THERAPEUTICS

Grass pollen immunotherapy for treatment of allergic rhinitis

Anna Slovick,[1] Stephen R Durham,[2] Stephen J Till[1 3]

[1]Division of Asthma, Allergy and Lung Biology, King's College London, School of Medicine, Guy's Hospital, London SE1 9RT, UK
[2]Section of Allergy and Clinical Immunology, National Heart and Lung Institute, Faculty of Medicine, Imperial College, London SW3 6LY, UK
[3]Department of Allergy, Guy's and St Thomas' NHS Foundation Trust, London SE1 9RT, UK
Correspondence to: S J Till
stephen.till@kcl.ac.uk

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic, please email us at practice@bmj.com

A 33 year old female teacher presented with a history of troublesome allergic rhinoconjunctivitis and seasonal asthma. Since her teens, from May through to August she had experienced sneezing, nasal congestion, rhinorrhoea, itchy red eyes, and occasional breathlessness. In previous summers, her general practitioner had prescribed daily intranasal budesonide, oral cetirizine, and cromoglicate eye drops, together with inhaled salbutamol as needed. Although she had experienced a modest improvement with this treatment, symptoms continued to impair her concentration in the classroom and her quality of sleep. Her general practitioner referred her for consideration of "desensitisation."

What is grass pollen immunotherapy?

Grass pollen immunotherapy involves repeated administration of high doses of grass pollen allergen with the aim of inducing clinical and immunological tolerance in the recipient. Immunotherapy formulations contain an extract of one or more species of grass pollen and are administered either as a course of subcutaneous injections ("subcutaneous immunotherapy") or as daily sublingual drops or dissolving tablets ("sublingual immunotherapy") for three years. Experience with subcutaneous immunotherapy, first described more than 100 years ago,[1] is extensive; experience with sublingual immunotherapy is less so. In the United Kingdom, grass pollen immunotherapy is indicated in selected patients whose allergic rhinitis remains highly bothersome despite conventional medical treatment with intranasal corticosteroid sprays and oral or topical antihistamines.[2] The clinical effect is believed to derive from induction of T cells that produce interleukin 10 (regulatory T cells) and B cells that produce allergen specific IgG antibodies.[3] Interleukin 10 has multiple anti-inflammatory properties, and grass pollen specific IgG blocks some of the actions of IgE, which largely mediates the immediate hypersensitivity reaction. Side effects mainly occur as IgE mediated reactions to the vaccines.

THE BOTTOM LINE

- Grass pollen subcutaneous immunotherapy and sublingual immunotherapy are safe and effective treatments for summer allergic rhinitis
- Grass pollen immunotherapy should be considered when symptoms continue to affect quality of life despite regular treatment with antihistamines and intranasal corticosteroid sprays
- Both subcutaneous and sublingual grass pollen immunotherapy have been shown to have long lasting benefits that are maintained for several years after a three year course is finished

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We are grateful to patients attending the NHS allergy clinic at Guy's Hospital who reviewed and provided feedback on the "Tips for patients" box, were pleased to be involved and happy with its contents, and did not ask us to amend anything

How well does grass pollen immunotherapy work?

Many clinical guidelines support use of immunotherapy for treatment of refractory allergic rhinitis that affects quality of life, sleep, work, or social activities. A Cochrane systematic review found that subcutaneous immunotherapy was effective at reducing symptoms of allergic rhinitis (15 evaluable studies; 1063 participants), reduces the use of drugs for rhinitis (13 studies; 963 participants), and improves quality of life scores measured with a validated rhinitis specific questionnaire (Rhinoconjunctivitis Quality Of Life Questionnaire) (table 1).[4] These findings were reaffirmed in a more recent meta-analysis that updated the Cochrane review, including a subgroup analysis of trials of grass pollen only subcutaneous immunotherapy.[5] The largest UK multicentre double blind randomised controlled trial of subcutaneous grass pollen immunotherapy (410 participants) compared two doses of vaccine with placebo over a single grass pollen season.[6] Mean daily seasonal nasal symptom scores (maximum score 12 points) were 2.75 in the placebo group and 1.88 in those receiving the higher vaccine dose (difference of −1.26, 95% confidence interval −1.89 to −0.62). Mean daily medication scores (including up to 6 points daily for antihistamines and 8 points daily for corticosteroid nasal spray) were 4.21 in the placebo group and 2.85 in the immunotherapy group (difference −1.36, −2.14 to −0.58). These values may seem low, but such trials typically express symptom and medication scores as a mean daily value over a summer lasting months, whereas the peak of the grass season typically lasts only weeks: immunotherapy is typically given because of debilitating symptoms during this peak.

Sublingual immunotherapy efficacy is supported by a Cochrane systematic review that included a meta-analysis of 25 randomised controlled grass pollen trials (table 1).[7] These findings were reaffirmed in a more recent meta-analysis, which found that grass pollen sublingual immunotherapy reduced seasonal symptom scores (42 studies; 4819 participants) and rescue medication use (35 studies; 3779 participants) and improved Rhinoconjunctivitis Quality Of Life Questionnaire scores.[5] In the largest international double blind randomised controlled trial of grass pollen sublingual immunotherapy to include UK participants, mean daily seasonal nasal symptom scores over the entire first grass season (maximum score 12 points) were 2.32 in the placebo group and 1.69 in the sublingual immunotherapy group (difference

Table 1 | Summary of subcutaneous and sublingual immunotherapy

Characteristic	Subcutaneous immunotherapy	Sublingual immunotherapy
Clinical effectiveness	Effective at reducing symptoms, drug use, and quality of life in Cochrane review[4]	Effective at reducing symptoms, drug use, and quality of life in Cochrane review[7]
	Efficacy demonstrated up to three years after discontinuation (Alutard SQ)[11]	Up to two years' recorded effectiveness (Grazax)
Major contraindications	Asthma: severe or poorly controlled asthma	Asthma: severe or poorly controlled asthma
	β blockers	β blockers
	Not to be initiated in pregnancy	Not to be initiated in pregnancy
Adverse reactions: local	Pruritus and swelling at injection site	Oropharyngeal pruritus and swelling
Adverse reactions: systemic	Small risk of anaphylaxis; no fatalities reported in Cochrane or Health Technology Assessment reviews, as exclusion of patients with severe/uncontrolled asthma and subcutaneous immunotherapy administration in specialist clinics	Minimal risk of anaphylaxis; no fatalities reported worldwide in literature
	Risk of milder reactions such as flushing or urticaria (see table 2)	Milder reactions such as nausea, abdominal pain, rhinitis, conjunctivitis, headache, cough
Administration	Typically four to seven pre-seasonal injections for each of three years for allergoid; updosing initiation phase	Grazax is started four months before pollen season, then taken daily for three years; no updosing initiation phase
	For continuous subcutaneous immunotherapy (such as Alutard SQ), approximately 25 injections in first year and 12 maintenance injections per year thereafter	Some sublingual immunotherapy vaccines taken for only approximately five months per year (for example, Oralair)
	Given in specialist clinic with resuscitation facilities	Taken in home setting, with first dose in specialist clinic with resuscitation facilities

−0.63, −0.86 to −0.62).[8] Mean daily medication scores (including up to 6 points daily for antihistamines and 8 points daily for corticosteroid nasal spray) were 2.23 in the placebo group and 1.38 in the immunotherapy group (difference −0.85, −1.20 to −0.50). Patients who received sublingual immunotherapy had an average of 11.43 (95% confidence interval 6.68 to 16.17) more symptom-free and medication-free days during the 2005 summer grass pollen season.[9]

The clinical benefit may be maintained in future seasons after treatment is stopped. This has been convincingly shown up to three years after discontinuation of grass pollen subcutaneous immunotherapy given continuously for three or four years and up to two years after discontinuation of grass pollen sublingual immunotherapy.[10 11] Comparable data are lacking for short pre-seasonal courses of subcutaneous immunotherapy. The relative efficacy of subcutaneous immunotherapy and sublingual immunotherapy is unknown; no adequately powered comparative trials have been done. An indirect comparison was attempted in a meta-analysis, but heterogeneity of the trials precluded a firm conclusion.[5] In practice, a decision to prescribe grass pollen subcutaneous immunotherapy or sublingual immunotherapy often reflects the patient's and doctor's preference, together with local availability and funding arrangements.

How safe is grass pollen immunotherapy?

Local reactions

Grass pollen subcutaneous immunotherapy and sublingual immunotherapy both commonly cause local reactions (table 1). In general, these effects are short lived and well tolerated and need no specific treatment. Subcutaneous immunotherapy may induce itching, redness, and swelling at the injection site. Sublingual immunotherapy frequently causes oropharyngeal pruritus and localised swelling in the mouth during the early stages of a course, but this typically settles with repeated dosing. In one large trial, 46% of participants who received sublingual immunotherapy reported oral pruritus.[12]

Systemic reactions

Anaphylaxis triggered by immunotherapy is of greater concern. In 1986 the Committee on Safety of Medicines reported on 26 fatalities attributed to subcutaneous immunotherapy in the United Kingdom between 1957 and 1986, mostly in patients being desensitised for asthma in facilities without cardiopulmonary resuscitation facilities.[13] Asthma is no longer considered a primary indication for subcutaneous immunotherapy in the United Kingdom. A similar US report attributed fatalities to poor selection of patients, failure to use adrenaline (epinephrine), dosing errors, and lack of resuscitation facilities.[14] Better selection of patients and administration of immunotherapy in the specialist setting have greatly reduced these risks; no deaths have been subsequently reported in the United Kingdom.[4 5]

However, a 2007 Cochrane meta-analysis showed that mild systemic reactions do occur relatively frequently, although severe reactions are infrequent (table 2). In 13 trials comprising 14 085 patients treated with subcutaneous immunotherapy, injectable adrenaline was administered only 19 times (1/741 injections).[4]

Systemic reactions are much less common with sublingual immunotherapy than with subcutaneous immunotherapy, and most are mild and self limiting (table 1).[5] Nevertheless, two randomised placebo controlled trials reported use of injectable adrenaline in a single participant each from a total of 383 participants who received grass pollen sublingual immunotherapy.[15 16] Occasional case reports of anaphylaxis also exist in the literature.[17 18] Systemic reactions to grass pollen subcutaneous immunotherapy generally occur during the initial updosing phase. In contrast, grass pollen sublingual immunotherapy is generally administered as a fixed daily dose; if it is tolerated initially, it can be taken unsupervised thereafter.

What are the precautions?

Severe or poorly controlled asthma—This remains an absolute contraindication to both subcutaneous immunotherapy and sublingual immunotherapy (table 1). In

Table 2 | Number of subcutaneous immunotherapy systemic reactions reported in Cochrane meta-analysis based on World Allergy Organisation Grading System[16]

WAO SCIT systemic reaction classification	Grade 1	Grade 2	Grade 3	Grade 4
Description	Symptom(s)/sign(s) of one organ system present	Symptom(s)/sign(s) of more than one organ system present	Lower respiratory: asthma (for example, 40% PEF or FEV_1 drop, not responding to inhaled bronchodilator)	Lower or upper respiratory: respiratory failure with or without loss of consciousness
	Cutaneous: generalised pruritus, urticaria, flushing, or sensation of heat or warmth	Or lower respiratory: asthma: cough, wheezing, shortness of breath (for example, <40% PEF or FEV_1 drop, responding to inhaled bronchodilator)	Or upper respiratory: laryngeal, uvula, or tongue oedema with or without stridor	Or cardiovascular: hypotension with or without loss of consciousness
	Or angio-oedema (not laryngeal, tongue, or uvular)	Or gastrointestinal: abdominal cramps, vomiting, or diarrhoea		
	Or upper respiratory: rhinitis (sneezing, rhinorrhoea, nasal pruritus, and/or nasal congestion)	Or other: uterine cramps		
	Or throat clearing (itchy throat)			
	Or cough perceived to come from upper airway, not lung, larynx, or trachea			
	Or conjunctival: conjunctival erythema, pruritus, or tearing			
	Or other: nausea, metallic taste, or headache			
Cochrane 2007[4]:				
No of studies	Not recorded	17	13	9
No of participants	Not recorded	n=1272	n=1078	n=720
No of events: active subcutaneous immunotherapy/placebo	Not recorded/not recorded	154 (22%)/44 (8%)	43 (7%)/3 (0.65%)	3 (0.72%)/1 (0.33%)

FEV_1=forced expiratory volume in one second; PEF=peak expiratory flow.

the United Kingdom, patients who have seasonal asthma caused by grass pollen in addition to rhinitis may receive subcutaneous immunotherapy and often respond well, although updosing should be completed before the start of the pollen season. However, perennial asthma requiring inhaled steroids is a relative contraindication to immunotherapy.[2] Any decision to proceed with grass pollen immunotherapy in this group should be made only after careful evaluation by a specialist.[2] This is largely a historical legacy of the 1986 Committee on Safety of Medicines' report rather than based on current evidence.[13] European and US guidelines are less stringent, and stable moderate well controlled asthma is not a contraindication.[19 20]

β blockers—These (but not other antihypertensive drugs) are an absolute contraindication, as they antagonise adrenaline used to treat anaphylactic reactions.[21 22]

Medical conditions that reduce the patient's ability to survive a potential systemic allergic reaction or its treatment—These (for example, malignancy or chronic cardiorespiratory disease) are relative contraindications for allergen immunotherapy.

Relative contraindications—Other commonly cited relative contraindications include autoimmunity, immunodeficiency, and immunosuppression, although little or no direct evidence suggests that systemic immunological disease is exacerbated by grass pollen immunotherapy.

Pregnancy—Do not start immunotherapy during pregnancy, owing to concerns about the potential effect of a systemic allergic reaction on the fetus. Treatment may be continued if it is established and well tolerated.

Breast feeding—This is not a contraindication to immunotherapy.[2] There is no evidence of a risk to either mother or infant from starting or continuing grass pollen allergen immunotherapy while breast feeding.

Supervision and facilities—Subcutaneous immunotherapy injections should be administered only by trained clinical staff able to recognise and treat systemic allergic reactions, with ready access to resuscitation equipment and adrenaline.[14] For sublingual immunotherapy, the first dose should always be given under medical supervision, with access to antihistamines and injectable adrenaline, to allow observation of any adverse reaction and to "enable patient and physician to discuss any side effects and possible actions (20-30 minutes)."[20] Thereafter, the sublingual immunotherapy vaccine may be self administered at home but with regular contact to check tolerability and adherence to the treatment schedule. In the United States, but not in Europe, regulatory authorities require that patients treated with sublingual grass pollen immunotherapy be prescribed and trained in the use of auto-injectable adrenaline.

How is grass pollen immunotherapy given and monitored?

Selecting patients

Potential immunotherapy patients include those with troublesome allergic rhinitis not adequately controlled by anti-allergic drugs or in whom such treatment causes unacceptable side effects. Symptoms must coincide with the local grass pollen season, and IgE sensitisation to grass pollen must be confirmed by allergy testing. It is an adjunct rather than a replacement therapy, although in practice successful immunotherapy often reduces the clinical need for rhinitis drugs.

Administering treatment

Both subcutaneous and sublingual immunotherapies are started several months before the onset of the pollen season (table 1). In contrast to sublingual immunotherapy, the subcutaneous immunotherapy initiation phase always involves an initial dose escalation phase ("updosing"). The duration of treatment each year varies according to the vaccine used. Subcutaneous immunotherapy vaccines given as a

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pre-seasonal course are chemically modified (so-called "allergoids") with the aim of reducing side effects. In contrast, unmodified grass pollen subcutaneous immunotherapy vaccines are usually given year round with maintenance injections every four to six weeks for the entire three year treatment period. These are also widely used in UK allergy clinics on an unlicensed ("named patient") basis. Grass pollen sublingual immunotherapy is taken daily for three years. Some sublingual immunotherapy vaccines are halted at the end of the pollen season and restarted pre-seasonally for each of the three years.

Evaluating treatment

All patients receiving grass pollen immunotherapy should be evaluated after the first pollen season to assess clinical efficacy and tolerability, before a decision is made to proceed to the second year of treatment. In addition, regular follow-up for the entire duration of the three year course is necessary to monitor for adverse reactions, engage patients and encourage adherence. This is particularly the case for sublingual immunotherapy, in contrast to subcutaneous immunotherapy, for which injection visits provide regular opportunities for such interaction with healthcare providers. In a recent real life study from the Netherlands, only 23% of patients prescribed subcutaneous immunotherapy and 7% of those prescribed sublingual immunotherapy were found to have completed the full three year course.[23] However, further studies are needed to confirm whether such poor adherence is a more widespread phenomenon.

TIPS FOR PATIENTS

- You may benefit from grass pollen immunotherapy if your hay fever affects your sleep or daily activities and is not relieved by conventional treatments, such as regular antihistamines (oral/eye drops) or intranasal corticosteroid sprays (taken as directed)
- Immunotherapy involves repeated administration of high doses of grass pollen allergen; many large studies have shown that this effectively reduces hay fever symptoms, reduces the need for medication, and improves quality of life
- It is given for up to three years either as injections in a specialist clinic or taken daily at home as drops or fast dissolving tablets under the tongue
- Treatment is started several months before the grass pollen season, so a specialist referral should be made well in advance of symptoms starting
- Large reviews of immunotherapy have shown both forms of treatment to be safe when administered by trained specialist staff
- You may not be able to receive immunotherapy if you have asthma that needs regular treatment
- Immunotherapy injections may cause swelling and itching around the injection site, and immunotherapy taken under the tongue may cause swelling and itching in the mouth; in most cases, these symptoms resolve without a need for treatment
- More severe allergic reactions can occur from time to time, especially with injection immunotherapy; for this reason, all injections must be given in a specialist setting by trained staff with facilities for treating such reactions
- Immunotherapy taken under the tongue may be self administered daily at home; there is a remote risk of a severe reaction with the first dose, which should always be taken under supervision of a specialist
- Grass pollen immunotherapy can have long lasting benefits that are maintained for several years after a three year course is finished

How cost effective is grass pollen immunotherapy?

A recent economic evaluation estimated the cost per quality adjusted life year (QALY) for subcutaneous immunotherapy (Alutard SQ) and sublingual immunotherapy (Grazax) compared with standard treatment (antihistamines and intranasal corticosteroid spray), assuming that clinical improvement achieved during three years of subcutaneous immunotherapy or sublingual immunotherapy is maintained for another three years after cessation. Modelling this cautiously suggested that both treatments may achieve a cost per QALY within a £20 000 to £30 000 range after six years. Although grass pollen immunotherapy is not approved by the National Institute for Health and Care Excellence, this range represents the arbitrary threshold adopted for decisions on cost effectiveness of NHS funded treatments.[5 24]

How does this compare with other drugs?

Grass pollen immunotherapy alone and anti-allergic drugs alone have not been directly compared in clinical trials. However, indirect comparisons based on meta-analyses estimated that the "relative clinical impact" of subcutaneous or sublingual pollen immunotherapy is greater than that of second generation antihistamines and comparable to intranasal corticosteroids.[25 26]

Case outcome

The patient was assessed by an allergy specialist and was considered suitable for grass pollen immunotherapy. She was unable to attend for subcutaneous immunotherapy because of work commitments. An application was made to fund sublingual immunotherapy, with the first dose to be taken in January in the clinic. She was also encouraged to take her hay fever drugs and to have regular follow-up to monitor response to treatment. If effective, sublingual immunotherapy would be continued daily for a total of three years.

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References are in the version on thebmj.com.