www.dtb.navarra.es

02/2011

Grass pollen allergen *Phleum pratense*▲ (Grazax®) Allergic rhinitis and conjunctivitis induced by grass pollen

A long and expensive preventive treatment with very modest results

Therapeutic indications

Treatment of allergic rhinitis and conjunctivitis caused by grass pollen in adults and children (≥5 years) with clinically relevant symptoms and diagnosed with a positive skin prick test and/or specific IgE test.

Mechanism of action[1]

It has been demonstrated that treatment with *Phleum pratense* extract induces a competitive response with antibodies against grass pollen, and produces a sustained increase in specific IgG for the two year period of treatment. The clinical significance of these findings has not been established.

Posology and method of administration[1]

The recommended dose in adults and children (≥5 years) is one oral lyophilisate (75,000 standardised quality units per tablet (SQ-T)) daily. Treatment should be introduced by specialists in allergy related disorders.

In the case of children, careful selection of patients should be considered given the expected efficacy for this age group. The lyophilisate should be removed from the blister with dry fingers and placed under the tongue. Swallowing the tablet should be avoided for at least a minute. No food or beverage should be taken for at least 5 minutes after taking the tablet. It is recommended that the first dose be taken under medical supervision (20-30 minutes of observation), with the aim of detecting any adverse reaction. If no important improvement in symptoms is achieved during the first grass pollen fever season then treatment should not be continued. There is no available data on efficacy of the treatment of children for more than one year.

Treatment should be initiated at least 4 months before the expected grass pollen season in order to achieve the clinical effect. If treatment begins 2-3 months ahead, certain efficacy can be achieved. The manufacturer recommends treatment for 3 years.

It does not offer further relevant advantages to symptomatic treatment

- Pollen extract from Phleum pratense (Timothy grass) has been introduced in the market for the treatment of allergic rhinitis and conjunctivitis caused by a grass pollen when clinically relevant symptoms are present and specific tests confirm the origin of the allergy.
- Four clinical trials studying this agent have been published. In three of them, the agent proved slightly more effective than placebo in the improvement of symptoms, and in one trial the efficacy of the agent was not higher than placebo.
- A significant percentage of patients was affected by adverse effects, oral pruritus the most frequent reaction reported (46-56%).
- There are no comparative trials with subcutaneous immunotherapy.

Clinical efficacy

Three double blinded, randomized, placebo controlled clinical trials have been pub-

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

lished to evaluate the efficacy of the standardised allergen extract from the pollen of Timothy grass (*Phleum pratense*) employed in sublingual tablets for seasonal allergic rhinoconjunctivitis (hayfever)[2-4].

In the first trial[2] (n = 634), patients received either the P. pratense 75000 SQ or placebo. Treatment commenced 16 weeks before the grass pollen season and was continued for 3 years. The primary endpoint was the average symptom score of rhinoconjunctivitis during the pollen season. During the first year, patients under treatment with the extract presented lower scores than those under placebo (2.4 vs 3.4 respectively, with a maximum of 18 points; p<0,0001). Patients under treatment with the extract presented 27 (53%) "good days" (with no medication or with a score of ≤2) vs 23 (44%) in the placebo group. The average score with regard to the use of rescue medication was also evaluated. Patients taking the extract showing lower scores than those under placebo (1.5 vs 2.4 over a maximum score of 30). From this trial data has been published posteriorly after the second[5], third and fourth year (by then with no treatment)[6]. However, there was a considerable percentage of drop-offs over the years which conditions the validity of the trial. Patients under treatment with the extract presented lower symptom scores (4th year, 2.7 vs 3.6) and rescue medication (4th year, 2.3 vs 3.3).

In the second trial[3] (n = 855), patients received placebo or the *P. pratense* extract at doses of 2500, 25000, or 75000 SQ for an average of 18 months. There were no significant differences between groups in symptom scores (75000 SQ, 2.47 compared to placebo 2.94; p<0.071). Only at doses of 75000 SQ was there a lower score with regard to use of rescue medication, although the results were at the limits of statistical significance (1.46 compared to 2.05; p = 0.047).

In the third trial (n = 114) the primary endpoint was to confirm the safety profile of the extract in patients who, besides rhinoconjunctivitis, presented mild to moderate asthma induced by pollen grass. The secondary endpoint was to evalute the efficacy in rhinoconjunctivitis. The average score in the use of medication for asthma was 0.71 in patients under treatment with the extract vs 0.66 in patients under placebo over a maximum score of 32 (with no statistical significance). The symptom scores of rhinoconjunctivitis were lower in patients taking the extract (2.1 vs 3.3 over a maximum score of 18; p =0,004).

One trial has also been published studying children (5-16 years). The trial included 253 children with rhinoconjunctivitis. The children treated with the extract showed on average lower symptom scores when compared to placebo (2.7 vs 3.2 over a maximum score of 18; p<0.0195) and also a lower score with regard to use of rescue medication (2.1 vs 2.5, over a maximum score of 34 points; p<0.0156)[7].

Safety

Adverse reactions[1-4]

During the research carried out on this medication, 70% of the patients reported adverse reactions. The most frequent (>10%) included local reactions in the mouth (mouth oedema, pruritus (46-53%)), throat irritation, ear pruritus, and sneezing). These reactions appeared at the onset of treatment and gradually disappeared spontaneously after 1 to 7 days.

With a frequency between 1-10% other reactions reported include: headache, oral paresthesia, itchy eyes, conjuntivitis, cough, asthmatic allergic reactions, pharyngitis, rhinorrea, nasal congestion, oppression in the throat, oropharyngeal inflammation, dyspepsia and nausea, discomfort in the mouth, blisters in the oral cavity, swelling of the tongue or glosodinia, pruritus and fatigue. Other adverse effects with a frequency under 1% were mainly allergic reactions.

Some reactions were observed more frequently in children and include upper respiratory tract infections, abdominal pain, vomiting, and swelling of the lips. Various agencies have recommended special consideration and close follow-up when using this medication given the high potential for adverse effects.

Precautions and contraindications[1]

This agent should not be employed in cases of hypersensitivity to any of the excipients, malign tumours, or diseases affecting the immune system, inflammatory disorders affecting the oral cavity with severe symptoms or patients with severe or uncontrolled asthma. Treatment should be discontinued for 7 days in case of programmed surgery involving the oral cavity, dental extractions, and falling of the milk teeth in children in order to allow for adequate healing in the oral cavity. In any child with concomitant asthma and with an acute upper tract respiratory infection, treatment with the extract should be suspended until the child is cured of the infection.

In cases of important local adverse reactions, antiallergic agents can be considered. If severe systemic reactions occur then treatment should be discontinued. Should the clinical condition of any patient with asthma worsen then treatment with the extract should also be stopped and its use in the future should be reconsidered.

Severe allergic reactions can be treated with adrenaline. The effects of adrenaline can be potentiated by the use of tricyclic antidepressants and monoamine oxidase inhibitors which can provoke fatal consequences. There is no experience with respect to combined treatment of this form of immunotherapy and vaccination.

Use in special situations[1]

Pregnancy: treatment should not be initiated. If a patient becomes pregnant during treatment then this can be continued after an evaluation of the patient. **Lactation:** no data is available. No effects in babies are expected. **Children:** there is no experience in children under 5 years. **Patients over 65 years:** there is no experience available.

Place in therapy

Allergic rhinitis is the most frequent allergy related disease. The elective management option is symptomatic based on the use of oral antihistamine agents and intranasal steroids. Subcutaneous specific immunotherapy has been indicated in allergic rhinitis when IgE mediated hypersensitivity to a specific antigen or a reduced number of antigens has been demonstrated and when patients do not present adequate control with medical treatments. Sublingual immunotherapy has been proposed as an alternative.

Up to now only trials comparing the P. pratense extract to placebo have been published. Patients under therapy with the extract show a small improvement in symptoms when compared to the placebo group which is of doubtful clinical relevance. In one of the trials, patients treated with the extract gained 4 free days (27 vs 23 days) of symptom based treatment during the grass pollen season. Therefore, taking into account the modest efficacy shown, the high frequency of adverse effects, the high percentage of patients that continue requiring rescue medication and the high cost involved with this therapy (1,282 €/year) it does not seem worth employing this treatment when compared to symptomatic management.

Presentations

Grazax® (Abelló Laboratories) 75000 SQ-T 30 oral lyophilisates (106.84 €). Requires a medical prescription with special authorization.

References:

A complete report on the *Phleum pratense* extract can be consulted at: www.dtb.navarra.es

Servicio Navarro de Salud
Osasunbidea

INFORMATION:
Servicio de Prestaciones Farmacéuticas Plaza de la Paz s/n, 4ª planta - 31002 Pamplona **T** 848429047 **F** 848429010

NEW DRUGS ASSESSMENT COMMITTEE:
Iñaki Abad, Mª José Ariz, Ana Azparren, Juan Erviti, Javier Garjón, Javier Gorricho, Antonio López, Rodolfo Montoya, Mikel Moreno, Lourdes Muruzábal