

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 Latina 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. © 2016 American Academy of Allergy, Asthma & Immunology (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 rhinoconjunctivitis¹; 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.

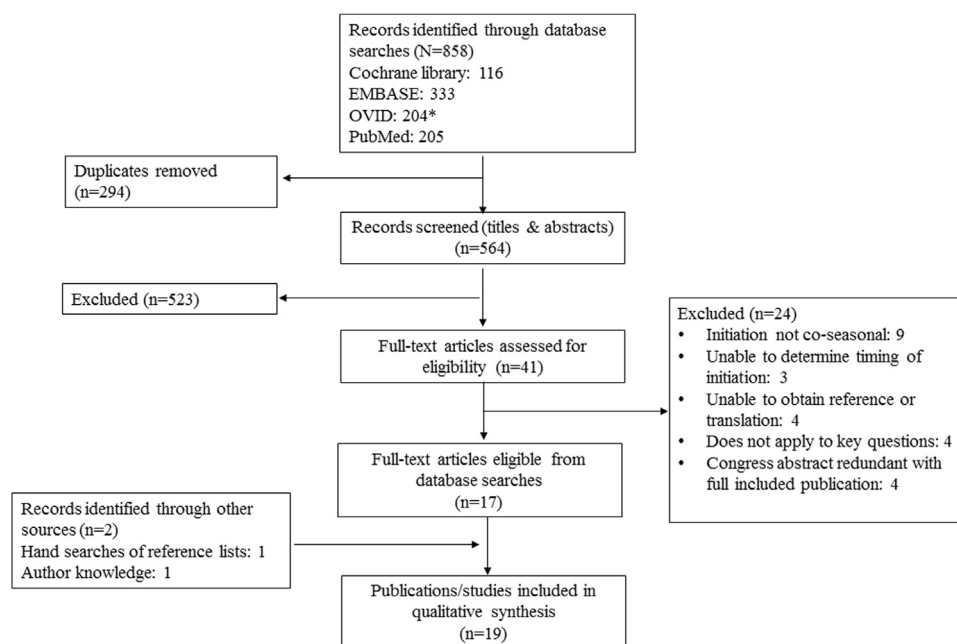


FIGURE 1. Flow diagram of publication search and selection. *An initial search that did not contain the terms “coseasonal” or “co-seasonal” returned 204 records. The final search terms that included “coseasonal” or “co-seasonal” returned only 100 records for unknown reasons. The initial 204 records were used to ensure completeness.

RESULTS

Search results

The database searches identified 858 potential publications (Figure 1); 41 full-text publications were further assessed for eligibility. Of these, 20 were excluded because treatment initiation was not coseasonal, timing of treatment initiation could not be confirmed, the reference or an English translation was not available, or there was no information applicable to the key safety questions. In addition, 4 congress abstracts were excluded because they were later published as 4 of the included full publications. Two additional eligible publications were identified from author knowledge and manually searching the reference lists from the other eligible publications. In total, 19 publications representing 19 individual studies and 3615 subjects were included in the systematic review.

Of the 19 eligible studies, 8 were for SCIT ($n = 947$ subjects total; $n = 340$ DBPC-RCT) and 11 were for SLIT ($n = 2668$ subjects total; $n = 565$ DBPC-RCT). Most (5 of 8) of the SCIT studies were published as congress abstracts only. The type of allergen extract, dosing, and the comparator versus coseasonal initiation were highly variable among the SCIT studies (Table I).

Most (10 of 11) of the SLIT studies were published as full manuscripts. The dosing regimens and comparator versus coseasonal initiation were highly variable among the studies (Table II).

Study designs and quality

The designs of the SCIT studies were 3 DBPC-RCTs; 2 prospective, observational studies; and 3 retrospective studies. Three SCIT studies directly compared coseasonal AIT initiation

with out-of-season initiation (1 prospective observational study and 2 retrospective studies).¹³⁻¹⁵ The designs of the SLIT studies were 3 DBPC trials; 3 prospective, observational studies (Sieber et al¹⁶ reported 3 separate studies in 1 publication, for a total of 5 prospective, observational studies); 4 prospective, open-label, RCTs; and 1 retrospective study. Five SLIT studies directly compared coseasonal AIT initiation with out-of-season initiation (3 prospective, observational studies and 2 prospective, open-label, RCTs).¹⁶⁻²⁰ Study bias and quality are described in this article’s Online Repository at www.jaci-inpractice.org.

In general, safety reporting among the eligible SCIT publications was heterogeneous and the incidence or number of events for the safety outcomes of interest often was not reported. This was likely because 5 of the studies were published as congress abstracts only. Safety reporting for the SLIT publications was more consistent versus SCIT publications. Reporting heterogeneity in both the SCIT and SLIT studies was apparent in that definitions of “systemic” AEs varied (when it was defined), and details of systemic or severe AEs were often not described.

Discontinuations in SCIT coseasonal initiation studies

Of the 3 SCIT studies that directly compared coseasonal initiation with out-of-season initiation, only 1 reported discontinuation rates, which were 3% for “up-to-peak season” initiation and 2% for “after peak season” initiation (Table III).¹³ The frequency of discontinuations with coseasonal initiation was 6% or less in the remaining SCIT studies (see Table E3 in this article’s Online Repository at www.jaci-inpractice.org).

TABLE I. Characteristics of SCIT studies

Citation	Comparator vs coseasonal initiation	Study design	No. of patients	Allergen	Extract	Disease (AR, asthma, or both)
Reiber et al, 2013 ¹³	Up to peak season initiation vs after peak season initiation	Prospective, observational	250	Grass pollen	Sustained-release formulation adsorbed to aluminum hydroxide (Alutard SQ)	AR with or without asthma
Lee et al, 1982 ²²	Placebo	DBPC-RCT	90	Mountain cedar pollen	Mountain cedar extract in glycerol-saline	AR with or without asthma
Pfaar et al, 2012 ²³	Placebo	DBPC-RCT	148	Grass pollen	Sustained-release formulation adsorbed to aluminum hydroxide (Alutard SQ)	AR
Congress abstracts						
Werner, 2013 ¹⁵	Initiation outside of pollen season	Retrospective	84	Grass pollen	Highly polymerized grass extract adsorbed onto aluminum hydroxide (Clustoid)	AR
Stelzer and Bubel, 2013 ¹⁴	Initiation outside of pollen season	Retrospective	122	Tree pollen	Highly polymerized birch, alder, hazel mixture adsorbed onto aluminum hydroxide (Clustoid)	AR
Klimek et al, 2013 ²¹	Placebo	DBPC-RCT	202	Birch pollen	Modified depigmented gluteraldehyde polymerized (Depiquick Birch)	AR
Bubel, 2010 ²⁵	None	Prospective, observational	20	Grass pollen	Highly polymerized grass extract adsorbed onto aluminum hydroxide (Clustoid)	AR
Paterok, 2012 ²⁴	None	Retrospective	31	Grass pollen	Highly polymerized grass extract adsorbed onto aluminum hydroxide (Clustoid)	AR

AR, Allergic rhinitis; NA, not available; PNU, protein nitrogen unit; SQ-U, standardized quality unit.

Systemic allergic reactions in SCIT coseasonal initiation studies

Of the 3 SCIT studies that directly compared coseasonal initiation with out-of-season initiation, all 3 reported results on the rate of systemic allergic reactions (Table III). In the prospective observational study that compared “up to peak season” versus “after peak season” SCIT initiation, the frequency of systemic allergic reactions (defined as respiratory symptoms) was “low” or 0%, respectively.¹³ The frequency of systemic allergic reactions (defined as MedDRA preferred terms of pruritus or generalized pruritus) was 2% for “up to peak season” and 6% for “after peak season” initiation. In the 2 retrospective SCIT studies with comparative data, the rate of systemic allergic reactions in both studies was 0% in subjects receiving coseasonal initiation versus 0.2% for subjects who initiated outside the pollen season (described as Grade 1⁴³ in one of the studies).^{14,15}

In the 3 DBPC-RCTs, the rate of systemic allergic reactions ranged from 1% to 7% in subjects receiving SCIT coseasonal initiation and 0% to 7% in subjects receiving placebo (Table E3).²¹⁻²³ In one of the DBPC-RCTs,²³ the rate of systemic allergic reactions (defined as any reaction not related to the injection site) was similar between coseasonally initiated SCIT (7%) and placebo (6%; $P = .74$). However, these data must be interpreted with caution given the relatively small sample size. In the retrospective SCIT study that had no comparator group, no systemic allergic reactions were observed with coseasonal initiation (Table E3).²⁴

Epinephrine use in SCIT coseasonal initiation studies

No epinephrine use was noted in any of the SCIT coseasonal initiation studies. However, this does not exclude unreported use of epinephrine as part of standard management of AEs.

TABLE I. Continued

Timing of coseasonal initiation	Duration of updosing	First dose		Maintenance dose		End points
		Reported unit	Major allergen (μg)	Reported unit	Major allergen per dose (μg)	
Up to peak = increasing pollen exposure Peak = July 15, 2009 After peak = declining pollen exposure	1-3 d	100 SQ-U	NA	10,000 SQ-U through pollen season at week 2 and week 6 after updosing; then 100,000 SQ-U every 1-2 wk	NA	Safety
Late December	Varied	0.16 and 6.99 PNU	NA	82 and 245 PNU/2× per week	NA	Symptoms, medication use, safety, immunology
After ≥3 consecutive days of grass pollen counts >5 grains/m ³	8 d	100 SQ-U	NA	10,000 SQ-U every 2 wk	NA	IgE-blocking factor
Congress abstracts						
May, June, July	1 d	2000 TU/mL	4.8 μg of group 1	5,000 TU/mL once a month	12 μg of group 1	Safety, compliance
February to April	1 d	2000 TU/mL	NA	5,000 TU/mL once a month	NA	Safety
Initiated once subject achieved coseasonal symptom score of defined magnitude	1 d	0.2 and 0.3 mL of 1000 DPP/mL	NA	0.5 mL of 1,000 DPP/mL per week	NA	Symptoms, medication use, safety
NA	7 d	3333 TU/mL	8 μg of group 1	5,000 TU/mL every month	12 μg of group 1	Safety, compliance
NA	1 d	2000 TU/mL	4.8 μg of group 1	5,000 TU/mL once a month	12 μg of group 1	Safety, compliance

Serious treatment-related AEs in SCIT coseasonal initiation studies

Of the 3 SCIT studies that directly compared coseasonal initiation with out-of-season initiation, only 1 reported results for serious treatment-related AEs (Table III). In the prospective, observational study that compared “up to peak season” versus “after peak season” coseasonal SCIT initiation, the frequency of serious treatment-related AEs was 2% in both groups (5 events total).¹³ Two of the 5 events were considered medically important: anaphylaxis with generalized urticaria, dizziness, and itching during “after peak season” coseasonal initiation and cough, dyspnea, and hives during “up to peak season” coseasonal initiation. The other 3 serious treatment-related AEs were dyspnea and urticaria during updosing “after peak season” and dyspnea (n = 1) and laryngeal edema, urticaria, flushing, and cough (n = 1) during “up to peak season” coseasonal initiation. More

details are provided in this article’s Online Repository at www.jaci-inpractice.org. All episodes were successfully treated with intravenous corticosteroids and antihistamine, and all but 1 patient continued treatment.

In the DBPC-RCT reported by Pfaar et al²³ and a prospective, observational study that had no comparator group,²⁵ there were no serious treatment-related AEs associated with coseasonal initiation (Table E3).

Severe reactions in SCIT coseasonal initiation studies

Most severe AEs with coseasonal SCIT initiation were large, local injection site swellings (Table III and Table E3). Of the 3 SCIT studies that directly compared coseasonal initiation with out-of-season initiation, all 3 reported the rate of severe AEs (Table III). In the prospective, observational study that

TABLE II. Characteristics of SLIT studies

Citation	Comparator vs coseasonal initiation	Study design	No. of patients	Allergen	Formulation	Disease (AR, asthma, or both)
Schwab et al, 2013 ²⁰	Postseason initiation	Prospective, observational	662	Grass pollen	Timothy grass tablet (Grazax)	AR with or without asthma
Ariano et al, 2009 ¹⁷	Preseasonal, peak initiation, and after peak initiation	Prospective, observational	70	Grass or tree pollen	5-grass pollen extract drop mixture or birch, alder, hazel drop mixture	AR with or without asthma
Sieber et al, 2010 ¹⁶	Study 1: preseasonal Study 2: coseasonal Study 3: preseasonal or coseasonal	3 Prospective, observational studies	1052	Grass, rye, weeds, or tree pollen	Standardized 5-grass pollen extract drop mixture; birch, alder, hazel extract drop mixture; standardized rye extract drops; standardized weed extract drops	AR with or without asthma
Leonardi et al, 2010 ¹⁸	Preseasonal; standard pharmacotherapy control	Prospective, open-label, RCT	33	Olea pollen	Monomeric carbamylated allergoid Olea tablet (Lais)	AR with or without asthma
Pajno et al, 2011 ¹⁹	Preseasonal	Prospective, open-label, RCT	80	Grass pollen	5-grass pollen extract drop mixture (Staloral)	AR with or without asthma
Novembre et al, 2004 ²⁸	Standard pharmacotherapy	Prospective, open-label, RCT	113	Grass pollen	5-grass pollen extract drop mixture	AR
D'Anneo et al, 2008 ²⁶	Standard pharmacotherapy	Prospective, open-label, RCT	65	Parietaria pollen	Monomeric carbamylated allergoid Parietaria tablet (Lais)	AR with or without asthma
Reich et al, 2011 ³⁰	Placebo	DBPC-RCT	276	Grass pollen	Timothy grass tablet (Grazax)	AR with or without asthma
Vervloet et al, 2007 ³¹	Placebo	DBPC-RCT	76	Tree pollen	Purified standardized <i>J ashei</i> extract drops	AR
Ott et al, 2009 ²⁹	Placebo	DBPC-RCT	213	Grass pollen	5-grass pollen extract drop mixture (Staloral)	AR with or without asthma
Congress abstracts						
Dichmann, 2011 ²⁷	None	Retrospective, single center	28	Tree pollen	Aqueous perlingual spray (SULGEN spray) of birch or birch, elder, hazel extract mixture	AR

AR, Allergic rhinitis; AU, allergic unit; BAU, bioequivalent allergen unit; BU, biologic unit; IR, index of reactivity; NA, not available; VAS, visual analog scale.

TABLE II. Continued

Timing of coseasonal initiation	Duration of up dosing	First dose		Maintenance dose		End points
		Reported unit	Major allergen (μg)	Reported unit	Major allergen per dose (μg)	
June to August	None	2800 BAU	~ 15 μg <i>Phl p 5</i>	2800 BAU/d	~ 15 μg <i>Phl p 5</i>	Symptoms, medication use, safety, compliance
Peak season defined as pollen counts >50/m ³	1 d	30 IR	2.4 μg <i>Phl p 5</i> or 4.92 μg <i>Bet v 1</i>	300 IR/3× per week	24 μg <i>Phl p 5</i> or 49.2 μg <i>Bet v 1</i>	Safety
Anticipated beginning of season based on local pollen calendars	Study 1: 24 d Study 2: 1 d Study 3: 11 d	Study 1: 1 IR Study 2: 30 IR Study 3: 10 IR	NA	Study 1: 150 IR/d, 5 d/wk Study 2: 240 IR/d Study 3: 240 IR/d coseasonal or 240 IR/every other day preseasonal	NA	Symptoms, medication use, safety
May to mid-June	4 d	300 AU	NA	Preseasonal: 1000 AU 3× per week Coseasonal: 1000 AU 5× per week	0.5 μg <i>Ole e 1</i>	Well- being on VAS, medication use, safety
Within first few days of GPS (March)	6 d	NA	NA	6 drops of 300 IR/mL for 5 d/wk	4.2 μg <i>Phl p 5</i>	Symptoms, medication use, immunology
February 15 to June 15	15 d	1 drop of 0.04 BU/mL	0.00016 μg group 5	5 drops of 25 BU/mL/d, 5 d/wk	0.5 μg group 5	Asthma development, symptoms, medication use
April	3 d	1000 AU	NA	1000 AU/wk or 3000 AU/wk	NA	Well- being on VAS, medication use, bronchial hyperreactivity
Within first 3 wk of GPS, defined as first of 3 consecutive days of grass pollen counts ≥10 grains/m ³	None	2800 BAU	~ 15 μg <i>Phl p 5</i>	2800 BAU/d	~ 15 μg <i>Phl p 5</i>	Immunology, safety
January, February, March	1 d	30 IR	22.8 μg <i>Jun a 1</i>	300 IR/d	228 μg <i>Jun a 1</i>	Symptoms, medication use, safety, immunology
First day of GPS, defined as ≥100 pollen grains/m ³	1 d	30 IR	2.1 μg <i>Phl p 5</i>	300 IR/d	21 μg <i>Phl p 5</i>	Symptoms, medication use, safety, immunology
Congress abstracts						
NA	NA	NA	NA	2 puffs daily	NA	Safety and compliance

TABLE III. Safety outcomes of SCIT studies that directly compared coseasonal and out-of-season initiation

Citation	Discontinuations due to any AEs, n (%)	Systemic allergic reactions, n (%)	Serious treatment-related AEs, n (%)	Severe AEs, n (%)
Reiber et al, 2013 ¹³	Up to peak GPS: 8 (3%) • Asthma, urticaria, angioedema, cardiac pain, oral pruritus, allergic rhinoconjunctivitis, injection site swelling, laryngeal edema, flushing, cough After peak GPS: 1 (2%) • Injection site swelling, dyspnea	Respiratory symptoms: Up to peak GPS: “low frequency” After peak GPS: 0 Pruritus: Up to peak GPS: 2% After peak GPS: 6%	Up to peak GPS: 4 (2%) • Cough, dyspnea, hives, urticaria, laryngeal edema, flushing After peak GPS: 1 (2%) • Anaphylaxis with generalized urticaria, dizziness, itching	Up to peak GPS: 8 (7%)* • Pyrexia, headache, asthma, dyspnea, angioedema, urticaria After peak GPS: 6 (12%)* • Anaphylactic reaction, dizziness, pruritus, urticaria, hot flush ≥5 cm to <8 cm diameter local swelling: Up to peak GPS: 97 (4%) After peak GPS: 16 (3%)
Congress abstracts				
Werner, 2013 ¹⁵	NR	Coseasonal: 0 Outside pollen season: 1 (0.2%) • Grade 1 as described by Pfaar et al ⁴³	NR	Coseasonal: 0 Outside pollen season: 0
Stelzer and Babel, 2013 ¹⁴	NR	Coseasonal: 0 Outside pollen season: 0.2% • Headache and cold symptoms	NR	Coseasonal: 0 Outside pollen season: 0

GPS, Grass pollen season; NR, not reported.

*Noninjection site reactions.

compared “up to peak season” versus “after peak season” coseasonal SCIT initiation, the frequency of severe AEs other than injection site reactions was 7% with “up to peak season” and 12% with “after peak season.”¹³ One of these was an anaphylactic reaction in the “after peak season” group (described above). In the 2 retrospective studies that compared coseasonal initiation with out-of-season initiation, there were no severe AEs reported in either group.^{14,15}

There were no severe AEs other than local injection site swelling in the DBPC-RCTs or studies with no comparators to coseasonal initiation (Table E3).

Discontinuations in SLIT coseasonal initiation studies

Of the 5 SLIT studies that directly compared coseasonal initiation with out-of-season initiation, 4 reported discontinuation rates, which were 10% or less for coseasonal initiation and 12% or less for out-of-season initiation (Table IV). The frequency of discontinuation with coseasonal initiation was 7% or less in the remaining SLIT studies (see Table E4 in this article’s Online Repository at www.jaci-inpractice.org).^{17-20,26-31} This discontinuation rate is similar (ranges from 1% to 6%) to published data for treatment initiation outside of the season.^{32,33}

Systemic allergic reactions in SLIT coseasonal initiation studies

Of the 5 SLIT studies that directly compared coseasonal initiation with out-of-season initiation, 3 reported results on systemic allergic reactions (Table IV). Although the rate of systemic allergic reactions was not specifically reported in the

prospective, observational study reported by Ariano et al,¹⁷ it was noted that regardless of the timing of SLIT initiation (preseasonal, peak season, or after peak season), the systemic AEs were “mild and self-resolving.” No systemic allergic reactions were reported in the prospective, observational study of coseasonal and postseasonal initiation by Schwab et al,²⁰ or in the prospective, open-label RCT of coseasonal initiation, preseasonal initiation, and pharmacotherapy controls reported by Leonardi et al.¹⁸

In the 3 SLIT DBPC-RCTs, the rate of systemic allergic reactions ranged from 0.3% to 2% in subjects receiving coseasonal initiation and 0% to 1% in subjects receiving placebo (Table E4).²⁹⁻³¹ In a prospective, open-label RCT of coseasonal initiation versus pharmacotherapy, systemic allergic reactions occurred in 4% (n = 2) of coseasonally initiated patients and 2% (n = 1) of pharmacotherapy treated patients (Table E4).²⁸ No systemic allergic reactions occurred with coseasonal initiation in the retrospective study that had no comparator group.²⁷

Epinephrine use in SLIT coseasonal initiation studies

No epinephrine use was noted in any of the SLIT coseasonal initiation studies. However, unreported use of epinephrine as part of standard management of AEs cannot be excluded.

Serious treatment-related AEs in SLIT coseasonal initiation studies

Of the 5 SLIT studies that directly compared coseasonal initiation with out-of-season initiation, 2 reported results on serious treatment-related AEs (Table IV). In the prospective, observational study reported by Schwab et al,²⁰ 2 serious

TABLE IV. Safety outcomes of SLIT studies that directly compared coseasonal and out-of-season initiation

Citation	Discontinuations due to any AEs, n (%)	Systemic allergic reactions, n (%)	Serious treatment-related AEs, n (%)	Severe AEs, n (%)
Schwab et al, 2013 ²⁰	Coseasonal: 46 (7%) • Specific symptoms not reported Postseasonal: 5 (12%) • Specific symptoms not reported	Coseasonal: 0 Postseasonal: 0 • Defined as MedDRA preferred terms of hypersensitivity or anaphylactic reaction	Coseasonal: 2 (0.3%) • Asthma attack, dyspnea, swollen lips/tongue, loss of voice, nausea, fainting, hypotension, bradycardia, diarrhea, vomiting, stomach pain Postseasonal: 0	Coseasonal: 48 (8%) • Various Postseasonal: 5 (12%) • Local application site reactions, abdominal discomfort, pruritus, and sensation of foreign body
Ariano et al, 2009 ¹⁷	Preseasonal: 0 Peak initiation: 0 After peak initiation: 0	• Rate not specified in detail,* but systemic AEs in entire study described as “mild and self-resolving,” and included 6 cases of asthma Preseasonal: Conjunctivitis, wheezing, headache, fever Peak initiation: Abdominal pain, urticaria, conjunctivitis, rhinitis, nasal itching, wheezing, headache, fever, faintness After peak initiation: Urticaria, eczema, rhinitis, wheezing, headache, fever, faintness	NR	Preseasonal: 0 Peak initiation: 0 After peak initiation: 0
Sieber et al, 2010 ¹⁶	NR	NR	Coseasonal: 0 Preseasonal: 0	Rate not specified in detail; reported 89% of total AEs during titration and 87% of total AEs during maintenance were mild to moderate
Leonardi et al, 2010 ¹⁸	Coseasonal: 0 Preseasonal: 0 Pharmacotherapy: 0	Coseasonal: 0 Preseasonal: 0 Pharmacotherapy: 0	NR	Coseasonal: 0 Preseasonal: 0 Pharmacotherapy: 0
Pajno et al, 2011 ¹⁹	Coseasonal: 4 (10%) • Specific symptoms not reported Preseasonal: 1 (3%) • Recurrent abdominal pain	NR	NR	NR

NR, Not reported.

*Number of events reported, but not number of subjects.

treatment-related AEs were experienced by subjects who initiated coseasonal SLIT; one subject experienced an asthma attack, dyspnea, swollen lips/tongue, and loss of voice for 2 hours on day 5 of treatment; the other subject experienced nausea, fainting, hypotension, bradycardia, diarrhea, vomiting, and stomach pain 5 hours after the first treatment administration. None of the subjects in the postseasonal initiation group experienced a serious treatment-related AE. In the prospective, observational SLIT studies reported by Sieber et al,¹⁶ no subject in either the coseasonal initiation group or the preseasonal initiation group experienced a serious treatment-related AE.

No serious treatment-related AEs were reported with coseasonal initiation in the 3 SLIT DBPC-RCTs (Table E4).²⁹⁻³¹ In the prospective, open-label RCT versus pharmacotherapy by Novembre et al,²⁸ and the retrospective study that had no comparator group,²⁷ no serious treatment-related AEs were reported (Table E4).

Severe AEs in SLIT coseasonal initiation studies

Of the 5 SLIT studies that directly compared coseasonal initiation with out-of-season initiation, 4 reported results on severe AEs (Table IV). In the prospective, observational study reported by Schwab et al,²⁰ the rate of severe AEs was 8% in subjects receiving coseasonal initiation and 12% in subjects receiving postseasonal initiation; these varied from local reactions, to ear and eye disorders, gastrointestinal disorders, and others. In the prospective, observational study reported by Ariano et al,¹⁷ there were no severe AEs reported for any of the treatment initiation schedules (preseasonal, peak season, or after peak season). In the prospective, observational studies reported by Sieber et al,¹⁶ the severe AEs were not specifically described, but 89% of all AEs (coseasonal and out-of-season initiation combined) during titration were assessed as mild to moderate. In the prospective, open-label RCT reported by Leonardi et al,¹⁸ no severe AEs were reported with coseasonal initiation or preseasonal initiation.

In the SLIT DBPC-RCT published by Reich et al,³⁰ the rate of severe AEs was 4% in subjects receiving coseasonal initiation versus 0% in subjects receiving placebo (Table E4). In the SLIT DBPC-RCT published by Ott et al,²⁹ the rate of severe AEs was 7% in subjects receiving coseasonal initiation and 8% in subjects receiving placebo; symptoms were described as “nonsystemic” (Table E4). In the prospective, open-label RCT reported by Novembre et al,²⁸ no severe AEs were reported with coseasonal initiation or in the pharmacotherapy-only group (Table E4). No severe AE occurred with coseasonal initiation in the retrospective study that had no comparator group.²⁷

DISCUSSION

Traditionally, AIT is initiated many weeks before the onset of the pollen season to achieve a sufficient therapeutic effect before pollen-related symptoms begin. Realistically, patients may not seek evaluation and treatment until symptoms appear. Without the option of coseasonal initiation, these patients would remain dependent on pharmacotherapy that is not effective or tolerated in all patients, and may not return after the season to initiate AIT. Coseasonal initiation would enable more patients to begin treatment earlier in order to experience a potential long-term, disease-modifying benefit of AIT. The concern that AIT should not be initiated during the pollen season is likely due to survey data that suggest an increased risk in severe or life-threatening systemic allergic reactions (grades 3 and 4 by World Allergy Organization criteria³⁴) with SCIT during a pollen season.²⁻⁵ However, the survey data results were not confirmed in a prospective study⁶ and did not include SLIT, which appears to have a more benign safety profile than does SCIT.³⁵ This systematic review of 19 eligible studies representing 947 SCIT subjects and 2668 SLIT subjects suggests that there is no increase in AEs of concern with SCIT or SLIT coseasonal initiation.

The heterogeneity of the safety reporting made evaluation of the safety between studies difficult, highlighting the need for standardized methods of reporting for AIT trials. No attempt was made to recategorize reported AEs on the basis of more current or more accepted criteria. For example, if an AE was reported as “serious” in the publication, it was reported as a serious AE in this review even if it did not fulfill the regulatory criteria for seriousness. The World Allergy Organization suggests that publications from AIT studies report the total number of AEs, the total number of treatment-related AEs, AEs occurring in 5% or more subjects, and descriptions of severe, local, and systemic AEs.³⁶ We also recommend consistent reporting of epinephrine use for treatment of AEs. Differences in the AIT formulations (ie, depot, glycerinated, tablets, drops, allergoids), and in single versus multiple allergen administration, also complicated the analysis and added to the potential limitations of the study. The rates of safety outcomes did not appear notably different between coseasonal initiation and out-of-season initiation. Importantly, no epinephrine use was reported in any of the trials included in this review, although unreported use as standard treatment for AEs cannot be excluded. No obvious increase in AEs of concern with coseasonal initiation was apparent compared with the general safety profiles of SCIT and SLIT. In a review by Senna et al³⁷ of SLIT DBPC-RCTs published up to June 30, 2013, for active treatment the overall rate of discontinuations due to AEs was 33%, the prevalence of systemic allergic reactions was 18%,

and the rate of severe reactions was between 1% and 2% per subject. The rates for these outcomes were lower in the SLIT coseasonal initiation cohorts assessed in this current review, except for the severe AE rate, which was also higher in the placebo and non-coseasonal initiation cohorts ($\leq 12\%$).

The current analysis was to review the safety of coseasonal initiation and did not attempt to review efficacy. Because efficacy with AIT may take several weeks to develop, patients should not expect any benefit during the initiating pollen season. However, in 7 of the 10 studies in this review that examined efficacy, improvements in efficacy measures (ie, “well-being,” symptoms, and/or rescue medication use) were observed. Thus, there is limited evidence that coseasonal initiation provides relief to some patients during the initiating season. Time-to-onset studies in environmental exposure chambers have demonstrated that SLIT-tablets for seasonal allergens can significantly improve symptom/medication use in as early as 4 weeks.^{38,39} Field trials suggest that effect can be observed after 8 to 14 weeks.⁴⁰ Thus, depending on the length of the season, a treatment effect may or may not be observed.

Another limitation of this review was that it was often difficult to determine whether the studies administered therapeutic doses that would be used in real-world practice. Dose equivalents in micrograms of major allergen were reported in only 3 of the SCIT studies, and the use of low doses may result in a more favorable safety profile, but could have a negative impact on efficacy. The amount of major allergen was reported or obtained in 8 of the SLIT studies, but the doses varied. For example, the first doses of *Phl p 5* ranged from 0.00016 μg to 15 μg . For SLIT, an association between dose and the rate or severity of AEs has been demonstrated, and tolerability may be less at higher doses.^{41,42}

The main concern with coseasonal initiation is that the AIT allergen content, in addition to high levels of environmental allergen, could push the immune system of the already “primed” patient past a safety “threshold” and induce systemic or more severe allergic reactions. If this were true, then regional and yearly differences in pollen levels or perennial allergens would have an impact on the safety of coseasonal initiation. In this systematic review there was no way to account for differences in environmental pollen levels, and it is unknown whether there is a pollen “threshold” for each allergen that would increase safety risks with coseasonal initiation.

CONCLUSIONS

The available published data indicate that there is no increase in AEs of concern with SCIT or SLIT coseasonal initiation. Notwithstanding the quality of the trials, inconsistent characterization of allergenic potency of the AIT products and relatively small sample sizes make it difficult to come to a definitive conclusion based on the data set. Thus, more clinical data with standardized safety reporting, immunization regimens, and doses are needed to develop a more complete safety database on AIT coseasonal initiation relative to out-of-season regimens.

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ONLINE REPOSITORY**Methods**

Risk of bias and quality assessment. The Cochrane Collaboration's risk of bias tool was used to assess the quality of the RCTs (Table E1).^{E1} For each of the RCTs, selection bias, performance bias, detection bias, attrition bias, and reporting bias were assessed as high, low, or unclear according to judgement statements provided by the Cochrane Collaboration risk of bias tool.^{E1} No validated risk of bias tool is available for observational or retrospective analysis; therefore, a tool used to assess the quality and risk of bias in case series as described by Chambers et al^{E2} was used for these types of studies. This tool mainly addresses selection and attrition bias, but does not address publication bias. The criteria in the tool were as follows: 1. Were selection/eligibility criteria adequately reported? 2. Was the selected population representative of that seen in normal practice? 3. Was an appropriate measure of variability reported? 4. Was loss to follow-up reported or explained? 5. Were at least 90% of those included at baseline followed up? 6. Were patients recruited prospectively? 7. Were patients recruited consecutively? 8. Did the study report relevant prognostic factors? The criteria were rated as "yes" or "no" for each study. Quality was considered "good" if "yes" was answered for all 8 criteria, "satisfactory" if "yes" was answered for criteria 2, and 4–7, or "poor" if "no" was answered for criteria 2, or 4–7.

Results

For many of the RCTs there was incomplete information in the publications to fully assess all the potential bias categories using the Cochrane Collaboration's risk of bias tool (Table E1). Two trials (Pfaar et al^{E3} and Reich et al^{E4}) had complete information and rated a low risk of bias in every category. Four of the studies (Leonardi et al,^{E5} Novembre et al,^{E6} D'Anneo et al,^{E7} and

Pajno et al^{E8}) had a high risk of performance and detection bias due to their open-label study designs. According to the tool described by Chambers et al,^{E2} the quality of all 9 of the observational and retrospective studies was considered "poor" (Table E2). The lack of prospective subject recruiting was generally the reason for a "poor" quality rating.

Details of serious treatment-related AEs in SCIT co-seasonal initiation studies.

Of the 3 SCIT studies that directly compared co-seasonal initiation with out-of-season initiation, only 1 reported results for serious treatment-related AEs. In the prospective, observational study that compared "up to peak season" versus "after peak season" co-seasonal SCIT initiation, the frequency of serious treatment-related AEs was 2% in both groups (5 events total).^{E9} Two of the 5 events were considered medically important; anaphylaxis with generalized urticaria, dizziness, and itching was experienced by a 15 year old female patient 45 minutes after a titration dose (10,000 standardized quality units [SQ-U]) during "after peak season" co-seasonal initiation, and cough, dyspnea, and hives were experienced in a 17 year old female patient 2 hours after a titration dose (10,000 SQ-U) during "up to peak season" co-seasonal initiation. The other serious treatment-related AEs were symptoms of dyspnea and urticaria in a 17 year old male patient 45 minutes after a titration dose (20,000 SQ-U) during up-dosing after the pollen season; dyspnea in a 22 year old male 50 minutes after a titration dose (10,000 SQ-U) during "up to peak season" co-seasonal initiation; and laryngeal edema, urticaria, flushing, and cough in a 29 year old male 20 minutes after a titration dose (10,000 SQ-U) during "up to peak season" co-seasonal initiation. The serious treatment-related AEs were all successfully treated with intravenous corticosteroids and antihistamine, and all but 1 patient continued treatment.

TABLE E1. Risk of bias of eligible RCT

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of subjects and study personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
SCIT studies							
Lee et al, 1982 ^{E10}	?	—	—	—	?	—	—
Pfaar et al, 2012 ^{E3}	—	—	—	—	—	—	—
Klimek et al, 2013 ^{E11}	?	?	—	—	?	?	?
SLIT studies							
Reich et al, 2011 ^{E4}	—	—	—	—	—	—	—
Vervloet et al, 2007 ^{E12}	—	?	—	—	—	—	—
Ott et al, 2009 ^{E21}	+	?	—	—	—	—	—
Leonardi et al, 2010 ^{E5}	?	+	+	+	?	—	—
Novembre et al, 2004 ^{E6}	+	+	+	+	—	—	—
D'Anneo et al, 2008 ^{E7}	—	—	+	+	?	—	—
Pajno et al, 2011 ^{E8}	—	—	+	+	—	—	—

RCT = randomized controlled trial; SLIT = sublingual immunotherapy; SCIT = subcutaneous immunotherapy.

“—” represents low risk of bias, “?” represents unclear risk of bias, and “+” indicates high risk of bias. Italicized citations indicate publication as a congress abstract only.

TABLE E2. Quality assessment of eligible observational and retrospective studies

	Quality Criteria								Quality Rating
	1	2	3	4	5	6	7	8	
SCIT studies									
Reiber et al, 2013 ^{E9}	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Poor
Bubel, 2010 ^{E13}	Yes	Yes	No	No	?	Yes	?	No	Poor
Paterok, 2012 ^{E14}	Yes	Yes	No	NA*	NA*	No	No	No	Poor
Werner, 2013 ^{E15}	Yes	Yes	No	NA*	NA*	No	No	No	Poor
Stelzer et al, 2013 ^{E16}	No	?	No	NA*	NA*	No	No	No	Poor
SLIT studies									
Schwab et al, 2013 ^{E17}	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Poor
Ariano et al, 2009 ^{E18}	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Poor
Sieber et al, 2010 ^{E19}	Yes	Yes	Yes	No	?	Yes	?	Yes	Poor
Dichmann, 2011 ^{E20}	Yes	Yes	No	NA*	NA*	No	No	No	Poor

SLIT = sublingual immunotherapy; SCIT = subcutaneous immunotherapy.

Italicized citations indicate publication as a congress abstract only. Criteria were as follows: 1. Were selection/eligibility criteria adequately reported? 2. Was the selected population representative of that seen in normal practice? 3. Was an appropriate measure of variability reported? 4. Was loss to follow-up reported or explained? 5. Were at least 90% of those included at baseline followed up? 6. Were patients recruited prospectively? 7. Were patients recruited consecutively? 8. Did the study report relevant prognostic factors? Quality was considered “good” if “yes” was answered for all 8 criteria, “satisfactory” if “yes” was answered for criteria 2, and 4–7, or “poor” if “no” was answered for criteria 2, or 4–7.

*Study was retrospective, follow-up is not applicable (NA).

TABLE E3. Safety outcomes of subcutaneous immunotherapy (SCIT) studies that compared co-seasonal initiation with placebo or had no comparator

Citation	Discontinuations Due to Any AEs, n (%)	Systemic Allergic Reactions, n (%)	Serious Treatment-Related AEs, n (%)	Severe AEs, n (%)
Lee et al, 1982 ^{E10}	NR	Traditional: 3 (1%) SDET: 3 (1%) P: 0 (0%) • “Systemic” defined as exacerbation of nasal symptoms	NR	NR
Pfaar et al, 2012 ^{E3}	SCIT: 2 (6%) • Circulatory problem; local swelling + unspecific systemic reaction P: 0	SCIT: 8 (7%) P: 2 (6%) $P = 0.74$ vs SCIT • Specific symptoms not reported; defined as any reaction not related to injection site	SCIT: 0 P: 0	≥5 cm diameter local swelling: SCIT: 12% P: 0%
Congress Abstracts				
Klimek et al, 2013 ^{E11}	NR	SCIT: 7% P: 7% • Specific symptoms not reported	NR	SCIT: 0 P: 0
Bubel, 2010 ^{E13}	NR	NR	SCIT: 0	≥5 cm diameter local swelling: SCIT: 1% of injections
Paterok, 2012 ^{E14}	SCIT: 0	SCIT: 0	NR	SCIT: 0 ≥5 cm diameter local swelling: SCIT: 0

AE = adverse event; NR = not reported; P = placebo; SCIT = subcutaneous immunotherapy; SDET = serial dilution end point titration.

TABLE E4. Safety outcomes of sublingual immunotherapy (SLIT) studies that compared co-seasonal initiation with placebo or had no comparator

Citation	Discontinuations Due to Any AEs, n (%)	Systemic Allergic Reactions, n (%)	Serious Treatment-Related AEs, n (%)	Severe AEs, n (%)
Novembre et al, 2004 ^{E6}	SLIT: 1 (2%) • Eye pruritus Pharmacotherapy: 0	SLIT: 2 (4%) • Diarrhea; blocked nose, throat pruritus Pharmacotherapy: 1 (2%) • Urticaria	SLIT: 0 Pharmacotherapy: 0	SLIT: 0 Pharmacotherapy: 0
D’Anneo et al, 2008 ^{E7}	SLIT: 0 Pharmacotherapy: 0	NR	NR	NR
Reich et al, 2011 ^{E4}	SLIT: 6 (3%) • Pharyngitis, headache, influenza, hypotonia, salmonellosis, paresthesia P: 1 (2%) • Specific symptoms not reported	SLIT: 4 (2%) • Anaphylactic reactions P: 0	SLIT: 0 P: 0	SLIT: 9 (4%) • 1 event (nausea) was treatment-related P: 0
Vervloet et al, 2007 ^{E12}	SLIT: 1 (3%) • Gastric pain/vomiting P: 0	SLIT: 1 (3%) • Facial hot flush P: 0	SLIT: 0 P: 0	NR
Ott et al, 2009 ^{E21}	SLIT: 10 (7%)* • Upper abdominal pain, diarrhea, application site irritation, eye swelling, application site edema, application site paraesthesia, respiratory problems P: 4 (6%)*	SLIT: 9 (0.3%) • Specific symptoms not reported P: 6 (1%) • Specific symptoms not reported	SLIT: 0 P: 0	SLIT: 25 (7%) • Described only as “non-systemic” P: 12 (8%) • Described only as “non-systemic”
Congress Abstracts				
Dichmann, 2011 ^{E20}	SLIT: 0	SLIT: 0	SLIT: 0	SLIT: 0

AE = adverse event; NR = not reported; P = placebo; SLIT = sublingual immunotherapy.

*Number reported in Sieber et al, 2012^{E22}, which was a more in-depth reporting of the safety first reported by Ott et al, 2009.

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