INPLASY

Efficacy of 300 IR 5-grass sublingual immunotherapy tablet for allergic rhino-conjunctivitis

INPLASY202430066

doi: 10.37766/inplasy2024.3.0066

Received: 15 March 2024

Published: 15 March 2024

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ADMINISTRATIVE INFORMATION

Support - Stallergenes Greer.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - DDB reports having received fees from Stallergenes Greer. GWC reports having received research grants as well as being lecturer or having received advisory board fees from: Menarini, Anallergo, Allergy Therapeutics, AstraZeneca, Chiesi Farmaceutici, Faes, Firma, Genentech, Guidotti-Malesci, GlaxoSmithKline, Hal Allergy, Innovacaremd, Novartis, OmPharma, RedMaple, Sanofi-Aventis, Sanofi-Genzyme, Stallergenes Greer, Uriach Pharma, ThermoFisher, Valeas. GP, MO and SD declare they have no conflict of interest. SS and JCS are employees of Stallergenes Greer.

INPLASY registration number: INPLASY202430066

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 March 2024 and was last updated on 15 March 2024.

INTRODUCTION

Review question / Objective For patients with seasonal allergic rhino-conjunctivitis to grass pollen, is the 300 IR 5 grass sublingual immunotherapy tablet used as add on treatment more effective in reducing symptoms than conventional pharmacological treatment alone?

Rationale Allergen immunotherapy (AIT) is an established treatment option for allergic diseases and the only one able to modify the disease course by targeting the underlying immunologic mechanisms. Efficacy has been deminstratateb by several studies, but the evidence quality for individual allergen immunotherapy (AIT) products is heterogeneous, and extensions of overall conclusions ("class effects") on the efficacy to all AIT products are unjustified, according to the WAO and EAACI.

The aims of this focused systematic review and meta-analysis of RCTs were to more precisely assess efficacy and safety of the 300 IR 5-grass SLIT-tablet in patients with ARC with or without mild intermittent asthma and evaluate the overall evidence certainty.

Condition being studied Seasonal allergic rhino-conjunctivitis (ARC) is one of the most prevalent allergic diseases in the developed world. The symptoms of the disease can have a pronounced effect on the patient's quality of life, affecting sleep quality, school and work performance, and social activities.

The subcutaneous and the sublingual routes are the most commonly used in clinical practice for the etiological treatment of this condition, with

considerable differences worldwide. Although subcutaneous immunotherapy (SCIT) has been used in the treatment of ARC for decades, more recently, there has been a shift toward sublingual immunotherapy (SLIT), particularly in Europe, where SLIT is prescribed nearly as frequently as SCIT, and, in particular, preferred to SCIT in southern Europe, accounting for about 80% of immunotherapies.

METHODS

Search strategy 1 #2 AND #3 AND #4 AND #5 AND #6
2 (5 grass sublingual immunotherapy) OR 300IR
3 ((rct) OR (randomized controlled trial*)) OR (placebo-controlled)
4 (grass) OR (grass pollen)
5 ((sublingual immunotherapy) OR (AIT)) OR (SLIT)
6 rhinoconjunctivitis) OR (rhinitis)) OR (allergic rhinitis)) OR (asthm*).

Participant or population Patients with allergic rhino-conjunctivitis to grass pollen with or without mild intermittent asthma will be assessed in this review.

Intervention 300 IR 5-grass sublingual immunotherapy tablet.

Comparator Placebo.

Study designs to be included Randomized controlled trials.

Eligibility criteria Studies were included in the meta-analysis if: 1) they were RCTs assessing efficacy and safety of 300 IR 5-grass SLIT tablet vs. placebo in patients with moderate or severe rhino-conjunctivitis to grass pollen with or without mild intermittent allergic asthma; 2) there was a pre-seasonal treatment duration of 4 months (16 weeks); 3) they assessed the efficacy of 300 IR 5-grass SLIT tablet; 4) they used symptom score (SS) and medication score (MS) or daily combined symptom and medication score (DCS) as primary outcome measures of treatment effect. We excluded studies not published as full paper or not reporting on the primary outcomes. We did not use any language restrictions. We checked all reference lists and articles citing included studies and recent reviews or meta-analyses for any additional relevant studies. We also asked the study sponsor to help provide a complete list of RCTs on 300 IR 5-grass SLIT tablet for ARC for additional data.

Information sources A comprehensive literaturesearch of the Cochrane Library, Web of Scienceand, MEDLINE databases (viathePubMedsearchengine) was performed to identify studies meeting the inclusion criteria. In addition, the reference lists of retrieved studies and review articles were further manually searched for additional publications. No language restriction was used.

Main outcome(s) We prioritised outcomes that were patient-important events of ARC, consistent with the established approach for AIT, as informative of treatment efficacy and safety. The critical/important outcomes were as follows: symptom severity assessed as symptom score (SS); decrease in anti-symptomatic drug use, assessed as medication score (MS); a combined score encompassing the previous two, the daily combine symptom and medication score (DCS); adverse events (AEs).

Quality assessment / Risk of bias analysis
Risk of bias
We assessed the risk of bias (RoB) of RCTs using the version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2). The domains included in RoB 2 cover all types of bias that are currently understood to affect the results of randomized trials. These are: 1) bias arising from the randomization process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome; and 5) bias in selection of the reported result.
Judgement can be 'Low' or 'High' risk of bias or can express 'Some concerns”. A study is judged to be at low risk of bias if it is at low risk of bias for all domains for this result. A study is judged to be at high risk of bias if it is at high risk of bias in at least one domain or have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Certainty of evidence
We evaluated the certainty (quality) of evidence using the GRADE approach.TheGRADE 2013 GRADE defines high certainty evidence when confidence that the true effect lies close to that of the estimate of the effect is very high; moderate certainty evidence when confidence in the effect estimate is moderate (i.e., the true effect is likely to be close to the estimate, but there is a possibility that it is substantially different); low certainty evidence when the confidence in the effect estimate is limited (i.e., the true effect might be substantially different from the estimate of the effect); and very low certainty when confidence in

the effect estimate is very low (i.e., the true effect is likely to be substantially different from the estimate of effect).
We used GRADEpro GDT (available from gradepro.org) to create the summary of finding tables.

Strategy of data synthesis We pooled summary measures using DerSimonian and Laird random-effects, estimating heterogeneity using the Mantel-Haenszel model. We combined continuous outcomes across studies (SS, MS, DCS) using standardized mean difference (SMD) if the outcomes were measured with different scales, or mean difference (MD) if the outcome was measured with the same scale.
We tested between-study heterogeneity using $\chi 2$ (threshold p=0.10) and quantified it using I2 statistic, which describes the percentage of variability due to heterogeneity rather than sampling errors. The sources of heterogeneity were explored by removing possible study outliers and conducting prespecified subgroup and sensitivity analyses. The selection of characteristics defining subgroups was motivated by clinical and methodologic hypotheses. Sensitivity analyses to test robustness of the findings was based on fixed-effect meta-analysis.
Influential analysis—that is, the exclusion of outlying studies until homogeneity has been achieved—was also used to explore heterogeneity. This approach was used to examine the effect of studies identified as being aberrant in either results or methodology.
Then, we in turn excluded each study to ensure that no single study would be solely responsible for the significance of any result (robust analysis).
We assessed publication bias by inspecting funnel plots, Egger's linear regression test, Begg's rank test, and fail-safe calculation, a simple procedure by which one can estimate whether publication bias (if it exists) may be safely ignored. A fail-safe number indicates the number of insignificant, unpublished (or missing) studies that would need to be added to a meta-analysis to reduce an overall statistically significant result to insignificance. If this number is large relative to the number of observed studies, one can feel fairly confident in the summary conclusions.Higgins2022
We did all meta-analyses using RevMan 5.0 and ProMeta 3.0 softwares.

Subgroup analysis Subgroup analysis was carried on based on age of participants, geographical area in which the study was performed (Europe vs. USA), and asthma status.

Sensitivity analysis Besides analyses based on the fixed effects model, other sensitivity analyses will be conducted if necessary (e.g. by study quality).

Language restriction We did not use any language restriction.

Country(ies) involved Italy, Poland, France.

Keywords SLIT, tablet, randomize controlled trial, Oralair®, meta-analysis.

Contributions of each author

Author 1 - Danilo Di Bona - DDB developed the concept of this work, did the article search, assessed the articles, and extracted the data. Furthermore, he did all the analyses and wrote the first manuscript draft.
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