedule Used by Allergy Partners

Schedule for missed injections for the build-up	
Time elapsed since the last dose	
2-14 d	Continue increasing per schedule
15-21 d	Repeat the last dose, then increase per schedule
More than 21 d	Reduce the dose by 1 step for each week over 3 wk, then increase per schedule
More than 63 d	Ask physician
Schedule for missed injections for maintenance	
Time elapsed since the last dose	
0-35 d	Continue the maintenance dose
More than 35 d	Reduce the dose by 1 step for each wk over 5 wk, then increase per schedule
More than 91 d	Ask physician
Schedule for refills	
First dose from refill	Reduce to 1/3 of the maintenance dose
Second dose from refill	Reduce to 2/3 of the maintenance dose
Third dose from refill	Back to usual dose, reset phase to maintenance

eTable 4
Dose Adjustment Schedule for Gaps in SCIT Administration, University of Cincinnati

For lapses in therapy in the 1:10,000, 1:1000, and 1:100 vials, adjust the dose as follows:	
Weeks overdue	
1 wk overdue	Repeat the last dose
2 wk overdue	Decrease by 1 dose
3 wk overdue	Decrease by 2 doses
4 wk overdue	Ask MD
For lapses in therapy in the 1:10 vial, adjust the dose as follows:	
Wk overdue	
2 wk overdue	Reduce by 50%
3 wk overdue	Start at the beginning of vial
4 wk overdue	Ask MD
For lapses in therapy in the 1:1 vial, adjust the dose as follows:	
Weeks overdue	
1-2 wk overdue	Repeat the last dose
3-4 wk overdue	Decrease by 1 dose
4-6 wk overdue	Decrease by 2 doses
>6 wk overdue	Ask MD

Abbreviation: MD, doctor of medicine.
NOTE: Normal dosing of vials 1:10,000 and 1:1000 is with 0.10 mL increments, 1:100 and 1:10 with 0.05 increments, and 1:1 with 0.03 increments.

eTable 5
Dose Adjustment Schedule for Gaps in SCIT Administration, Northwestern University

Immunotherapy dose adjustments for lapses in SCIT during the build-up phase	
Review IT chart for past reactions	
10 d overdue	No adjustment
2 wk overdue	If no history of reaction: repeat dose If the history of reaction: decrease by 0.05 mL
3 wk overdue	Decrease by 0.10 mL
4 wk overdue	Decrease by 0.15 mL
For lapses in allergen immunotherapy during the maintenance phase:	
Weeks overdue	
2 wk overdue	Repeat dose
3 wk overdue	Decrease by 0.05 mL
4 wk overdue	Decrease by 0.10 mL
2 months overdue	Decrease by 0.05 for each week missed after 2 wk
3 months overdue	Will need to discuss compliance with the patient and attending before stopping IT or restart at 1:1000 of 0.05 mL

Abbreviation: IT, immunotherapy; SCIT, subcutaneous allergen immunotherapy.

eTable 6
Practice Parameters (Third Update) of Online Repository Proposed Schedule (eTable 5)

Build-up phase for weekly or biweekly injections	
Modify dosage accordingly to time interval since missed injection	
Up to 7 d[a]	Continue as scheduled
8-13 d after missed scheduled injection	Repeat the previous dose[b]
14-21 d after missed scheduled injection	Reduce the dose by 25%[b]
21-28 d after missed scheduled injection	Reduce the previous dose by 50%[b]
A similar dose reduction protocol should be developed for gaps in maintenance immunotherapy.	

[a]If on weekly build-up, then it would be up to 14 days after administered injection or 7 days after the missed scheduled injection.
[b]Then increase dose each injection visit as directed on the immunotherapy schedule until the therapeutic maintenance dose is reached.

eTable 7
Dose Adjustment Schedule, Mexican Guidelines on Immunotherapy 2019

Prolonged interval between doses (aqueous extracts)[a]	
Up-dosing phase. Time since last SCIT injection.	
○ < 2 wk	Increase normally
○ 2-3 wk	Repeat the last dose
○ 3-4 wk	Decrease by 1 dose
○ 4-5 wk	Decrease by 2 doses
○ 6-8 wk	Reboot from vial 1
Maintenance phase. Time since last SCIT injection.	
○ < 5 wk	Administer normally
○ 5-6 wk	Decrease by 1 dose
○ 6-8 wk	Decrease by 2 doses or 50%
○ 2-3 mo	Start vial from 0.05 mL
○ 3-4 mo	Start from previous vial 0.05 mL
○ > 4 mo	Reboot from vial 1
Prolonged interval between doses (allergoid or adsorbed extracts)[b]	
○ Maintenance <8 wk	Maintain normal dose (For details, see manufacturer recommendations)

Abbreviations: AIT, allergen immunotherapy; SCIT, subcutaneous allergen immunotherapy.
[a]Based on the experience of approximately 1000 allergist members of the American Academy of Allergy, Asthma, and Immunology. Adapted from Larenas-Linnemann DE, Gupta P, Mithani S, Ponda P. Survey on immunotherapy practice patterns: dose, dose adjustments, and duration. *Ann Allergy Asthma Immunol*. 2012;108(5): 373-378.e3.
[b]Preferably continue normally or suspend. It is debatable whether reducing the AIT dose of European extracts results in loss of efficacy.