Canadian Agency for Drugs and Technologies in Health

Issues in Emerging Health Technologies

Grazax®: An Oral Vaccine for the Treatment of Grass Pollen Allergy (Hay Fever)

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Summary

- ✓ **Grazax® is a self-administered, once-daily, tablet-based vaccine that offers an alternative to allergy shots for adults with grass pollen allergy (hay fever).**
- ✓ **Evidence from three randomized controlled trials indicates modest improvements in hay fever symptoms, with reduced use of medication to control symptoms (rescue medication use) in adults who took Grazax compared with placebo. No studies have compared Grazax with injection-based allergen immunotherapy.**
- ✓ **It is not yet known if patients treated with Grazax will have a sustained tolerance to grass pollen following treatment discontinuation.**
- ✓ **Adverse effects of Grazax are generally mild to moderate local allergic reactions of short duration, and include itching and swelling of the mouth, and throat irritation.**
- ✓ **If Grazax becomes widely prescribed and is covered by provincial drug plans, the costs to the Canadian health care system and the impact on allergy specialist services could be substantial.**

Background

Seasonal grass pollen-induced allergic rhinitis and conjunctivitis are characterized by inflammation of the mucous membranes lining the nose and eyes, causing sneezing, nasal itching and congestion, runny nose, and itchy, red, watery eyes.[1,2] Allergic rhinoconjunctivitis is one of the main reasons for visits to primary care physicians.[3] Symptoms may interfere with cognitive tasks, impair work or school performance, and affect quality of life.[4-6] Allergic rhinoconjunctivitis is also a major risk factor for the development of asthma.[1,3]

The Technology

Grazax is the European brand name for a tablet-based immunotherapy treatment, or oral vaccine, for grass pollen-induced allergic rhinitis and conjunctivitis, or what is commonly called hay fever. Tablets contain 75,000 standardized quality units (SQ-T) of a purified extract of timothy grass pollen (*Phleum pratense*), which has extensive cross-reactivity against other grass pollens.[7] The mechanism of immunotherapy treatment is not fully understood, but it is believed to restore normal immune regulation by modifying the T-cell response to allergens, thereby reducing allergy symptoms such as runny nose, congestion, and itchy eyes.[8,9] Grazax is an oral alternative to injection immunotherapy, or "allergy shots," which must be administered in a specialist clinic. Grazax is manufactured by ALK-Abelló A/S (Copenhagen, Denmark); Schering-Plough manages the product's development and marketing in North America.[10]

Regulatory Status

Grazax is not currently approved for use in Canada or the United States. It is, however, approved in Europe[10] for treating adults (18 to 65 years of age) with clinically relevant symptoms of grass pollen-induced rhinitis and conjunctivitis who test positive with a skin prick test or a specific immunoglobulin E (IgE) test to grass pollen.[11]

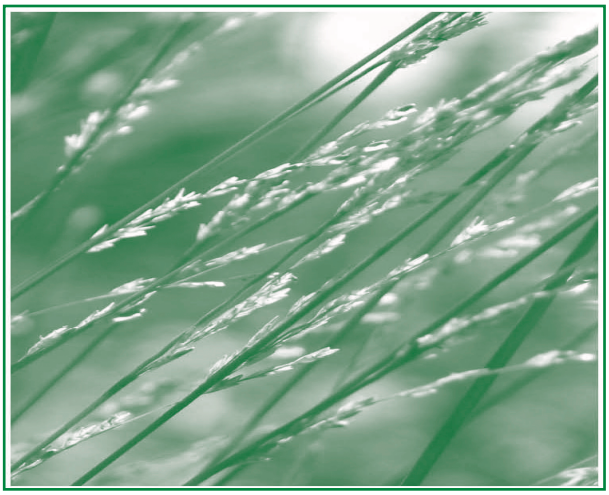

Photo courtesy of C. Allison

Patient Group

The prevalence of grass pollen allergy in Canada is not well established. If prevalence is assumed to be similar to European rates, approximately 25% of adult Canadians have allergies, and of these about 50% are allergic to grass pollen.[12]

Current Practice

Current treatment options for hay fever include allergen avoidance — although the ubiquitous presence of grass makes this difficult — followed by symptom control, principally with antihistamines, intranasal corticosteroids, decongestants,

cromolyn sodium, and ipratropium.[2,5] Even with symptomatic treatment, more than 40% of patients describe their control as partial or poor, especially if symptoms are severe.[3,6,12]

If symptomatic treatment fails, allergen immunotherapy (desensitization) with a series of monthly subcutaneous injections, given over three to five years, has been shown to reduce symptoms and the need for rescue medications to control symptoms, decrease the rate of progression to allergic asthma, and improve quality of life.[13,14] These effects persist for at least three years following treatment discontinuation.[15]

Pre-seasonal short courses of injection immunotherapy have also been reported to decrease symptoms and medication requirements, with four to seven injections of gradually increasing doses of a chemically modified grass pollen allergen given before the pollen season.[16]

Local injection reactions to allergy shots may cause discomfort, and severe systemic reactions have occurred, including anaphylaxis and, rarely, death.[15] It is recommended that allergy shots be given in specialist centres where resuscitation equipment is available (although injections are often administered by primary care physicians), and that patients be observed for 30 to 60 minutes after injections.[13,15,17]

For these reasons, a safer and more convenient route of administration for allergen immunotherapy is appealing. In Europe, sublingual drop-based immunotherapy has been used since 1986 as an alternative to injections.[9,18] Sublingual drop-based immunotherapy is not available in Canada.[9]

The Evidence

No clinical studies have compared Grazax with injection-based immunotherapy. Two[3,13] of three industry-sponsored, double-blind, randomized controlled trials (RCTs) reported a statistically significant lowering of symptom scores and rescue medication use in adults receiving Grazax, compared with placebo, for the treatment of allergy-induced rhinoconjunctivitis.[3,6,13]

In all three trials, patients had access to rescue medication as needed (antihistamines, intranasal corticosteroids, and oral corticosteroids), in a stepwise manner. Outcome measures were the number of self-reported symptoms and use of rescue medication. Patients rated and recorded daily symptoms on a scale from zero to three (none, mild, moderate, severe).[13] Nasal symptoms rated were runny nose, blocked nose, sneezing, and itchy nose. Ocular symptoms included gritty feeling, red and watery eyes. The use of rescue medication was also recorded daily.

Study 1 (GT-02)

A dose-finding study in 855 adults established Grazax 75,000 SQ-T as the optimal effective dose (compared with 2,500 SQ-T and 25,000 SQ-T) when given for approximately eight weeks before and during the grass pollen season. Outcomes included rhinoconjunctivitis symptom and rescue medication usage scores, quality of life, and number of well days during the pollen season. Mean daily symptom and medication usage scores were 16% (p=0.071) and 28% (p=0.047) lower, respectively, in 294 patients who received Grazax 75,000 SQ-T compared with 286 patients who received placebo.* (The remaining 175 patients received lower doses of Grazax.) According to a combination of self-reported ratings, diary entries and standardized measurement scales, patients receiving Grazax 75,000 SQ-T reported higher quality of life scores (p=0.021) compared with those taking placebo.[2,6] The number of well days was also 18% higher (p=0.041) in those taking Grazax compared with placebo.

Study 2 (GT-07)

A smaller trial reported on 114 patients with moderate to severe rhinoconjunctivitis and mild to moderate allergy-induced asthma who were randomized 2:1 to receive Grazax or placebo 10 to 14 weeks prior to and during the 2004 grass pollen season.[3] Primary endpoints were average asthma medication and symptom scores; secondary endpoints were average rhinoconjunctivitis symptoms and rescue medication usage scores. Rhinoconjunctivitis symptoms were 37% (p=0.004) lower in the patients who received Grazax compared with those who received placebo; the use of rescue medication was also 41% (p=0.036) lower in the Grazax group. Differences in asthma medication use and symptom scores were negligible; the mean asthma symptom score differed between the two groups by 0.3 (maximum score was 32), and the mean asthma medication score differed by 0.05 (to put this into proportion, a single inhalation of asthma rescue medication scored 2).[3]

Study 3 (GT-08) 13

A trial of 634 adults compared 316 patients who took Grazax with 318 patients who took placebo. All patients started treatment at least 16 weeks before the 2005 pollen season. Outcomes were average rhinoconjunctivitis symptom scores and rescue medication usage scores. Symptom scores of patients who took Grazax were 30% (p<0.001) lower than symptom scores of those who took placebo. As well, the use of rescue medication was 38% (p<0.001) lower with Grazax. The trial will continue for two more pollen seasons, with a two-year follow-up to evaluate the sustained efficacy of Grazax versus placebo. Based on a preliminary review of the results, ALK-Abelló A/S reported that patients who took Grazax for two consecutive pollen seasons had 36% fewer rhinoconjunctivitis symptoms and used 46% less rescue medication compared with those who took placebo.[7] Full study results have not yet been published.

One small RCT with 60 children (aged five to 12 years) reported that Grazax 75,000 SQ-T was generally well tolerated in 45 children who received the drug for 28 days outside the pollen season, compared with 15 children who received placebo.[19] Drug efficacy was not evaluated in this study.

* p value < 0.05 indicates statistical significance

Adverse Effects

In clinical trials of Grazax, adverse effects were reported in 70% of adult patients.[11] These were mostly mild to moderate local allergic reactions of short duration, including itching and swelling of the oral mucosa, throat irritation, and sneezing.[11] In Study 1, 18 participants (2%) withdrew because of unspecified probable or possible treatment-related adverse events. One serious adverse event (uvular edema) was reported.[6] In Study 2, oral pruritis (itchiness) was reported by 53% of patients receiving Grazax compared with 5% taking placebo, but was generally mild and did not lead to withdrawals.[3] In Study 3, there were five treatment-related adverse events (angioedema, throat swelling, and pharynx edema) that led to patient withdrawal.[13] No life-threatening systemic reactions or deaths were reported in any of the trials. Among 45 children aged five to 12 years who received Grazax for 28 days in one trial, oral pruritis was reported in 28 children (62%) compared with one child (7%) in the placebo group.[19] Two children treated with Grazax withdrew from the trial due to adverse events; one child had an asthma attack requiring hospitalization.

Administration and Cost

The sublingual Grazax tablet is dissolved under the tongue once daily throughout the year, beginning four months before the grass pollen season,[11] which typically runs from late May to August.[12] While not optimal, some benefit may be obtained if treatment is started two to three months before the season.[11] Due to the risk of adverse effects, the first dose is taken under medical supervision for 20 to 30 minutes. If there is no improvement in symptoms during the first pollen season, treatment should be discontinued.[11]

In the UK, 30 Grazax tablets cost £67.50.[12] This is equivalent to approximately C$145.00. Assuming once daily, year-round dosing, the approximate annual Canadian cost per patient is C$1,764.00. If treatment is continued for three years, the total cost would be C$5,292.00 per patient. By contrast, the cost of the injection-based allergen vaccine ranges from C$300 to $400 for a three-year treatment period, not including physician fees for 36 monthly clinic visits (Dr. Stuart Carr, Division of Clinical Immunology & Allergy, University of Alberta, Edmonton: personal communication, 7 Aug 2007). Prior to treatment with either injection or oral immunotherapy, a grass pollen allergy must be diagnosed from a positive skin-prick or IgE test.

Two industry-sponsored pharmacoeconomic analyses estimate that Grazax is cost-effective at an annual European treatment cost ranging from €1500 to €2200 (equivalent to C$2,160 to C$3,168). Both analyses were based on clinical data from Study 3,[13] and used £20,000 (equivalent to C$43,000) as the threshold of willingness to pay for one quality-adjusted life-year gained. The costs of rescue medication use, physician visits, and hours missed from work were compared between patients receiving symptomatic treatment alone or Grazax plus symptomatic treatment. The analyses assumed that after three consecutive years of once-daily Grazax dosing, patients would have a sustained tolerance to grass pollen for six more years following treatment discontinuation.[20,21] However, data on the six-year sustained effects of Grazax and, therefore, its actual cost-effectiveness, are unknown.

Concurrent Developments

Grazax phase 3 safety and efficacy trials are underway in the US (in adults) and in Germany (in children).[10] ALK-Abelló A/S is also developing tablet-based immunotherapy products for dust mite and ragweed allergies.[10] A phase 3 trial is underway to compare the efficacy and safety of a sublingual immunotherapy tablet (made by Stallergenes) with placebo in the treatment of grass pollen rhinoconjunctivitis in children.[22]

Rate of Technology Diffusion

Presently, only a small minority of patients with severe, unresponsive hay fever receive immunotherapy with subcutaneous injections of allergen extracts. However, the advantages of self-administered treatment (fewer visits to an allergist, no waiting periods after the injections, and a reduced likelihood of serious side effects compared with immunotherapy injections) could result in greater numbers of Canadians receiving sublingual immunotherapy for hay fever.

The number of people affected by allergic diseases, including hay fever, is increasing worldwide.[23,24] This could increase the demand for Grazax. Global warming and climate change may also affect the incidence, prevalence, and severity of allergic disease, by causing the grass pollen season to start earlier and last longer.[24] The length of the growing season in Europe has increased by 10 to 11 days over the last 30 years.[24]

It is likely that Grazax will initially be prescribed by allergy specialists for patients who fail to respond to symptomatic treatment.[25] However, patient demand could potentially result in wider prescribing as an initial therapy by primary care physicians.

Implementation Issues

A sublingual form of immunotherapy in a standardized, self-administered tablet offers a convenient and potentially safer alternative to subcutaneous immunotherapy injections. Modest improvements in symptoms, rescue medication use, and quality of life were reported in patients who took Grazax continuously for 22 months in one clinical trial.[13]

It is unknown if three years of Grazax treatment will induce sustained tolerance with reduced symptoms during future pollen seasons, as has been demonstrated with injection immunotherapy. Until this is known, it is difficult to assess Grazax's long-term efficacy and cost-effectiveness.

Many patients with hay fever currently control symptoms with non-prescription medications purchased at their own expense. If Grazax becomes a widely prescribed initial allergy treatment and is covered by provincial drug plans, the costs to

the Canadian health care system and the impact on allergy specialist services could be substantial.

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