

## Systemic reactions to immunotherapy during mountain cedar season: implications for seasonal dose adjustment

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### Clinical Implications

- The administration of subcutaneous immunotherapy during pollen season has been identified as a possible risk factor for systemic reactions. This multiyear study in polysensitized patients demonstrates that in-season pollen exposure to mountain cedar tree does not increase systemic reaction rates, and dose adjustment may not be warranted.

### TO THE EDITOR:

Although allergen-specific subcutaneous immunotherapy (SCIT) is effective and safe, systemic reactions (SRs) occur at 0.2% per injection<sup>1</sup> with conventional build-up schedules. Factors reported to be associated with increased risk of SRs include poorly controlled asthma, delayed epinephrine delivery, inadequate observation time after SCIT, medically unsupervised administration, use of beta-blockers, dosing error, and administration during pollen season.<sup>1,2</sup> Some of these factors demonstrate a consistent risk association across multiple studies. However, the administration of SCIT during the peak pollen season remains a matter of controversy with conflicting reports.

We sought to examine the effects of in-season pollen exposure on SRs to SCIT in an environment with a robust and predictable winter pollinating tree, mountain cedar (MC) (*Juniperus ashei*). MC is an ideal model to study high pollen levels in the natural environment<sup>3</sup> where it ubiquitously induces formidable symptoms described as “cedar fever.” This multiyear retrospective cohort study (2005-2013) examined SCIT-associated SRs at an academic allergy clinic where seasonal dose adjustment is not practiced. Only SRs to SCIT treated with at least 1 dose of epinephrine were included. SRs to venom immunotherapy were excluded. All patients who received aeroallergen SCIT followed conventional build-up schedules. Before SCIT, asthmatic patients performed screening peak expiratory flows. A positive mountain cedar allergy (MCA) status was established by positive skin testing (minimum 3-mm wheal with surrounding flare) or serologic testing ( $>0.35$  kU/L via ImmunoCap). The World Allergy Organization SCIT systemic reaction grading system was utilized to define and grade SRs. Clinicians consistently administered epinephrine as the first-line therapy for SRs. Mountain cedar season was defined between December 1 and March 15 based on historical sampling data. Certified pollen counts were measured by the Burkard sampler (R.A.G.) and provided by Sylvana Research (San Antonio, Tex). Statistical analyses were performed using Statistical Analysis System (Cary, NC). The study was approved by the Institutional Review Board.

Over the study period, the SR rate for aeroallergens was 0.25% per injection (Figure 1). The overwhelming majority of SRs (96%, 208/216) were mild grade 1 or 2 (Figure 1). No fatalities occurred. The MCA status was determined in 216 SRs (Figure 1), and 75% (161/216) of those occurred in MCA patients. SRs occurred during MC season in 29% (63/216), and the remaining 71% (153/216) occurred out of MC season. There was no significant difference between SRs occurring in MCA patients during MC season (73%, 46/63) and SRs occurring in MCA patients out of MC season (75%, 115/153) (Table 1). Similarly, there was no significant difference between SRs occurring in non-MCA patients during MC season (27%, 17/63) and SRs occurring in non-MCA patients out of MC season (25%, 38/153) (Table 1). Among MCA versus non-MCA patients, no significant difference was observed in gender, immunotherapy phase, potency or number of injections, asthma status, and history of previous SR (Table 1). No difference in the SR grade severity (odds ratio [OR] = 1.12,  $P = .6$ ), doses of epinephrine (OR = 0.99,  $P = .4$ ), or time to resolution of symptoms (OR = 1.01,  $P = .5$ ) was observed. The SRs did not appear to be associated with peak pollen counts ( $P = .3$ ; Figure E1, available in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

Long-standing controversy persists surrounding the risk of SRs during pollen season originating from data on fatal and near fatal SRs from the 1980s to 1990s and indirect survey data. In contrast, observational studies report no increase in SRs during pollen season. Lin et al<sup>2</sup> reported more than 13 years of data among polysensitized patients and observed no relationship between SRs and seasonal variations in grass and ragweed pollen counts. Tinkelman et al<sup>3</sup> also reported that ragweed season was not correlated with increased SRs. A recent meta-analysis of nearly 950 SCIT subjects suggest no increase in SRs with coseasonal SCIT initiation.<sup>4</sup> An annual physician survey study reported 64% of SCIT SRs occurred during pollen seasons.<sup>5</sup> Practices cited grass season, not during a pollen season, and ragweed season among the major associations.<sup>6</sup> Studies also demonstrate heterogeneous in-season dose adjustment practices. Ponda et al<sup>7</sup> reported that 42% of allergists worldwide adjust their dosage during peak pollen seasons, although less commonly in younger clinicians and the southern US<sup>8</sup> where long, variable, and overlapping pollen seasons make dose adjustment practically and scientifically unjustified. The survey reported that practices that “always” dose adjust in season reported fewer grade 2 or 3 SRs, without specifying SR severity or frequency in season.<sup>8</sup> The largest proportion of SRs did not occur during pollen season (35%), interestingly.<sup>5</sup> These survey-based studies suffer from significant and concerning limitations including indirect, voluntary, and variable participation, recall bias, imprecisely defined pollen seasons unverified by pollen counts, incomplete longitudinal consideration of multifactorial precipitators, and lack of in-versus-out-of-season SR rates among the nonsensitized.

In contrast, our study is the first to report SR rates both during pollen season and out-of-season among mountain cedar allergic and nonallergic patients. Survey data indicate that 63% of practices dose reduce in cases of previous in-season SRs<sup>9</sup>; however, a history of previous SR was not a significant risk factor in our data (Table 1). To our knowledge, this study is the first to

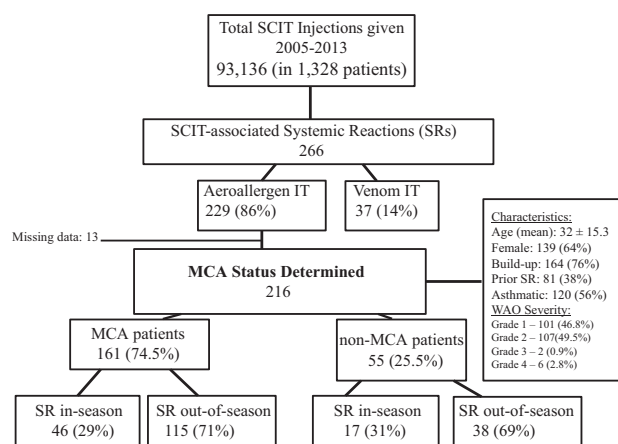


**FIGURE 1.** Characteristics of SCIT-associated systemic reactions. *MCA*, Mountain cedar allergy; *SCIT*, subcutaneous immunotherapy; *WAO*, World Allergy Organization.

**TABLE I.** Comparison with mountain cedar allergic and non-mountain cedar allergic systemic reaction occurrences and precipitating factors

|                                                        | Mountain cedar allergic<br>n = 161 | Non-mountain cedar allergic<br>n = 55 | Totals<br>n = 216 | P value |
|--------------------------------------------------------|------------------------------------|---------------------------------------|-------------------|---------|
| Experienced SRs during mountain cedar season           | 46 (29%)                           | 17 (31%)                              | 63 (29%)          | .73     |
| Experienced SRs outside mountain cedar season          | 115 (71%)                          | 38 (69%)                              | 153 (71%)         |         |
| Precipitating factors for SR*                          |                                    |                                       |                   |         |
| Female                                                 | 101 (63%)                          | 38 (69%)                              | 139               | .42     |
| Build-up phase                                         | 120 (75%)                          | 44 (80%)                              | 164               | .47     |
| Greater than 1 SCIT shot                               | 99 (61%)                           | 32 (58%)                              | 131               | .75     |
| High potency vial (yellow [1:10 v/v] or red [1:1 v/v]) | 123 (76%)                          | 35 (64%)                              | 158               | .078    |
| Asthmatic                                              | 67 (42%)                           | 27 (49%)                              | 94                | .35     |
| Treated with more than 1 dose of epinephrine           | 55 (34%)                           | 18 (33%)                              | 73                | .87     |
| Prior Hx of SCIT systemic reaction                     | 62 (39%)                           | 19 (35%)                              | 81                | .63     |
| Systemic reaction severity (WAO grade 3 or 4)          | 8 (5%)                             | 0 (0%)                                | 8                 | .21     |

*SCIT*, Subcutaneous immunotherapy; *SR*, systemic reaction; *WAO*, World Allergy Organization.

\*Denominators differ for each factor based on available data.

investigate these variables among SRs occurring within a single institution. We found no difference in reaction grade severity between the MCA and non-MCA SRs during or outside pollen

season. Study limitations include that the majority of SRs were mild, frequency or duration of IT was unavailable, and most patients were polysensitized to seasonal and perennial aeroallergens, which is commonly seen in clinical practice but may itself be a SR risk factor.

Yet, the negative consequences of unsubstantiated seasonal dose adjustment should not be overlooked and are not inconsequential. They include the risk of dosing error, false reassurance of lowered SR risk, and delivering subtherapeutic immunotherapy.

In conclusion, natural in-season pollen exposure, in a model as robust as MC pollination, does not appear to impact SR rates. No pattern between pollen counts and the number, timing, or severity of SRs was observed over 8 seasons. These data suggest that administration of SCIT during pollen season is not a risk factor for SR, and the practice of seasonal dose adjustment may not be warranted.

## Acknowledgments

The authors wish to thank Paul Ratner, MD, MBA, for the pollen count data and Kevin M. White, MD, for his valuable review of the manuscript.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication June 8, 2016; revised February 24, 2017; accepted for publication March 17, 2017.

Available online May 9, 2017.

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2213-2198

Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2017.03.021>

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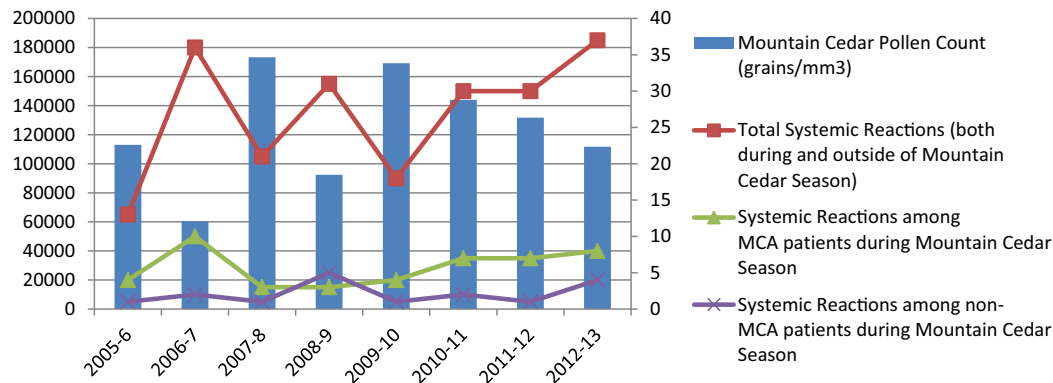


**FIGURE E1.** This graph compares mountain cedar pollen counts and systemic reactions from 2005 to 2013. Despite yearly variability in pollen counts, no consistent correlation between pollen count and systemic reaction occurrences was observed. Systemic reactions occurred among both the mountain cedar allergic and nonallergic in season irrespective of pollen count variations, suggesting that pollen counts/exposures are not a direct risk factor for systemic reactions. *MCA*, mountain cedar allergy.

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