

Hay Fever – Available Options When Pharmacotherapy Fails

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Introduction

Hay fever, or also seasonal allergic rhinitis, is an IgE mediated hypersensitivity most commonly in Britain to grass pollen, with seasonal symptoms in June or July corresponding to the peak pollen counts. It is characterised by sneezing, watery nasal discharge, nasal congestion, tearing of the eyes as well as itching of the nose, conjunctiva and palate. Due to its high and increasing prevalence, its impact on quality of life, the association with multiple comorbidities and the considerable socio-economic burden, hay fever is a major respiratory disorder and represents a global health concern. Comorbidities include serous otitis media, sinusitis and asthma¹.

Disease Mechanisms

Hay fever develops in people with a tendency for an exaggerated IgE mediated immune response, or atopy, and has overlap with other conditions such as eczema and asthma. Not all atopics develop hay fever but in those who do, the immune response to the pollen trapped in the nasal mucosa is aberrant. Pollen binds to the IgE to form a complex that then triggers a degranulation of histamine and other cytokines from the basophiles and mast cells via their high affinity receptor, FcεR1. Histamine is responsible for causing some of the symptoms, such as sneezing and itching via the type 1 histamine receptor (H1R) on the nasal sensory neuron, and nasal congestion by mediating dilatation of the nasal arterioles via the H1R and the type 3 histamine receptor (H3R) found on the endothelial cells¹.

Aetiology and Risk Factors

The increase in prevalence of hay fever is against a background of shorter and less intense pollen seasons, at least in the London area, and pollution is considered to be a possible cause of the rise. Firstborn boys have the

greatest risk of developing hay fever later on in life compared to their siblings, and many theories have been put forward to explain why this is the case, and why hay fever has become more prevalent in the hope that it may lead to a strategy of preventing the condition. Avoidance of the allergen is a sensible way of preventing the symptoms but it is often impractical, hence many people with severe enough symptoms opt for treatment with medications¹.

Treatments

Conventional pharmacotherapy for hay fever include antihistamines and nasal steroids which are established treatments that adequately control symptoms in many people. Antihistamines block the histamine receptors to control potentially all the symptoms, apart from the nasal congestion, and can be applied either directly to the nose or the eyes or be taken orally. Corticosteroids reduce the cytokine production and can be sprayed to the nose to decrease all nasal symptoms without significant amounts of absorption systemically. Systemic steroids are only indicated in acute exacerbations of hay fever, and even then for a short period of time for rapid and the most effective control of the symptoms. There still remains a significant minority of people who do not respond adequately to the pharmacotherapy and are considered for other treatments, of which immunotherapy has historically been the main option². The rest of the essay will review the role of treatments outside the group of drugs used as first-line treatments for hay fever.

Immunotherapy

Subcutaneous immunotherapy (SIT) has been practiced for the treatment of allergic conditions since 1911 although at the beginning it was very much on an empirical basis without predictable efficacy or much understanding of the mechanism of action⁴. It has now gained evidence-based credibility of its effectiveness for even severe hay fever, although a few reports of serious adverse events, including death from anaphylactic shock, have limited the use of SIT¹.

Immunotherapy for hay fever involves repeated administration of the disease-causing pollen by subcutaneous injections or alternatively through the sublingual, nasal or the oral route. With the repeated administration of immunotherapy, the immune response in the receiver is modulated over time to become less hypersensitive to the pollen. It is an allergen-specific therapy that potentially alters the course of hay fever due to the long-lasting effects of immunomodulation that can last four to five years after its discontinuation³.

Those who cannot avoid the allergens and do not benefit adequately or are intolerant of the drug therapy are considered for immunotherapy. It is also only suitable for those who have identifiable allergens and are hypersensitive to one or at the most two pollens because of the decreased efficacy of immunotherapy for multiple allergens. There are contraindications for SIT including significant medical illness as well as concurrent treatment with drugs likely to impair treatment in the event of anaphylaxis (e.g. β -blockers or other adrenoceptor antagonists)¹.

Immunotherapy may work by altering the balance from an allergic T helper cell type 2 (Th2) profile to a non-allergic T helper cell type 1 (Th1) profile, termed 'immune deviation'. However the failure of Th1 cells to reverse established Th2 response has focused attention on T helper type 3 cells (Th3) and regulatory lymphocytes carrying the CD4+CD25+ antigens, which actively suppress inflammation by releasing IL-10 and transforming growth factor- β . The 'Ig-E blocking' IgG1 and IgG4 antibody levels are also increased after immunotherapy, although this concept lost favour as an explanation with the failure of serum levels of allergen-specific IgG to correlate with clinical improvement and with the alternative explanations suggested by the effect of immunotherapy on T lymphocytes. Nevertheless, the generation of allergen-specific IgG is a consistent finding after successful immunotherapy, together with a variable decline in allergen-specific IgE, and a reduction in both the number and activation of mucosal mast cells, basophiles and eosinophiles⁵.

Subcutaneous Immunotherapy (SIT)

A meta-analysis of the effectiveness of SIT showed to a statistically significant level that it is effective in the treatment of allergic rhinitis compared to placebo in reducing symptoms (odds ratio 1.81, 95% confidence interval 1.48 to 2.23) and reducing the amount of other hay fever medications required. This systematic review did not distinguish amongst the studies with respect to the difference in the allergen extracts used in immunotherapy, but did mention that grass pollen were commonly administered extracts, which would be relevant for the treatment of hay fever⁶. Another review identified twelve additional randomised control trials (RCT) and grouped them depending on whether the injection regimen was perennial or pre-seasonal. Five out of the six RCTs of perennial treatment showed significant reduction in both the symptoms and the medication required, but one did not find that the improvements were statistically significant. Four out of the six RCTs of pre-seasonal regimes showed significant reduction in the symptom score, but one found immunotherapy ineffective whilst for the other no findings were reported. No meta-analysis was carried out on these twelve trials, and neither was the difference in efficacy of the perennial and the pre-seasonal regimes compared. It was impossible to pool the data of adverse reactions because the methods of defining these were diverse - for example the frequency of local reactions varied from 2-79%⁷.

A more recent RCT of 347 hay fever sufferers has shown that SIT is effective over placebo in reducing symptoms as well as reducing the requirements for medication. This was especially the case for the treatment regime with 100,000 standardized units of altuward grass pollen during the peak pollen season where symptom and medication scores were 32% and 41% lower respectively (both $P < .001$). Moreover the quality of life measures improved in treated participants, and it was found that 100,000 standardized quality units of altuward grass pollen was more effective than 10,000 standardized quantity units, although there were more side effects including 4.4% with urticaria or asthma but none with serious anaphylactic reactions⁸.

Some RCTs have compared SIT with conventional pharmacotherapy. Two RCTs compared SIT with pharmacotherapy and found SIT more effective in reducing symptoms^{9,10}. Another RCT compared SIT against nasal steroids, and showed that nasal steroids were significantly better than SIT in reducing the symptoms¹¹. All studies however were very small and had fewer than 50 participants and therefore the comparative efficacy of pharmacotherapy and immunotherapy remains unclear.

Compliance can be disappointing with SIT due to the double inconvenience of the need for regular injections coupled with it having to be administered in the hospital setting in case emergency measures need to be carried out for anaphylactic shock. One study reported that only half the subjects completed a full course over a period of two and a half years, with over half of the non-compliant people citing inconvenience as the main reason for giving up. However these people were receiving a perennial course of weekly injections in the 1st year of treatment in an outpatient clinic¹², and other less demanding SIT regimes exist, with more successful rates of compliance¹³.

Sublingual Immunotherapy (SLIT)

Due to the inconveniences and some of the associated adverse effects of SIT, the SLIT has gained popularity as an alternative route of administration. SLIT seems to lack the adverse effects, with no reports of adverse reactions in a systematic review that included 979 participants. SLIT's safety profile is a benefit in itself but also makes it more convenient compared to injection immunotherapy because it can be administered in the home environment.

In a Cochrane's systematic review of 22 trials involving 979 participants, SLIT was administered for various allergies, including five RCT for hay fever. When compared to placebo the reduction in symptoms (standard mean difference= 0.42, 95% confidence interval -0.69 to -0.15) and the pharmacotherapy requirements (SMD=-0.43, 95% CI -0.63 to -0.23) were statistically significant for SLIT; this was also the case when the trials specifically for hay fever were considered separately¹⁴. A more recent RCT with 855 participants showed moderate reductions of symptoms (16%, $p = 0.0710$) and medication use

(28%, $p=0.0470$) with the use of SLIT compared with placebo. In the same RCT, there was also a statistically significant improvement in the quality of life scores in participants receiving SLIT and no safety concerns were observed¹⁵.

The effectiveness of injection immunotherapy and SLIT compared together has been studied in 2 RCTs, one using grass pollen and the other birch pollen. Both RCTs showed statistically beneficial effects both in terms of reducing symptoms and the amount of pharmacotherapy needed. However no significant difference could be found in either study between sublingual and injection therapies, perhaps due to the study size being small, one with 20 participants and the other with 58 participants^{16,17}.

Intranasal and Oral Immunotherapy

Immunotherapy via the nasal or the bronchial route is effective but may be limited by local side effects. The newer freeze-dried pollen suspensions have fewer local side-effects¹⁸, although a few symptoms seem to still remain¹⁹. The nasal application of immunotherapy also requires a certain amount of skill and seems to relieve only the nasal symptoms of hay fever²⁰. Studies assessing the oral route have indicated a lack of efficacy, presumably due to failure of absorption of the allergen¹⁴.

Other Important Considerations of Immunotherapy

SIT and SLIT, like other hay fever treatments, can prevent complications of hay fever such as asthma²². The extent of the preventative effect is not quantifiable because of the small study sizes, but the fact that immunotherapy can alter the course of disease is an argument to have a lower threshold for treating someone with hay fever so as to prevent complications^{31,32}.

Where the efficacy of SIT and SLIT is unclear is its use in children, because at present only a few studies have been conducted with children and they all have small numbers of participants. These do not support the effectiveness of immunotherapy but final judgment should wait until further trials have been conducted and analysed^{6,33}.

Hay fever is considered to be a maladaptive response of the human immune system because there appears to be no obvious evolutionary advantage in being hypersensitive to grass pollen. Atopy may however be an adaptive trait due to the increasing exposure to viral infections associated with urbanisation, based on observations of atopic children suffering less during respiratory tract infections when compared to non-atopic children. It is proposed that the Th2 profile of atopics has anti-inflammatory activities and therefore lead to less severe symptoms when infected by viruses. Many of the hay fever treatments, excluding immunotherapy, lower the Th2 immune profile thereby in theory making the individual more susceptible to viral infections. Immunotherapy is the only conventional hay fever treatment that would not affect the immune response against microbes, because of its unique mode of action whereby the immunomodulation is very specific to the grass pollen³⁴. This fear of making hay fever sufferers more prone to respiratory tract infections with pharmacotherapy is likely to be irrelevant in practice. Many people on pharmacotherapy gain benefits from symptom control, whilst finding the treatment acceptable and there are not many reports of serious adverse effects.

Alternatives to Immunotherapy

Until recently immunotherapy has been the only alternative if the pharmacotherapy failed to control the hay fever. Today clinicians and patients have other options to consider including leukotriene receptor antagonists, humanised anti-IgE and a range of complementary medicines, as well as the surgical removal of the inferior turbinate.

Leukotriene Receptor Antagonist - Monteleukast

One systematic review and two additional RCTs found that the oral leukotriene receptor antagonist monteleukast improved nasal symptoms and quality of life compared with placebo. Three RCTs identified by the systematic review found that although monteleukast and loratadine (an antihistamine) taken together improved nasal symptoms and quality of life compared with placebo, that there was no evidence that combined treatment was any more effective than loratadine or monteleukast alone²¹. Results to date also suggest

that monteleukast is not more efficacious than intranasal corticosteroids²². Thus monteleukast is unlikely to play a significant role in the treatment of severe hay fever where other treatments have failed.

Anti-IgE Antibody - Omalizumab

Omalizumab is a newly licenced humanised anti-IgE antibody that has been shown to be effective in the treatment of hay fever in a few RCTs²³⁻²⁵. Omalizumab is particularly useful because it reduces the symptoms of polysensitised individuals suffering from hay fever, which is a situation where immunotherapy is likely to fail²⁶. One RCT compared omalizumab and SIT, and only omalizumab was able to reduce the symptoms of hay fever to a statistically significant degree during one season of hay fever, suggesting that omalizumab may at least have a more rapid mode of action compared to SIT. When omalizumab and SIT were administered together, they were better at reducing the symptoms than either of the treatments alone, thus showing an additive therapeutic effect²⁶⁻²⁸. Omalizumab if administered before SIT has the additional benefit of reducing the number of SIT-induced adverse events by five-fold and this strategy may pave the way for allowing a more effective higher dose of immunotherapy to be delivered without invoking unwanted effects²⁷. Compared to SLIT, omalizumab is more than twice as expensive and has more side effects. Omalizumab also has to be administered subcutaneously at a regular interval of two to four weeks²⁹.

Complementary Medicine

Various types of complementary medicine including acupuncture, herbal remedies and homeopathy are popular in the treatment of hay fever, but evidence-based recommendations are lacking as yet. Most forms of complementary medicine have a good safety profile and there are no obvious objections to its use together with Western medicine. Herbal remedies show some efficacy in the treatment of hay fever but studies have been too few to be conclusive and there is unresolved safety concerns³⁰.

Inferior Turbinectomy

The surgical removal of the inferior turbinate can alleviate the symptom of nasal obstruction in hay fever, but some studies have shown that complications and morbidity outweigh the benefits. Common complications include profuse haemorrhage during the procedure and synechiae (adhesions) and crusting in the long term. The objective measurements of nasal patency do not always correlate with the subjective view of the nasal patency either, and the long term benefits of inferior turbinectomy remains controversial³⁵.

Conclusion:

Available Options when Pharmacotherapy Fails.

Hay fever is a condition of increasing prevalence that can be very disabling, and in a significant minority of the hay fever sufferer, conventional pharmacotherapy may not be enough to alleviate the symptoms. Both SIT and SLIT, when used with pharmacotherapy can ameliorate the symptoms of severe hay fever, at least in adults. Immunotherapy requires the allergen to be identified before its administration and there is doubt over how effective when it is used alone; thus it is best reserved as a second-line treatment after the conventional pharmacotherapy. There is a lack of evidence about the relative efficacy of SIT and SLIT, and so at present it would be reasonable to opt for SLIT based on its better safety profile and convenience.

The only real alternative to immunotherapy in severe hay fever is omalizumab. Omalizumab has a role in treating hay fevers due to multiple allergens that immunotherapy is incapable of ameliorating. Current evidence from a few RCTs suggests that omalizumab may be more effective than immunotherapy, or may have more immediate therapeutic effect. Until further studies clarify the difference between immunotherapy and omalizumab, those hay fever sufferers suffering from severe hypersensitivity to one or two identifiable pollens should be given a choice of taking either treatment based on what they prefer. Lastly, omalizumab and immunotherapy together may have a role in treating those with very severe symptoms that cannot be brought under control with either of the treatments alone.

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