INPLASY

ASSESSING IR ALLERGEN SUBLINGUAL IMMUNOTHERAPY-LIQUID EFFICACY FOR ALLERGIC RHINOCONJUNCTIVITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ADMINISTRATIVE INFORMATION

Support - This study was supported by Stallergenes Greer.

Review Stage at time of this submission - Risk of bias assessment.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202510049

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 January 2025 and was last updated on 14 January 2025.

INTRODUCTION

Review question / Objective 1. In patients with allergic rhino-conjunctivitis with or without asthma, is IR sublingual immunotherapy (SLIT) liquid as an add-on to conventional treatment more effective than placebo plus conventional treatment?
2. Is IR SLIT liquid treatment associated with significant safety concerns?
PICO Framework:
Population: Patients with allergic rhino-conjunctivitis with or without asthma
Intervention: IR sublingual immunotherapy (SLIT) liquid
Comparator: Placebo combined with conventional treatment
Outcomes: Efficacy (e.g., symptom reduction, medication use reduction) and safety (e.g., adverse events, tolerability).

Rationale Allergen immunotherapy (AIT) is a well-established treatment with demonstrated efficacy and safety. However, variability in study outcomes remains a challenge, driven by differences in patient characteristics, study designs, and treatment durations. Moreover, disparities in allergen composition and quality of AIT products across manufacturers contribute to significant heterogeneity, complicating the interpretation of efficacy and safety data.
AIM: This meta-analysis focuses on assessing efficacy and safety of a single manufacturer's AIT product for allergic rhino-conjunctivitis (ARC). By narrowing the scope to one specific product, this study seeks to reduce variability linked to product differences, aligning with recommendations from the World Allergy Organization to improve the reliability of meta-analytic findings.

Condition being studied Allergic rhino-conjunctivitis (ARC) with or without asthma.

METHODS

Search strategy

#1: sublingual immunotherapy grass AND (randomizedcontrolledtrial[Filter])
#2: sublingual immunotherapy house dust mite AND (randomizedcontrolledtrial[Filter]
#3: sublingual immunotherapy cypress AND (randomizedcontrolledtrial[Filter]
#4: sublingual immunotherapy juniper AND (randomizedcontrolledtrial[Filter])
#5: sublingual immunotherapy ragweed AND (randomizedcontrolledtrial[Filter]
#6: sublingual immunotherapy olive AND (randomizedcontrolledtrial[Filter]
#7: sublingual immunotherapy parietaria AND (randomizedcontrolledtrial[Filter]
#8: sublingual immunotherapy pellitory AND (randomizedcontrolledtrial[Filter]

#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8.

Participant or population Adult and pediatric ARC patients, regardless of asthma status, with common allergens (grass, house dust mites, trees, weeds).

Intervention IR SLIT liquid formulation (Staloral®) for ARC with different allergens (grass, house dust mites, trees, weeds).

Comparator Placebo plus conventional treatment.

Study designs to be included Randomized controlled trials.

Eligibility criteria Studies included in the analysis had to meet the following criteria: (1) adult and pediatric ARC patients, regardless of asthma status, with common allergens (grass, house dust mites, trees, weeds), (2) treatment with IR SLIT liquid formulation (Staloral®) for ARC, and (3) inclusion of relevant outcome measures such as symptom or medication scores. Reviews, discussion papers, non-research letters and editorials, animal studies, studies not employing double blind RCT designs, and studies not reporting necessary data were excluded.

Information sources We performed a comprehensive search for published and unpublished randomized controlled trials (RCTs) on the efficacy of IR SLIT liquid formulations for allergic rhino-conjunctivitis (ARC) in PubMed/MEDLINE, the Cochrane Library, ISI Web of Science, and ClinicalTrials.gov, up to December 20, 2024. No language restrictions were applied, and reference lists from relevant articles and reviews were manually checked for additional studies. We also asked the study sponsor to help provide a complete list of RCTs on IR SLIT liquid formulation (Staloral) with any allergen for ARC for additional data.

Main outcome(s) Key outcomes were symptom severity (measured by symptom score, SS, or visual analog score, VAS), reduction in medication use (measured by medication score, MS), and safety (side effects).

Quality assessment / Risk of bias analysis The risk of bias (RoB) in randomized controlled trials (RCTs) will be assessed with the Cochrane RoB 2 tool, which evaluates potential biases across five domains: randomization, adherence to interventions, outcome data completeness, measurement of outcomes, and selective reporting. Studies are rated as having a low or high risk of bias, or as raising some concerns. A study will be categorized as low risk if no domains showed concerns, while a high-risk rating required substantial issues in one or more domains.
The certainty of evidence will be appraised using the GRADE framework. Evidence will be classified as high, moderate, low, or very low certainty based on confidence in the effect estimate. For instance, high-certainty evidence reflects strong confidence that the true effect is close to the estimate, while very low certainty suggests substantial uncertainty about the effect size.

Strategy of data synthesis We will conduct meta-analyses utilizing both fixed-effects and random-effects models, with a preference for the latter to account for anticipated variability across studies, including differences in protocols, durations, and populations. Continuous outcomes (e.g., SS, MS, VAS) measured on differing scales will be combined using the standardized mean difference (SMD).
For studies examining outcomes over multiple pollen seasons, only data from the final year of treatment will be included. When standard deviations (SDs) were not reported, we will derive them using methods based on summary statistics (e.g., minimum, maximum, quartiles, median, or p-values). In cases where standard errors (SEs) were provided, SDs were calculated using the formula: $SD=SE\sqrt{n}$. Missing means and SEs will be estimated from graphs or obtained from the study sponsor.
To evaluate between-study heterogeneity, we will employ the χ^2 test (p-threshold < 0.10) and I^2

statistic, which quantifies the proportion of variability due to heterogeneity rather than chance. We will assess publication bias using funnel plots, Egger's regression test, and fail-safe calculations, which estimate the number of missing studies needed to overturn statistically significant results. A high fail-safe number provides confidence in the robustness of conclusions.
Summary of findings tables will be generated using GRADEpro GDT software. Statistical analyses and meta-analyses were performed using R with the Metafor package, RevMan 5.0, and ProMeta 3.0.

Subgroup analysis Pre-specified subgroup analyses by 1) age (adults vs. children), 2) allergen (grass, house dust mites, trees, weeds), sensitization status (mono-sensitized vs. poly-sensitized patients) will be performed. Meta-regressions will further explore the relationship between outcomes and explanatory variables.

Sensitivity analysis We will perform sensitivity analyses by: 1) estimated vs. actual data; 2) study quality (high quality vs. low quality studies and studies with some concerns); 3) sample size (below/above median); 4) excluding influential studies.

Language restriction There will be no language restriction.

Country(ies) involved Italy, France.

Keywords Meta-analysis; Randomized controlled trial; SLIT-liquid; Sublingual.

Dissemination plans Publication on a scientific journal.

Contributions of each author
Author 1 - Danilo Di Bona - DDB developed the concept of this work, will do all the analyses and write. the first manuscript draft.
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