

# In-season Dosage Adjustment for Pollen Subcutaneous Immunotherapy: The Controversy Continues



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Allergen-specific immunotherapy (AIT) for hay fever due to ragweed, grass, birch, and mountain cedar (MC) pollens relieves symptoms in controlled studies. The occurrence of systemic reactions (SRs) is a significant problem that hinders the continuation of such treatment. A number of patient and treatment factors increased SRs: delayed administration of epinephrine, short observation time after subcutaneous immunotherapy (SCIT), dosing error, use of high-potency vials, medically unsupervised SCIT administration, coexisting poorly controlled asthma, use of  $\beta$ -blockers, and coseasonal initiation of SCIT.<sup>1-3</sup> It is crucial for allergists to know these risk factors because most of them are avoidable. The most controversial of these risk factors for SRs is the initiation of SCIT during the pollen season, when different clinical trials and observational studies provided conflicting data for increased SRs during the pollen season. As a result, there is a substantial difference in the practices of allergists worldwide whether to adjust SCIT dosage during peak pollen seasons.<sup>4</sup>

*Juniperus ashei* is a drought-tolerant evergreen tree that is native to northeastern Mexico and the southcentral United States, with the largest areas being in central Texas. The pollen causes severe allergic reactions for some people in the winter, which is known in the area as MC or cedar fever. Exposure to MC is a robust model for studying the effects of natural pollen exposure as the tree pollinates consistently in winter every year. In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Wong et al<sup>5</sup> reviewed the occurrence of SRs in relation to SCIT during both in-season and out-of-season exposures to MC from 2005 to 2013. This multiyear retrospective cohort study examined different risk factors, including annual MC pollen exposure, for the occurrence of SCIT-associated SRs among patients with and without mountain cedar allergy (MCA). They found the SR rate for aeroallergens to be 0.25% per injection, which was comparable to published figure in the literature. No fatalities occurred. SRs occurred during the MC season in 29% (63 of 216) and the remaining 71% (153 of 216) occurred out of MC season. There was no significant difference between SRs occurring in patients with MCA during the MC

season (73%) versus SRs occurring in patients with MCA out of MC season (75%). Similarly, there was no significant difference between SRs occurring in patients without MCA during the MC season (27%) versus SRs occurring in patients without MCA out of the MC season (25%). Besides, the SRs did not appear to be associated with days of peak pollen counts during MC seasons.

The strengths of this study relate to the more homogeneous nature of real-life surveillance data of patients retrieved from this single-center cohort as well as the predominant, robust, and consistent exposure of these patients to MC pollen. All patients also followed fixed build-up schedules and standardized follow-up routine. The peak MC pollen counts fluctuated widely during the 8-year study period (see Figure E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)), but there was no clustering of SRs in years with high pollen counts. A previous survey revealed heterogeneous practices for in-season adjustment of SCIT dosages among allergists worldwide.<sup>4</sup> Different pollens account for hay fever in different geographical locations, and these pollens exhibit different aerodynamic properties that prohibit the generalizability of in-season dose adjustment practices. Another strength is that this study retrieved both in-season and out-of-season SR data from patients who are allergic and nonallergic to MC, which facilitated the more accurate delineation of the association between SRs and MC seasons. In addition, patients who underwent venom immunotherapy in their center were excluded because they tended to report higher SRs (14%-15% for bee venom and 3% for wasp venom).<sup>6</sup>

Nonetheless, this study analyzed data in a relatively small number of patients with SRs. Ninety-six percent of the reported SRs were mild (grade 1 or 2). Only 8 patients suffered from more severe SRs (World Health Organization grade 3 or 4). Therefore, this study had limited ability to detect risk factors for significant SRs in relation to MC. This limitation was supported by the lack of significant associations between SRs and known risk factors such as asthma, high-potency vials, history of SRs after SCIT, and administration of more than 1 SCIT shot (Table I). SRs of grade 3 or 4 severity occurred in 5% of MC-allergic patients but none in nonallergic patients, with the lack of statistical significance for this observation possibly explained by the small sample size. Besides, findings from this study might not be extrapolated to SCIT against pollens other than MC.

An annual surveillance study of SRs from SCIT was initiated in North America in 2008.<sup>7</sup> Up to 2013, 2 fatalities were reported that occurred under the care of allergists and another 2 under the care of nonallergists. The rate of SRs remained stable at 1.9% of patients, with 0.08% and 0.02% experiencing grade 3 and 4 SRs, respectively. This surveillance found fewer severe SRs in practices that never administered SCIT in patients with uncontrolled asthma, whereas lowering doses during pollen

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seasons for patients with highly positive skin test results reduced SRs of all severity grades. On the contrary, a recent SR of 8 studies for pollen allergens ( $n = 947$ ) found comparable SRs in coseason initiation of SCIT (0%-7%), "after peak season" or out-of-season initiation (0%-6%), and placebo (0%-7%).<sup>2</sup> Because serious adverse events were rare (0%-2%), this study might be underpowered to examine the effect of coseasonal initiation of SCIT for the more severe SRs. Additional data with standardized regimens and doses of SCIT are needed.

There is a concern of underreporting of SRs in surveys, clinical practice and trials, and pharmacovigilance data. The clinical features that define a reaction as anaphylaxis are applied inconsistently in research and clinical practice. The 2010 grading system of the World Allergy Organization classified SRs in relation to AIT on the basis of the organ system(s) involved and reaction severity. Cox et al<sup>8</sup> presented a proposed modification of this grading system that allows for classification of less severe SRs, whereby increasing the reporting accuracy of these SRs for better comparison across different studies and treatment protocols.<sup>8</sup>

The safety of patients undergoing AIT can be enhanced by alternative approaches. Food and Drug Administration–approved grass and ragweed sublingual immunotherapy tablets have been available in the United States since 2014. The national surveillance found that SRs occurred in 1.4% of patients receiving off-label SLIT,<sup>7</sup> including 0.03% with grade 3 SRs. There were no SLIT-related grade 4 SRs or fatalities. Ravi and Rank<sup>9</sup> reported sublingual immunotherapy to have low rates of SRs. A recent review discussed unresolved issues of SLIT such as prescription of epinephrine autoinjectors, regimens for polysensitized patients, and optimal timing and duration of administration.<sup>10</sup> Second, AIT using natural modified allergen vaccines is safe even at higher doses and in mixtures of unrelated allergen extracts.<sup>11</sup> In addition, novel approaches such as the encapsulation of allergens or DNA vaccines into nanostructures warrant further investigation. This treatment option may provide advantages compared with the conventional AIT with non-encapsulated allergen extracts by protecting protein/DNA molecule from degradation, delivering higher local allergen concentrations to the site of action, and preventing recognition of encapsulated allergens by the immune system.<sup>12</sup>

In conclusion, this study was unable to settle the debate on dosage adjustment for SCIT during pollen seasons. Although the controversy on this clinical practice continues, there is a clear appeal for collaborative surveillance studies that report the occurrence of SRs involving sufficiently large group of pollen-allergic patients. Until then, we expect to find differing practices about in-season dose adjustment in relation to pollen SCIT.

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