Safety of Grass Pollen Sublingual Immunotherapy for Allergic Rhinitis in Concomitant Asthma

Abstract:
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Introduction
Seasonal allergic rhinitis (AR) occurs predominantly as a result of grass pollen allergy. Grass pollen sublingual immunotherapy (SLIT) has been used for many years in the UK and Ireland in recent years as a result of availability of high dose sublingual immunotherapy (SLIT) in allergic rhinitis. Coexisting asthma is not a contraindication but must be mild, controlled and with a demonstrable FEV1 of 80% or more predicted for age and height. All showed strong positive reactions to grass pollen on skin prick testing. Of interest, most of the patients were polysensitized to multiple allergens particularly house dust mite, tree pollen, and animal danders. Only 4/30 were monosensitized to grass pollen. The range in duration of SLIT therapy in patients was six to thirty-six months. Figure 1 shows the TNSS before and after SLIT. TNSS pre therapy was 7.3 and improved to a mean score of 2.1. This was a statistically significant using Wilcoxon signed rank test (p<0.05). Figure 2 shows the change in categories (uncontrolled to controlled or uncontrolled to partially-controlled). Results for change in a patient's pharmacotherapy step (GINA Step 1-Step 5) before and after SLIT. -1 indicates the level of reduction in their pharmacotherapy step before and after SLIT was documented in a similar method. Zero (0) indicates no change in asthma pharmacotherapy. +1,+2,+3 indicates the improvement in asthma pharmacotherapy after SLIT (p<0.05). In conclusion, grass pollen SLIT is safe and can potentially treat dual allergic rhinitis- mild asthmatic patients.

Seasonal allergic rhinitis in Ireland occurs predominantly as a result of grass pollen allergy i.e. hay fever. Treatment currently is symptomatic with antihistamines and topical steroids. These treatments do not alter the natural history of the condition and some patients are poorly responsive. Interest in AIT has resurfaced in the UK and Ireland dramatically decreased since that time. SCIT continued to be a common treatment for AR in other jurisdictions such as the USA, most of Europe and Australasia. SCIT continued to be a common treatment for AR in other jurisdictions such as the USA, most of Europe and Australasia. SCIT continued to be a common treatment for AR in other jurisdictions such as the USA, most of Europe and Australasia. 

Methods
This was a cohort observational prospective study. 30 patients undergoing grass pollen SLIT with concomitant treated asthma were studied. SLIT in this study comprised of either a sublingual tablet Uralast® or Grazax®. Asthma was diagnosed based on clinical history and lung function testing in a specialist asthma center. Patients total nasal symptom score (TNSS) was recorded before and after SLIT as well. The TNSS comprised of the following symptoms of AR; sneezing, runny nose, and itchy nose. This was each graded on a 4-point scale, with the maximum severity of allergic rhinitis scored at 9. Asthma control was categorised as controlled, partially controlled, and uncontrolled using the GINA 2014 assessment tool. The assessment tool was based on whether a patient had daytime asthma symptoms more than twice a week, any night waking due to asthma, reliever needed for symptoms more than twice a week, and limitations of activity. The asthma control was also analysed using patients pharmacotherapy step based on GINA 2014 (GINA Step 1-Step 5) before and after SLIT. Individual data was plotted reflecting change from baseline asthma control status after at least 6 months of SLIT.

Each patient change in asthma control from baseline to end of study was documented as either a positive difference or a negative difference. The change in categories (uncontrolled, partially-controlled and uncontrolled) was documented as a numerical difference e.g. +1 indicating when a patients asthma control improved by 1 category; partially-controlled to controlled or uncontrolled to partially-controlled. Results for change in a patients pharmacotherapy step (GINA Step 1-Step 5) before and after SLIT was documented in a similar method. Zero (0) indicates no change in their asthma pharmacotherapy step after SLIT. +1 indicates the level of reduction in their pharmacotherapy step, indicating improvement e.g. if patient went from GINA Step 3 to GINA Step 2 after SLIT. +1,+2,+3 indicates the patient required increased pharmacotherapy e.g. a patient moving from GINA Step 2 to GINA Step 4 asthma pharmacotherapy in dual allergic rhinitis-asthmatic patients. The practice of SCIT in UK and Ireland dramatically decreased since that time. SCIT continued to be a common treatment for AR in other jurisdictions such as the USA, most of Europe and Australasia. 

Results
Patient demographics are summarized in Table 1. Average age was 36 years. The range of baseline FEV1 was 80-130% predicted and showed strong positive reactions to grass pollen on skin prick testing. Of interest, most of the patients were polysensitized to multiple allergens particularly house dust mite, tree pollen, and animal danders. Only 4/30 were monosensitized to grass pollen. The range in duration of SLIT therapy in patients was six to thirty-six months. There is evidence that SLIT improves asthma control when primarily used to treat AR. The aim was to assess the safety of SLIT in patients with severe seasonal allergic rhinitis who have co-existing stable mild asthma. The secondary aim was to determine whether asthma control improved post SLIT. There was no deterioration in asthma control after 6-36 months of SLIT. 27/30 (90%) patients asthma control remained stable or indeed improved (p<0.005). Of this 15 (50%) patients' asthma improved. There was no statistically significant change in asthma control before and after at least 6 months SLIT. 0 indicates no change in asthma control; -1 represents a deterioration in asthma control; + represents an improvement in asthma control. Overall there was no significant deterioration in asthma control before and after SLIT using the McNemar test (p=0.021). 27/30 patients asthma control remained stable or indeed improved. 12/30 showed no change in asthma control; 3 showed a 1 category deterioration. 15/30 patients showed an improvement in asthma score and out of this 7/30 showed a 2 category improvement and 8/30 showed a 1 category improvement. Using the Wilcoxon signed rank test, there was a significant improvement in overall asthma control after SLIT (p<0.005). Figure 3 shows the change in asthma pharmacotherapy after at least 6 months of SLIT. 0 indicates no change; + indicates an increase in pharmacotherapy; - represents a reduction in pharmacotherapy. Overall 26/30 patients remained stable or reduced their pharmacotherapy after SLIT (p<0.005). Four patients required a step up in their asthma pharmacotherapy.
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Discussion
This study demonstrates that grass pollen sublingual immunotherapy (SLIT) is safe in patients with controlled mild asthma while providing significant improvement in their nasal symptom score (TNSS) for allergic rhinitis. In addition it demonstrated a significant improvement in asthma control with no significant change in asthma pharmacotherapy management. Furthermore, as most of patients demonstrated polysensitization, the importance of clinical allergy as opposed to serological test such as "Oralair" or Grazax" tablet is placed under tongue for 1-2 minutes before swallowing it. "Oralair" is commenced pre grass pollen season in March and continued through to September for 3 consecutive years. It contains a mixture of freeze-dried extracts from the pollens of five grasses, including Timothy grass, Kentucky Blue Grass, Orchard, Perennial Rye, and Sweet Vernal. "Grazax" contains Timothy grass which is considered a major allergen in Ireland and UK and is commenced in March preseason and continued each day for 3 years without an inter seasonal break. We avoid instituting SLIT during the grass pollen season as there is documented increase in bronchial hyper responsiveness during pollen season. This increase in bronchial hyper responsiveness is similarly noted in perennial allergic rhinitis e.g. house-dust mite atopy, where there are seasonal fluctuations in mite prevalence due to weather variations and temperature changes. Perennial allergic rhinitis is currently treated with either corticosteroids without seasonal considerations. The first dose of both "Oralair" or "Grazax" tablet is initiated under medical supervision for one hour, however this is purely precautionary. Up dosing of Oralair is done over 3 days, while no up dosing is done with Grazax. SLIT is evidenced to be safer than SCIT, with no fatal events to date, and extremely rare reports of systemic adverse events. Commonly patients notice mild local reactions (e.g., perioral tingling, dyspepsia) during the first 2 weeks, which disappear with continued administration. If necessary, increased and decreased doses can be tried to facilitate tolerance. Our findings replicate the findings of a recent systematic review by Lin et al, which found that sublingual immunotherapy was safe and associated with improvements in asthma symptoms. All placebo-controlled studies demonstrated a high strength of evidence in SLIT for the control of asthma symptoms, with an overall reduction in asthma symptoms in 79 patients on daily grass pollen SLIT weighted asthma combined score when compared to placebo over the entire grass pollen seasons. The research and evidence above builds on the 2010 Cochrane systematic review where SLIT was shown to be effective for allergic rhinitis and a safe method of administration. This systematic review had intentionally excluded research trials exclusively dealing with dual allergic rhinitis-asthma patients. The British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) has acknowledged the positive benefits of sublingual immunotherapy in their 2014 guidelines on asthma. Despite this they did not advocate SLIT for routine management of asthma outside a specialist centre.

The 2014 Global Initiative for Asthma (GINA) consensus was that SLIT has potentially a role as an on-going therapy for uncontrolled asthma with concomitant symptomatic allergic rhinitis. GINA also advises that potential benefits of SLIT treatment in asthma and its remission and its cost of immunotherapy e.g. 3 years in our centre. Our study is limited by our small cohort and the heterogeneity of our study population. This is necessary to prove allergen-specific immunotherapy being a developing area in Irish asthma and allergy management. As current licensing also excludes SLIT from being used in patients with severe and uncontrolled asthma, we were limited to use SLIT for mild and moderate asthma with no significant side effects. It was an open label study which lends to treatment bias. There is also a lack of standardised scoring systems for asthmatic symptoms in patients with multiple allergic diseases. The standardisation of SLIT dosing (e.g. index of reactivity units) between different centres is another challenge to comparing different research trials. Professor David Crivellaro M, Savi E, Massolo A, Passalacqua G. A prospective Italian survey on the safety of subcutaneous immunotherapy for respiratory allergy. Clin Exp Allergy. 2009;39:1569-74. Renowned as a major allergen in Ireland and UK, this study is the first of its kind to look at SLIT for allergic rhinitis in patients with controlled mild asthma. We report a significant reduction in 79 patients on daily grass pollen SLIT weighted asthmatic combined score when compared to placebo over the entire grass pollen seasons. The research and evidence above builds on the 2010 Cochrane systematic review where SLIT was shown to be effective for allergic rhinitis and a safe method of administration. This systematic review had intentionally excluded research trials exclusively dealing with dual allergic rhinitis-asthma patients. The British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) has acknowledged the positive benefits of sublingual immunotherapy in their 2014 guidelines on asthma. Despite this they did not advocate SLIT for routine management of asthma outside a specialist centre.

The importance of our findings is consistent with WHO's position paper on allergen immunotherapy in 1998 which suggested that AIT can potentially be used in addition to asthma pharmacotherapy to get maximum benefit for asthmatics. In conclusion, this study demonstrates grass pollen SLIT is clinically effective in allergic rhinitis and is both safe and may improve asthmatic control in patients with dual allergic rhinitis and asthma.

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References