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Comments on: *"Allergen immunotherapy as a drug: the new deal of grass allergen tablets from clinical trials to current practice"*

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In their recent article (1) published in *European Annals of Allergy and Clinical Immunology*, Manzotti and Lombardi evaluated the available trials with Grazax® and Oralair® to support their use in clinical practice.

First, we have noted with particular interest the position of the authors regarding the pre-seasonal and co-seasonal schedule. They consider it to be: "*the most suitable schedule for pollens in clinical practice instead of continuous immunotherapy*". Though, the efficacy of Grazax® has been assessed with a continuous protocol over the 3 years of treatment, its long-term efficacy and safety when administered discontinuously has yet to be assessed. To date, Oralair® is the only allergen immunotherapy sublingual tablet with demonstrated efficacy and safety using a pre-seasonal and co-seasonal treatment regimen.

Moreover, the authors stated that *"Oralair® has been shown to be effective and safe in two Phases III double-blind placebo controlled trials"... "and in a trial based in an allergen challenge chamber."* In fact, since Oralair® has been marketed in 2008, two additional clinical trials (VO53.06 and VO61.08USA) have been completed, bringing the total to four natural field studies including 2012 patients, in addition to the 89 patients in the allergen challenge chamber study (VO56.07A).

Study VO53.06, a multicenter, randomized, controlled trial evaluated the long-term effect of pre-seasonal and co-seasonal administration of Oralair® over a period of three consecutive pollen seasons followed by an an observation time. The clinically relevant efficacy shown during the first three years (2) was maintained during the first treatment-free follow-up year indicating post-treatment long-term efficacy (3).

The VO61.08USA trial (4) conducted in US adult patients with grass pollen-induced allergic rhinoconjunctivitis showed that pre-seasonal and co-seasonal treatment with Oralair® demonstrated clinically meaningful efficacy.

With respect to Table 2 - Synopsis of Phase III Oralair® studies, we note a number of errors with respect to the results of study VO56.07. We have provided the corrected data below. In addition, the correct reference is "*Horak F, Zieglmayer P, Zieglmayer R, Lemell P, Devillier P, et al. Early onset of action of a 5-grass-pollen 300-IR sublingual immunotherapy tablet evaluated in an allergen challenge chamber. J Allergy Clin Immunol. 2009 Sep;124(3):471-7, 477.e1.*"

Lastly, the authors have noted that *"in fact, an extract with only Phleum pratense seems adequate for patients living in Northern Europe but not for patients living in*

Table 2

Oralair® study in pollen chamber

			Onset of action			
Trial	No. of pts	Type of pts /Type of the disease of pts included in the study	ARTSS after 1 month	ARTSS after 2 months	ARTSS after 4 months	Oralair® Improvement vs Placebo at 4 months
Horak et al, 2009	89	Adults / Grass pollen-induced rhinoconjuctivitis	-5.89±2,431 p=0.0042	-5.09±2.088 p=0.200	-4.85±1.995 p=0.0007	29.3%

Mediterranean areas." Actually, the 5-grass pollen extract better represents natural exposure conditions encountered by grass pollen-allergic patients because the 5 species are broadly distributed throughout Europe and North America and their allergen content has been well-characterized (5).

References

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Reply

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It's a great pleasure for us understanding that our colleague Dr. de Beaumont and Dr Yalaoui could find our paper interesting enough to publish their letter (1); it's a honor for us the opportunity to answer them on this journal.
As also they reported, the aim of our paper was to evaluate the available trials, at the date of article submission, with Grazax® and Oralair® to support their use in clinical practice.
Our position regarding the pre-seasonal and co-seasonal schedule is not a personal one, but is coming from international reports in literature. According with this administration schedule, we presented all phase III studies about

Grazax® and Oralair®, designed in a very similar way because focused to the same objective: to demonstrate efficacy and safety in order to obtain marketing authorization from European Medicine Agency (EMA). Our purpose was not to define if Grazax® used with a pre-co-seasonal schedule was the "best option" in using that, instead we were looking for evidence from the studies for a possible Grazax® use with a pre-seasonal schedule as we usually prescribe in clinical practice. We concluded with a clear position: "*Although no proper pre-seasonal trials with Grazax® are today available, we can be optimistic about the pre-seasonal use of this product because it seems to give worthwhile results since the first months of the first year of treatment, in adult, in children and adolescents, but more evidence is required*".

We have also reinforced this statement, reporting in Table 1 four studies conducted with Grazax® with a range of treatment duration from 5.3 months to 7 months.

We also reported that Oralair® is the only allergen immunotherapy sublingual tablet with demonstrated efficacy and safety using a pre-seasonal and co-seasonal treatment regimen.

We apologize for the mistake about table 2 and we are very grateful to the colleagues for the opportunity to make correction as they did.

Moreover, we would like to thank the colleagues to give us the opportunity to complete our overview about both immunotherapy drugs because the two studies they mentioned have been completed and published after the submission of our article (2,3).

Lastly, we concluded with the statement*: "Which patient for which grass pollen drug? We have no definite answer today*". At the moment there are no enough studies to define the best grass allergens to put into a grass pollen immunotherapy. Grass pollen allergy is common worldwide, and group 1 and group 5 allergens (Phl p 1 and Phl p 5) are the dominating grass pollen allergens. More than 90% o subjects with sensitization to grass pollen have IgE abs to Phl p 1 and/or Phl p 5 (4,5). The presence of specific components for grass (like Phl p 1 and/or Phl p 5) are fundamental for a better indication for SIT (6). SIT treatments are expensive and prescribed for several years and a correct diagnosis is therefore important.

In conclusion we like to thank our colleagues for the opportunity to make correction and to add data to an article that can be very useful to clinical allergists that deal with patients and their daily problems all the time.

References

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