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## Letter to the Editor

**Efficacy but not effectiveness of sublingual immunotherapy for grass pollen allergy: Time to avoid waste in health-care expenditure**

## Keywords:

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Last June JAMA Internal Medicine published an excellent systematic review and meta-analysis of clinical trials of sublingual immunotherapy for grass pollen allergy [1]. The team of Di Lorenzo of the University of Palermo reached an important result indicating a small, unimpressive effect of sublingual immunotherapy. These findings probably justify no longer this kind of intervention to be paid by any European health care system. Accordingly, the Editor of JAMA has thrown a “caveat emptor” [2] that is similar to a scream towards public welfare managers.

I previously underscored that critical thinking is needed to promote knowledge growth for effective decision-making [3]. Even in this case, given any possible effects on public welfare decisions and in particular within European healthcare systems, I believe it necessary to provide further reflection. In this view, I have had the pleasure to interview Danilo Di Bona and Gabriele Di Lorenzo about their systematic review's significant findings.

**1. What is the major finding, in your opinion?**

Di Lorenzo: The major finding of our systematic review is that the benefit of sublingual immunotherapy (SLIT) tablets is slight in comparison with placebo. The benefit reported in the original RCTs was overestimated by the metric used by various authors to calculate the difference between SLIT and placebo. With the metric we used, that is the one suggested by the World Allergy Organization, the real difference between SLIT and placebo has been correctly estimated.

**2. Are these results surprising?**

Di Lorenzo: The most important issue regards the benefit reported in the original RCTs that was overestimated by the metric used by the authors to calculate the difference between SLIT and placebo. With the metric used by us, the real difference between SLIT and placebo was correctly estimated, and the benefit was about 6%, comparable to placebo. Then, it was much lower than the 15% difference required by the US FDA for drug approval.

In a previous meta-analysis including only European studies that we published in 2012 [4], we had already highlighted that the benefit of SLIT tablets reported in the original RCTs was mild to moderate. In our new systematic review, we also included the most recent American

studies. The only surprise is that these studies showed a benefit that is even lower than that of the European studies.

**3. You found a small treatment benefit in the symptom score. Do you mean that statistical differences are not supported by clinically significant results?**

Di Bona: The benefit is less than 1 point-symptom score difference between SLIT and placebo; yet, this finding is statistically significant. However, consider that the Symptom Score Scale range is 18 points. So, less than 1 point difference cannot be considered clinically significant since it means that 5 out of 6 symptoms remain unchanged, and the remaining one improves only marginally. As mentioned above, when treatment benefit is calculated using the correct metric, this difference (less than 1 SS-point) is about 6%. Hence, it does not reach the 15% difference assumed by the FDA as the “minimum clinically significant difference”. This means that the treatment alone is not sufficient to control symptoms. The patients under SLIT treatment are allowed to take symptomatic drugs on demand such as antihistamines, nasal, and even oral steroids. These drugs control the majority of symptoms, if not all.

**4. The adverse events rate is high, at 61%. What kind were they? What about the number needed to harm?**

Di Bona: The adverse events are mainly local, and mild to moderate. Oral pruritus, throat irritation, and mouth edema are the most frequent. They can be bothersome for the patients and can lead to withdrawal from the treatment. The risk difference between treatment and placebo is 40%. Therefore, the number needed to harm is 2, indicating that treatment benefit is limited by the high frequency of side effects.

**5. If someone still wanted to try this, what would you say?**

Di Lorenzo: The reported benefit is modest. This means that some patients will respond, but the majority will not, and it is not possible to predict who will respond to treatment. So, the patient should be aware of his/her very low *a priori* chances. The subcutaneous route should be preferable, because of the higher rate of response. However, today we have drugs very effective and with few side effects such as antihistamines and nasal steroids. Hence, immunotherapy for allergic rhinitis is a therapy that should be used only in a few selected cases. Sublingual immunotherapy has hardly sustainable costs for patients, and we have to consider the economic crisis that is affecting several Western countries.

In our systematic review, the differences between the groups treated with sublingual immunotherapy and the groups treated with placebo were little more than marginal.

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## 6. What is the burden of seasonal grass pollen allergies? How many people suffer from them?

Di Lorenzo: Untreated or inadequately treated allergic rhinoconjunctivitis can cause sleep and mood disorders and impair social functioning and school or work performance. Many people would consider this a significant problem. Allergic rhinoconjunctivitis, the most prevalent condition, is estimated to occur in about 20% of Americans and Europeans. Grass pollens cause much of allergic rhinoconjunctivitis; in some regions of the United States and of Europe, an estimated 50% to 70% of patients with allergic rhinoconjunctivitis are sensitized to grass allergens.

## 7. How does immunotherapy work to change the disease process?

Di Lorenzo: The exact mechanism is poorly understood. It modifies the immune system inducing a sort of tolerance to the specific allergen. However, the effects of immunotherapy on the natural history of allergic rhinitis have not been proven by randomized controlled trial.

## 8. Are these sublingual tablets expensive, compared to other treatments?

Di Lorenzo: They are expensive, especially if you consider that treatment lasts at least three years, and patients undergoing SLIT also take symptomatic drugs on demand such as antihistamines, nasal, and even oral steroids, that control the majority of symptoms. SLIT treatment does not seem economically reasonable for the quite modest rate of symptom relief.

## 9. Finally, should SLIT no longer be offered for allergy treatment?

Di Bona: The reported benefit is slight on average. So, patients should be informed about the low *a priori* chances of clinical improvement. In any case, our findings support no longer that SLIT costs are paid by public welfare, because any health care system has to consider actively to address welfare investments towards therapies supported by strong evidence and clinically relevant results.

## Conflict of interest

We all declare no conflict of interest.

## Acknowledgments

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Salvatore Corrao

*Dipartimento BioMedico di Medicina Interna e Specialistica (Di.Bi.M.I.S),  
Università degli Studi di Palermo, Italy*

*Centre of Research for Effectiveness and Appropriateness in Medicine  
(C.R.E.A.M.), Italy*

*National Relevance Hospital Trust ARNAS Civico, Di Cristina e Benfratelli,  
Palermo, Italy*

Corresponding author at: Dipartimento BioMedico di Medicina Interna  
e Specialistica (Di.Bi.M.I.S), Via del Vespro, 141, 90127 Palermo, Italy.  
E-mail address: [s.corrao@tiscali.it](mailto:s.corrao@tiscali.it).

Daniilo Di Bona

*Unità Operativa di Immunoematologia e Medicina Trasfusionale Azienda,  
Ospedaliera Universitaria Policlinico di Palermo, Italy*

*Dipartimento di Scienze Statistiche e Matematiche "S. Vianelli", Università  
degli Studi di Palermo, Italy*

Gabriele Di Lorenzo

*Dipartimento BioMedico di Medicina Interna e Specialistica (Di.Bi.M.I.S),  
Università degli Studi di Palermo, Italy*

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