Original Article

Coseasonal Initiation of Allergen Immunotherapy: A Systematic Review

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What is already known about this topic? Patients may seek treatment during pollen season, but physicians may be reluctant to initiate allergen immunotherapy (AIT) coseasonally owing to a concern that AIT initiation during the allergy season may increase the risk of adverse events.

What does this article add to our knowledge? From published studies, coseasonal AIT initiation appears to be well tolerated. No safety risk of coseasonal initiation versus out-of-season initiation, or coseasonal initiation versus placebo was apparent.

How does this study impact current management guidelines? The available published data suggest that coseasonal initiation of AIT may be possible without increasing the risk of systemic, serious, or severe reactions. More well-controlled studies are needed to establish the safety of coseasonal initiation.

BACKGROUND: It is unclear whether allergen immunotherapy (AIT) can be safely initiated during the pollen season (coseasonal initiation [CSI]) because of a potential increased risk of systemic allergic reactions.

OBJECTIVE: To systematically review publications reporting the safety of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) CSI to validate or invalidate the perception of increased safety risk.

METHODS: PubMed, EMBASE, Ovid, Literatura Latino Americana em Ciências da Saúde (LILACS), and Cochrane Library databases were searched without limits for studies of any design reporting SCIT or SLIT CSI for pollen allergen. Congress abstracts were included.

RESULTS: Nineteen eligible studies were identified: 8 SCIT (n = 947 subjects total; n = 340 double-blind placebo-controlled [DBPC]) and 11 SLIT (n = 2668 subjects total; n = 565 DBPC). Study characteristics and safety reporting were heterogeneous. No epinephrine administrations were reported. Discontinuation frequencies were 6% or less and 10% or less with SCIT and SLIT CSI, respectively. In SCIT studies, systemic allergic reaction frequency was 0% to 7% with "up to peak season" or CSI, 0% to 6% with "after peak season" or out-of-season initiation, and 0% to 7% with placebo. In SCIT studies, serious treatment-related adverse event (AE) frequency with CSI ranged from 0% to 2%; few severe AEs were reported. In SLIT studies, systemic allergic reaction frequency ranged from 0% to 4% with CSI, 0% with out-of-season initiation, and 0% to 2% with placebo. Overall, 2 serious treatment-related AEs with SLIT CSI were reported. Severe AE frequency in SLIT studies ranged from 0% to 8% with CSI, 0% to 12% with out-of-season initiation, and 0% to 8% with placebo.

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Abbreviations used
AE- adverse event
AIT- Allergen immunotherapy
DBPC- double-blind, placebo-controlled
RCT- randomized controlled trial
SCIT- subcutaneous immunotherapy
SLIT- sublingual immunotherapy

CONCLUSIONS: No increase in AEs of concern was observed with SCIT or SLIT CSI; however, additional data with standardized regimens and doses are needed. **(J Allergy Clin Immunol Pract 2016;■:■-■)**

Key words: *Allergen immunotherapy; Allergic rhinoconjunctivitis; Co-seasonal; In-season; Initiation; Intra-seasonal; Safety*

Symptoms of allergic rhinoconjunctivitis may become bothersome enough for patients to seek treatment, particularly during the allergy season. Allergen immunotherapy (AIT) is a treatment option for allergic rhinoconjunctivitis[1]; however, there is a concern that AIT initiation during the allergy season (coseasonal initiation) may increase the risk of adverse events (AEs). This concern likely stems from survey results and case reports on subcutaneous immunotherapy (SCIT) systemic allergic reactions. In 2 American Academy of Allergy, Asthma & Immunology surveys of its members conducted for the years 1985 to 1989, and 1990 to 2001, it was found that 29% of the fatalities and 46% of near-fatal reactions associated with SCIT occurred during the pollen season.[2-4] Furthermore, a similar annual survey of American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology (ACAAI) members found that approximately 64% of systemic allergic reactions with SCIT occurred during pollen seasons.[5] In contrast, a prospective study of 4,578 patients in the United States who received 346,251 injections found no direct correlation between systemic allergic reactions and seasonal pollen counts.[6] These surveys and the study did not include patients receiving sublingual immunotherapy (SLIT), and it is unknown whether the identified risk factors for systemic allergic reactions with SCIT are applicable to SLIT.[7]

Most AIT treatment guidelines do not directly address the issue of coseasonal initiation. The US guidelines published by the American Academy of Allergy, Asthma & Immunology/ACAAI joint task force recommend not increasing, or perhaps reducing, AIT doses during the season, especially if symptoms are poorly controlled.[8] European allergy societies suggest adjusting dosage or postponing AIT during symptomatic periods.[9] Some AIT guidelines directly address coseasonal initiation, but either are not definitive in their recommendations or do not provide evidence for their recommendations. For example, the 2014 German AIT guidelines state that data are too sparse to provide a recommendation regarding SCIT coseasonal initiation, although the authors recognize that in a randomized, double-blind, placebo-controlled (DBPC) trial, coseasonal initiation with SCIT was generally well tolerated.[10] The authors state that SLIT may be initiated coseasonally, in accordance with specific product information leaflets.[10] In contrast, a 2006 European Academy of Allergy and Clinical Immunology guideline specifically recommends against initiating SCIT during allergen seasons,[11] but does not address SLIT. No background or evidence is given for the recommendation.

Given this discrepant data, this systematic review was performed to assess the published evidence regarding the safety of coseasonal initiation with SCIT and SLIT for pollen-related allergic rhinoconjunctivitis to validate or invalidate the perception of increased systemic, serious, and severe events.

METHODS

The review was executed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for reporting of systematic reviews.[12] The objectives and methods were decided via discussion among the authors; no protocol was developed or published for the review.

Search methods and eligibility

PubMed, EMBASE, Ovid, Literatura Latino Americana em Ciências da Saúde (LILACS), and the Cochrane Library were searched for studies of any design related to AIT coseasonal initiation published by March 18, 2015. The search string used was "immunotherapy AND (allergy OR allergen) AND ((in-season) OR (peak season) OR (season AND risk factor) OR (season AND initiation) OR (coseasonal) OR (co-seasonal))." No search limits were used. The resulting titles and abstracts were preliminarily assessed for relevance by 2 independent reviewers; disagreements at this stage were resolved by review of the full-text articles for fulfillment of inclusion criteria. Full-text articles of the relevant publications were further assessed for eligibility by 2 independent reviewers. Reference lists in the identified eligible publications were manually reviewed for additional relevant publications.

Eligible studies were those reporting the coseasonal initiation of SCIT or SLIT (drops or tablets) for a pollen allergen conducted in adults or children. Observational, retrospective, and randomized controlled trials (RCTs) published as full-length articles or congress abstracts were included. Publications were excluded if the timing of AIT initiation could not be confirmed. Publications that did not report at least 1 of the following safety outcomes were also excluded: discontinuations due to AEs, systemic allergic reactions, serious treatment-related AEs, or severe reactions. Risk of bias and quality assessment from the included studies are described in this article's Online Repository at www.jaci-inpractice.org.

Data extraction and interpretation

Data on study characteristics and safety outcomes from eligible publications were extracted by 1 reviewer, and data-checked by a second reviewer. Because of the heterogeneity in the designs, AIT formulations, doses, and safety reporting of the included studies, meta-analyses could not be performed. Data on AEs were extracted exactly as reported in each publication. No attempt was made to recategorize the reported AEs on the basis of more current or more accepted definitions.

The primary analysis was to assess the safety outcomes of interest in subjects receiving AIT initiated coseasonally versus out-of-season initiation. Secondary analyses compared safety outcomes of subjects receiving active treatment or placebo initiated coseasonally, or simply described safety outcomes of interest with coseasonal AIT initiation when no comparator was evaluated.