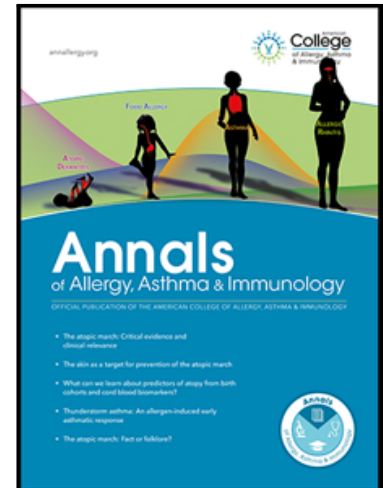


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Circadian and Seasonal Variations in Subcutaneous Allergen Immunotherapy Reactions

Jeremy C. McMurray, M.D.¹, Aubri M. Waters, M.D.², Christopher V. Macomb, D.O.², Daniel I.

Brooks, Ph.D.³, David J. Schwartz, M.D.²

¹Department of Pediatrics, Walter Reed National Military Medical Center, Bethesda, MD

²Department of Allergy, Immunology, and Immunizations, Walter Reed National Military Medical Center, Bethesda, MD

³Department of Research Programs, Walter Reed National Military Medical Center, Bethesda, MD

Corresponding Author: Jeremy C. McMurray, MD, 4494 North Palmer Road, Building 19; Bethesda, MD, 20889, Tel: (301) 295-4900, E-mail: jeremy.c.mcmurray.mil@mail.mil

Keywords:

immunotherapy; SCIT; diurnal; reactions; seasonal

Abbreviations/Acronyms:

SCIT subcutaneous immunotherapy

AIT allergen immunotherapy

VIT venom immunotherapy

SR systemic reaction

AR allergic rhinitis

USACAEL U.S. Army Centralized Allergen Extract Laboratory

ELMS Extract Lab Management System

Circadian and seasonal rhythms play an important role in many physiologic responses involving the immune system and allergic diseases^{1, 2} and may also have implications in the safety profile of subcutaneous immunotherapy (SCIT). Although rare following administration of conventional SCIT in a clinical setting, systemic reactions (SR) occur in about 1 in 1000 injections with roughly 67% classified as mild, 29% as moderate, and 4% as severe.³ The aim of our study was to determine if the time of immunotherapy administration, seasonality, or demographic factors impact the rate of SR following SCIT.

During the study period from March 2015 to March 2020, the Allergy and Immunology Clinic at Walter Reed National Military Medical Center administered a total of 26,680 injections to 1341 patients. Allergen immunotherapy (AIT) administration was grouped into three temporal blocks (7:00AM-9:59AM; 10:00AM-12:59PM; 1:00PM-3:59PM) and meteorological season was defined as the following: winter (December-February), spring (March-May), summer (June-August), and fall (September-November). Both single and multi-allergen AIT were administered.

Demographics of the patient study population are detailed in Table 1. Following administration of either conventional or cluster SCIT, 165 SR were identified, with 28 patients having multiple SR. Patients were on AIT for a mean of 8.7 months (0-82.3 months) prior to having their first SR. Of those with repeat SR, 22 reactions occurred after receiving a higher dose, 8 at the same dose, and 12 at a lower dose than the original SR. One hundred-nine (66.0%) of the SR occurred in those with perennial allergies (106 of whom were on multi-allergen immunotherapy). Only 10 SR (6.1%) occurred with single component AIT. Reactions were graded using the World Allergy

Organization standard grading system – Grade-1 [n=66 (40.0%)], Grade-2 [n=42 (25.5%)], Grade-3 [n=50 (30.3%)], Grade-4 [n=6 (3.6%)], and Grade-5 [n=1 (0.6%)]. One hundred-eighteen reactions (71.5%) occurred during build-up SCIT; epinephrine was administered in 73 reactions (44.2%). Eighteen reactions required multiple epinephrine doses, with one patient requiring six doses. Five patients with multiple SRs required epinephrine during separate SRs. Additionally, four of five patients who required three or more doses of epinephrine had not yet achieved maintenance dosing. The mean and median times between SCIT injection and SR were 46.6 and 30.0 minutes (0-430 minutes) respectively, with 48.5% occurring after 30 minutes of administration. Epinephrine was administered in 34 of these delayed reactions (42.5%).

To investigate factors influencing SR, we used a Poisson model with covariates of age group, sex, year, season, and time-of-day, with an offset as the log number of encounters with each covariate combination. The adjusted rate of reactions differed across time blocks ($p=.049$), and was highest at 10:00AM-12:59PM, with 7.98 per 1000 (95% CI: 6.1-10.5) compared to 4.97 per 1000 (95% CI: 3.7-6.7) at 7:00AM-9:59AM and 6.44 per 1000 injections (95% CI: 4.8-8.7) at 1:00PM-3:59PM. Compared to 7:00AM-9:59AM, there was a 1.61 (95%: 1.03-2.51) relative risk of a SR between 10:00AM-12:59PM. While the adjusted rate of SR per 1000 SCIT injections was highest in the winter season with 8.3 reactions (95% CI: 6.1-11.2) compared to 5.9 (95% CI: 4.2-8.2) in the spring, 5.7 (95% CI: 4.1-8.1) in the summer, and 5.8 (95% CI: 4.1-8.2) in the fall, these differences were not statistically significant ($p=.25$). There was no statistical significance in the rate of reactions across study years ($p=.38$), sex ($p=.80$), or patient age ($p=.53$). No relationship was found when a cumulative link model was used to evaluate the relationship between SR severity and time of day ($p=.46$) or seasonality ($p=.23$).

Our findings differed from those of a recent study in that there were higher odds of a SR during late morning to early afternoon administration of SCIT compared to more occurring in the late afternoon.⁴ This increased rate of SR around midday may be accounted for by the higher overall pollen exposure, as it is known that airborne pollen counts are typically higher at midday (10:00AM-2:00PM).⁵ Additionally, it is important to consider that the increased rate of reactions during the early afternoon may be secondary to increased activity, which may correlate with endogenous steroid levels. Interestingly, cortisol levels follow a diurnal pattern with levels high upon awakening, peaking around 30 minutes after awakening, and then rapidly dropping over the next few hours during the afternoon time period in those on a normal day-shift schedule.⁶ While it would not be practical to have all patients restricted to morning injections of SCIT, the results of our study combined with those from Bavishi et al.⁴ should prompt the allergist to consider early administration of SCIT for patients who have a higher risk of a SR to immunotherapy.

Importantly, in this study there was no statistically significant seasonal variation in the number of SR. These findings are consistent with previous studies.⁷

Another interesting finding is that approximately half of all SR occurred outside of the traditional observation period, and our study is not the first to report this.⁸ It is important to note that onset times outside of the 30-minute period were patient reported. This may suggest the need for a prolonged observation period following the administration of AIT, especially in those at higher risk including those with a history of a prior SR or comorbid asthma.

AIT is the only current disease modifying treatment for allergic rhinitis. Despite the demonstrated benefits of AIT, it is not without risk including life-threatening SR. Allergists should be vigilant and consider all potential risk factors when determining if immunotherapy is the best treatment option for a patient, particularly in the context of patients who have previously experienced an anaphylactic reaction to immunotherapy. This study suggests that administering AIT earlier in the day may help decrease the risk of having an initial or subsequent SR to AIT. Additionally, a significant number of patients had reactions which began more than 30 minutes after the time of administration. Additional studies are warranted to determine if the diurnal variation of SR following SCIT observed in this study is reproducible when studied in a prospective fashion.

Conflicts of Interest:

none

Funding Source:

none

Disclaimer

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Table 1. Total number of SCIT encounters and marginal systemic reaction rate by covariate. Systemic reaction rates are reported per 1000 injections assuming equivalent weighting of all other covariates. Year was treated as a continuous variable for analysis, but rates are shown here on a per year basis.

Category	Number of SCIT Encounters	Marginal Systemic Reaction Rate (95% CI)
Sex (%)		
Male	13988 (52.4%)	6.22 (4.85 – 7.97)
Female	12692 (47.6%)	6.47 (5.07 - 8.27)
Age Group (%)		
5-14 years	5120 (19.2%)	6.43 (4.53 – 9.13)
15-17 years	1204 (4.5%)	6.52 (3.25 – 13.07)
18-24 years	1629 (6.1%)	7.81 (4.53 – 13.48)
25-34 years	4550 (17.1%)	7.53 (5.40 – 10.52)
35-44 years	6002 (22.5%)	5.41 (3.85 – 7.61)
45-64 years	7038 (26.4%)	4.77 (3.41 – 6.67)
65+ years	1137 (4.2%)	6.50 (3.23 – 13.07)
Year (%)		
2015	4063 (15.2%)	5.71 (3.65 - 8.95)
2016	4558 (17.1%)	6.14 (4.14 – 9.10)
2017	4321 (16.2%)	4.35 (2.70 – 6.99)
2018	5639 (21.1%)	8.44 (6.19 – 11.50)
2019	6538 (24.5%)	6.96 (5.07 – 9.56)
2020	1561 (5.9%)	4.97 (2.50 – 9.90)
Time of Day (%)		
T1 (7:00AM-9:59AM)	10185 (38.2%)	4.97 (3.68 – 6.73)
T2 (10:00AM-12:59PM)	8569 (32.1%)	7.98 (6.11 – 10.43)
T3 (1:00PM-3:59PM)	7926 (29.7%)	6.44 (4.76 – 8.70)
Meteorological Season (%)		
Winter	6524 (24.5%)	8.26 (6.12 – 11.15)
Spring	7039 (26.4%)	5.90 (4.24 – 8.21)
Summer	6626 (24.8%)	5.72 (4.05 – 8.07)
Fall	6491 (24.3%)	5.82 (4.13 – 8.22)