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Frank Thien

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Sublingual immunotherapy with a grass allergen tablet improved symptoms and quality of life in allergic rhinoconjunctivitis

Durham SR, Yang WH, Pedersen MR, *et al.* Sublingual immunotherapy with once-daily grass allergen tablets: a randomized controlled trial in seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006;117:802–9.

Clinical impact ratings GP/FP/Primary care ★★★★★☆ Allergy & immunology ★★★★★☆

Q In patients with grass pollen-induced allergic rhinoconjunctivitis, how effective is sublingual immunotherapy with a grass allergen tablet?

METHODS

Design: randomised placebo controlled trial.

Allocation: unclear allocation concealment.*

Blinding: blinded (patients, healthcare providers, and outcome assessors).*

Follow up period: up to the end of grass pollen season.

Setting: 55 centres in Canada, UK, Germany, Belgium, Austria, Denmark, Sweden, and Norway.

Patients: 855 patients 18–65 years of age (mean age 35 y, 62% men) who had allergic rhinoconjunctivitis during grass pollen season for ≥ 2 years and positive result on skin prick test to timothy grass (*Phleum pratense*). Exclusion criteria included history of asthma, anaphylaxis, or angio-oedema; forced expiratory volume₁ <70% predicted; non-grass induced allergic rhinitis; recurrent acute or chronic sinusitis; conjunctivitis, rhinitis, or asthma at randomisation; hypersensitivity to trial medication; and immunotherapy for allergens in the past 5–10 years.

Intervention: oral *P. pratense* pollen tablets (GRAZAX, ALK-Abelló, Denmark), 0.5 µg pollen with rescue medication (RM) (n = 136), 5 µg pollen with RM (n = 139), 15 µg pollen with (n = 141) or without RM (n = 153), or placebo (no pollen) with (n = 136) or without RM (n = 150). Patients took medication once a day for 8 weeks before and during grass pollen season. *Rescue medication.* If symptoms persisted, patients took loratadine or placebo and if ineffective, took budesonide or prednisone; if patients developed asthma, salbutamol, fluticasone, or prednisone was given.

Outcomes: self reported rhinoconjunctivitis symptoms and medication use, number of well days (days without use of RM and symptom score ≤ 2), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and adverse events.

Patient follow up: 87% (intention to treat analysis).

*See glossary.

MAIN RESULTS

The 15 µg grass pollen allergen tablet led to less use of medication (table), 17% improvement in RQLQ scores ($p = 0.006$), 18% more well days ($p = 0.041$), and a non-significant improvement in rhinoconjunctivitis symptoms during grass pollen season than placebo (table). The 2 lower dose groups did not differ from placebo. 49% of patients had mild to moderate adverse events (eg, oral pruritis

For correspondence: Dr S R Durham, Royal Brompton and Harefield Hospitals National Health Service Trust, London, UK. s.durham@imperial.ac.uk

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or throat irritation) that lasted for median 4–10 days. 6 serious adverse events were reported across all groups.

CONCLUSION

In patients with grass pollen-induced allergic rhinoconjunctivitis, sublingual immunotherapy with a grass allergen tablet tended to improve symptoms and quality of life.

Commentary

The cornerstones of respiratory allergy management are threefold: allergen avoidance where possible, standard pharmacotherapy (symptom relief and prophylactic anti-inflammatory medication), and allergen immunotherapy. However, allergen avoidance is very difficult if not impossible with seasonal allergic rhinoconjunctivitis. Standard pharmacotherapy with antihistamines and intranasal steroids, particularly in patients with severe symptoms, is only of partial benefit. Since the underlying immunological allergic predisposition is not altered, patients have to take these medications every pollen season to control symptoms. Furthermore, the condition tends to worsen with exposure to pollen in subsequent seasons.

Subcutaneous allergen immunotherapy (SCIT) is very effective for seasonal pollinosis and alters the natural history of the condition by modifying the underlying immunological mechanisms. However, it is not very efficient and requires weekly to monthly injections for 3–5 years. There is also risk of adverse allergic reactions including anaphylaxis. Nevertheless, it is the only treatment that induces clinical remission with documented benefits lasting at least 3–6 years after cessation of treatment in clinical trials, and even longer in clinical experience. This is the current “gold standard” with which newer forms of immunotherapy should be compared.

The trial by Durham *et al* offers proof of concept that sublingual delivery of immunotherapy with specially formulated allergen tablets is clinically more effective than placebo. This is supported by the dose response and in vitro data, which confirm modulation of the underlying immunological process, similar to SCIT. The ease of administration with few serious side effects offers promising advantages, but efficacy compared with SCIT needs to be evaluated before direct differential judgements of risks and benefits are made. Furthermore, the highest dose for benefit is substantially greater than that required for SCIT, making commercial sublingual preparations more expensive than SCIT formulations. In the long term, this may be offset by obviating requirement for doctor visits to receive immunotherapy injections. Sublingual immunotherapy may also be used to treat a broader range of patients, such as those currently excluded from SCIT because of uncontrolled asthma or poor lung function.

Frank Thien, MD, FRACP
Alfred Hospital and Monash University
Melbourne, Victoria, Australia

15 µg grass pollen allergen (GA) tablet v placebo in allergic rhinoconjunctivitis during grass pollen season*

Outcomes	GA tablet	Placebo	Estimated adjusted mean difference (95% CI)
Rhinoconjunctivitis symptoms	2.5	2.9	−0.5 (−1.0 to 0.04)
Medication use	1.5	2.0	−0.6 (−1.2 to −0.01)

*CI defined in glossary.