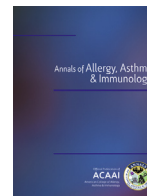




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Letter

Grazax sublingual immunotherapy in pre-co-seasonal and continuous treatment regimens: is there a difference in clinical efficacy?

In the United Kingdom, Grazax is a licensed allergen vaccine used in patients with grass pollen allergy with proven clinical efficacy and good safety profile.^{1,2} However, it remains under patent and is expensive compared with routine and conventional management. The full course of Grazax treatment involves daily tablet administration for 3 years, putting the medication costs alone at approximately £960 per patient per year (£80.12 × 30 tablets; British National Formulary, May 2014). Assuming that Grazax is taken for 3 to 4 months before and 3 to 4 months during the grass pollen season, this lowers the annual cost to approximately £480 to £640. Owing to its high cost, our department initially provided Grazax as pre-co-seasonal therapy. However, continuous treatment throughout the year was subsequently provided to all new patients, in line with published data.^{1–3} To justify these costs, we performed a non-interventional, open-labeled clinical trial to compare the clinical efficacy of pre-co-seasonal with continuous Grazax treatment in adult patients with severe seasonal grass-related allergic rhinoconjunctivitis based on the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline⁴ and confirmed by serology and skin testing. Patients 18 to 60 years old attending our department from 2008 to 2013 provided written consents to be treated with Grazax sublingual tablets (75,000 SQ-T/2,800 BAU; ALK-Abelló, Hørsholm, Denmark) for 3 years. Exclusion criteria were concomitant perennial allergic rhinitis, poor Grazax compliance, and standard contraindication for immunotherapy.⁵ Thirty-nine patients whose standard treatment failed according to the ARIA guidelines⁴ and were naive to sublingual and subcutaneous immunotherapy were included. Thirty followed a continuous regimen starting from February and continued uninterrupted for 3 years and 9 were on pre-co-seasonal treatment from February or March (approximately 6–8 weeks before the beginning of the pollen season, according to the local pollen calendar) to October or November, with a break in therapy to restart in the following spring, for 3 years.

Three outcome measurements were assessed before starting Grazax and subsequently after each pollen season by yearly review appointments or telephone consultations. In the outcome assessment, patients were asked to consider the disease severity over the previous season and medication intake based on ARIA guidelines. First, patients using a self-reported questionnaire graded symptom severity (Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ]) from 0 (no problems) to 5 (severe effects on life) in nasal (eg, sneezing), eye (eg, itchy), sleep (eg, poor night's sleep), and functioning (eg, fatigue) symptom categories.⁶ The average of these scores was taken as the final outcome measurement, in line with published evidence of the importance of each these categories in

disease severity assessment. A change in the score greater 0.5 point for each of the domains and overall scores was interpreted as the minimal important difference that is considered clinically significant. Second, a visual analog scale (VAS) of disease severity and symptom effect on life on a 100-mm line scale, with 0 mm indicating no impairment and 100 mm indicating maximal impairment, was assessed. A cutoff variation of 23 mm for the VAS was associated with a cutoff variation of 0.5 for the RQLQ and confirmed the significance of changes.^{7,8} Third, medication usage was estimated by a count of self-reported medications by the patient over the preceding season (ie, antihistamines, nasal spray, and/or eye drops).

Statistical analysis before therapy and after 1, 2, and 3 years of therapy was performed using *t* test, with a *P* value less than .05 considered significant.

Results of the RQLQ and VAS scores (Fig 1 shows the VAS results, and the RQLQ results were very similar) showed clear and significant improvement after each year of Grazax treatment in pre-co-seasonal and continuous regimens compared with baseline before therapy (*P* < .05 in all cases). Furthermore, there was a close correlation, with no significant difference detected between these groups at each time point. Medication intake was generally decreased during Grazax therapy in the 2 treatment regimens, in line with a decrease in symptom severity. However, there were large statistical fluctuations in the results, which probably reflect the inaccurate nature of this measurement. Nevertheless, there were no significant differences in medication count between treatment regimens at each time point analyzed.

Our trial is the first to compare pre-co-seasonal with continuous treatment regimens of Grazax in adult patients with severe seasonal grass-related allergic rhinoconjunctivitis. We have shown that Grazax is an effective treatment modality and that there is no significant difference in symptom decrease between pre-co-seasonal and continuous treatment regimens. Our results are in agreement with other published data comparing co-seasonal with continuous sublingual immunotherapy (SLIT) and their clinical efficacy in children.^{9,10} One notable exception was reported by Pajno et al,⁹ indicating that co-seasonal was less effective than continuous SLIT after the first year, but not subsequent years, of therapy. However, they admitted that differences in treatment duration between groups could have accounted for the observed difference. We found no such effect, which could be explained by our initiation of pre-co-seasonal and continuous SLIT several weeks before the start of the pollen season. Medication intake was difficult to assess in our patients. Most published evidence has involved fixed dosages and medication diaries,^{1,2,9,10} but this was not feasible in our study. Although self-reported count of medications was limited,

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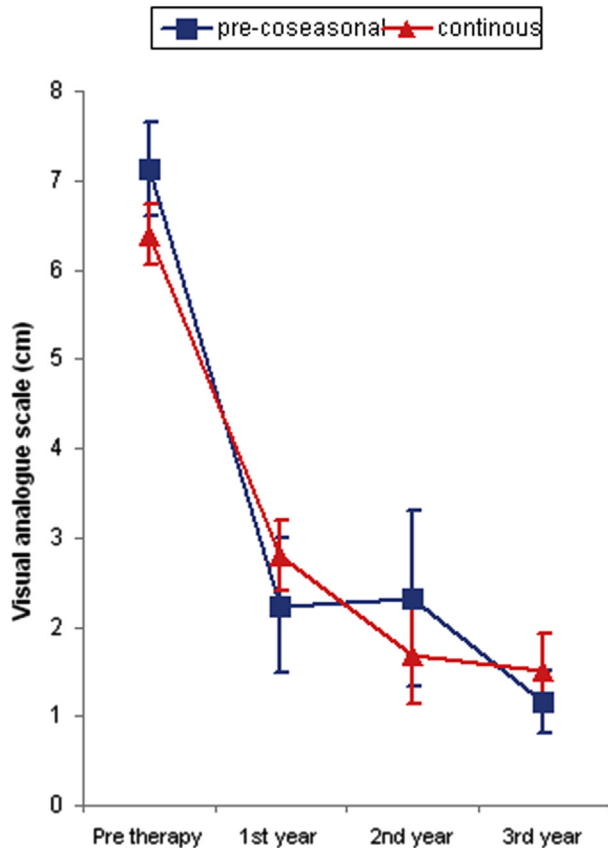


Figure 1. Comparison of pre-co-seasonal with continuous treatment regimens using Grazax on a visual analogue scale before starting treatment and yearly throughout the treatment period. The SEM (error bars) is displayed.

without accurate identification of dosage or frequency of administration, our results imply that medication usage was generally decreased throughout treatment in all patients.

We have shown in our study that pre-co-seasonal treatment with Grazax has a significant cost implication because it decreases the medication costs by approximately 33% without any impact on clinical efficacy. However, it was limited by the absence of a placebo arm, the absence of a double-blinded method, and a small sample. Therefore, larger controlled trials with larger patient numbers must

be conducted to evaluate the weighted benefits of different SLIT regimens and their cost-saving potential in different populations.

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