Seasonal allergic rhinoconjunctivitis: efficacy of grass pollen allergen sublingual immunotherapy tablets

A meta-analysis of 13 randomised controlled trials with 4659 participants found that for people with seasonal allergic rhinoconjunctivitis of varying severity, grass pollen allergen sublingual immunotherapy tablets were associated with a small improvement in symptom and medication scores compared with placebo. However, the clinical relevance of this benefit is unclear. Adverse events were reported by nearly two-thirds of people treated with sublingual immunotherapy and 9 adverse events required adrenaline. The BNF states that pollen extract immunotherapy, such as sublingual immunotherapy tablets should only be considered for people who remain symptomatic despite treatment with anti-allergy drugs, and only initiated under specialist supervision.

Overview and current advice

Allergic rhinitis is an inflammatory disorder of the nose which occurs when the membranes lining the nose become sensitised to allergens. Grass pollen is a common allergen for seasonal allergic rhinitis or rhinoconjunctivitis. Allergen avoidance is fundamental to the management of allergic rhinitis, although drug treatment may be necessary. Treatment options include antihistamines (oral, intranasal and eye drops) and corticosteroids (intranasal and oral)\(^1\).

Guidelines on immunotherapy for allergic rhinitis\(^2\) produced by the British Society for Allergy and Clinical Immunology (BSACI) in 2011 state that sublingual immunotherapy is an effective treatment for adults and children with severe allergic rhinitis that does not respond to conventional drug treatment and allergen avoidance measures, and has been shown to give long-lasting benefit for some years after stopping treatment.

The sublingual immunotherapy: World Allergy Organization position paper 2013 update\(^3\) recommends that sublingual immunotherapy may be particularly indicated for people:

- whose allergy is uncontrolled with optimal drug treatment (including those with severe chronic upper airway disease)
- in whom drug treatment induces undesirable side effects
- who refuse injections
- who do not want to be on frequent or long-term drug treatment.

A sublingual immunotherapy tablet containing extract of grass pollen from Timothy (Phleum pratense) was launched in the UK in 2009 (Grazax). Grazax is licensed for the disease-modifying treatment of
grass pollen induced rhinoconjunctivitis in adults and children aged 5 years or older, with clinically relevant symptoms and diagnosed with a positive skin prick test or specific IgE test to grass pollen. The summary of product characteristics states that a clinical effect in the first grass pollen season is expected when treatment is started at least 4 months prior to the expected start of the grass pollen season. It is recommended that Grazax treatment is continued for 3 years, but should be stopped if there is no relevant improvement of symptoms during the first pollen season.

Grazax costs £80.12 for 30 days treatment (MIMS, November 2015). Traditional anti-allergy treatments cost considerably less; 30 days of cetrizine 10 mg daily costs £1.05 and beclometasone dipropionate nasal spray costs approximately £0.79 to £1.58 for 30 days (Drug Tariff, December 2015). In 2014 there were approximately 2300 prescriptions for Grazax dispensed in primary care across England (Prescription Cost Analysis, England – 2014, HSCIC), at a net ingredient cost of £220,000. Another sublingual immunotherapy tablet containing 5 different grass pollens (Oralair) is available in the USA, and some European countries, but not in the UK.

A meta-analysis by Di Bona et al. 2010 found that sublingual immunotherapy was effective for the management of seasonal allergic rhinoconjunctivitis, although the authors suggested that the benefits compared with placebo were modest. The same group of researchers have published an updated meta-analysis which included more recent trial data, the results for which are discussed below.

New evidence

A systematic review and meta-analysis of placebo-controlled randomised controlled trials reported on the effectiveness of sublingual immunotherapy tablets for the treatment of seasonal allergic rhinoconjunctivitis (Di Bona et al. 2015). The meta-analysis included 13 RCTs, involving a total of 4659 participants with a clinical history of seasonal allergic rhinoconjunctivitis to grass pollen of varying severity, who had a positive grass pollen allergen-specific skin test and elevated serum grass pollen allergen-specific IgE levels (median mean age 35.9 years, median 56.9% men). Results were reported of an intention-to-treat analysis in 12 studies, with a rigorous method of randomisation reported in 8 studies, although none of the studies reported if allocation was concealed. Eight studies used the sublingual immunotherapy tablet available in the UK, Grazax, with 4 of these studies conducted in Europe and 4 studies in North America. Four studies used the sublingual immunotherapy tablet containing 5 grass pollens, Oralair (3 studies in Europe and 1 in the USA), and 1 study in Europe used the 5 pollen tablet but at a lower strength.

The meta-analysis included studies that reported outcomes using symptom score (usually from patient diaries, with higher scores indicating worse disease) or medication score (in which use of rescue medication, including antihistamines and corticosteroids, is recorded and scored, with higher scores indicating more rescue medication was required). Results of the meta-analysis were reported using standard mean differences (SMD) and effect size, where an effect size of 0.2, 0.5 and 0.8 corresponds to small, medium and large effects respectively.

Pooled analysis found that people treated with sublingual immunotherapy tablets experienced a statistically significant reduction in symptom score compared with placebo, with a SMD in treatment effect size of $-0.28$ (95% confidence interval [CI] $-0.37$ to $-0.19$, $p<0.001$); that is, a small treatment benefit. Medication score was reported in 12 studies ($n=4558$), with a statistically significant difference seen for sublingual immunotherapy tablets compared with placebo in the pooled analysis, with a SMD in effect size of $-0.24$ (95%CI $-0.31$ to $-0.17$, $p<0.001$); again a small treatment benefit.

Treatment-related adverse events were reported in 9 out of 13 studies, with a higher incidence of adverse events in the group receiving sublingual immunotherapy tablets (61.3%) compared with placebo (20.9%). Most adverse events were of moderate severity in both groups. However, there were 9 adverse events requiring adrenaline (epinephrine) in the sublingual immunotherapy tablet group.
compared with 3 such events in the placebo group. No episodes of anaphylaxis were reported. More people receiving sublingual immunotherapy tablets withdrew due to adverse events compared with placebo (6.0% and 2.2% respectively).

Commentary

Commentary provided by the Medicines and Prescribing Programme, NICE

This meta-analysis found that sublingual immunotherapy was associated with a small improvement in symptom and medication scores for people with allergic rhinoconjunctivitis compared with placebo. The clinical relevance of this small treatment benefit is unclear, and the authors discuss that it generally relates to a less than 1 point difference on an 18 point symptom score scale. This compares with a possible 7 to 8 point reduction on the same scale with on demand antihistamines or corticosteroids.

The incidence of adverse events was relatively high, reported by nearly two-thirds of people treated with sublingual immunotherapy, with 9 adverse events requiring adrenaline. The summary of product characteristics for Grazax states that very commonly reported adverse reactions are local allergic reactions in the mouth which are mostly mild to moderate. In most people these reactions started early in therapy, lasted from minutes to hours after each intake of Grazax and tended to subside spontaneously within 1 to 7 days. However, cases of serious anaphylactic reactions have been reported and medical supervision at the start of treatment is recommended.

There are a number of important limitations with the meta-analysis that should be considered. The majority of participants in the RCTs involving Grazax were from the USA or Canada, and subgroup analysis found that sublingual immunotherapy was less effective in the North American studies compared with the European studies. The North American studies were more recent, had larger sample sizes and less risk of bias, suggesting they provide a more reliable estimate of the treatment effect. However, in North America a 5-grass pollen product might be expected to better represent natural exposure and sensitisation conditions experienced by people with allergic rhinitis. Trials involving a 5-pollen sublingual immunotherapy tablet, which is currently not available the UK, were included, but these were mainly carried out in Europe.

The BNF states that pollen extract immunotherapy, such as sublingual immunotherapy tablets (Grazax) should only be considered for people who remain symptomatic despite treatment with anti-allergy drugs, and only initiated under specialist supervision. Careful patient-selection is essential to ensure people who may be better managed with traditional anti-allergy drugs aren’t exposed to more costly treatments that are associated with a high incidence of adverse events.

Study sponsorship

No sponsorship reported.

References

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