## Safety of grass pollen sublingual immunotherapy for allergic rhinitis in concomitant asthma

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

***Abstract:***

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**Abstract**

Seasonal allergic rhinitis (AR) occurs predominantly as a result of grass pollen allergy. Grass pollen sublingual immunotherapy (SLIT) has been proven effective in treating AR[1]. SLIT is currently licensed for use in AR with concomitant stable mild asthma. There is evidence that SLIT improves asthma control when primarily used to treat AR[2]. 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%) patientsâ   asthma control remained stable or indeed improved (p<0.021). Of this 15 (50%) patientsâ   asthma improved. There was no statistically significant change in their asthma pharmacotherapy after SLIT (p=0.059). In conclusion, grass pollen SLIT is safe and can potentially treat dual allergic rhinitis- mild asthmatic patients.

**Introduction**

In the presence of innocuous environmental aeroallergens, B cells in atopic individuals mature into plasma cells which produce allergen-specific IgE as opposed to IgM or IgG. This is carried out in conjunction with T helper (Th) lymphocytes which secrete a cytokine profile including IL-5, GM-CSF and IL-13 i.e. Th2-restricted. This process is called sensitization and renders the atopic individual at risk of subsequently developing allergic diseases such as rhinitis, eczema, and asthma. The allergen-specific IgE so generated binds inter alia, to the high affinity IgE receptor on mucosal and cutaneous mast cells (FCeRI). When these cells come into contact subsequently with the same allergen inhaled via the airway, they degranulate and generate newly formed mediators of inflammation and pro-inflammatory cytokines. Allergen immunotherapy (AIT) has been practiced for more than 100 years to treat allergic diseases, particularly rhinitis, venom anaphylaxis and controversially, asthma. AIT has been traditionally administered as subcutaneous injections (subcutaneous immunotherapy or SCIT) over a period of up to 3 years or even longer. The mechanism of action of AIT is unknown; however, best available evidence indicates that that administration of high dose allergen in sensitised individuals results in the production of allergen-specific inert IgG4 antibodies, as opposed to biologically active IgE, now under the control of T regulatory cells which produce IL-10 as opposed to the Th2 cytokines. In 1986, the UK Committee on the Safety of Medicines Report (CSM) reported 26 fatalities in primary care over the preceding 30 years involving SCIT[3]. They recommended that the use of SCIT be restricted to specialist hospital centers and that patients were observed for a period of time (then 2 hours; now 1 hour) post subcutaneous injection. As most of the fatalities occurred in patients with concomitant asthma, they advised strongly against its use 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[4].

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[5,6]. 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 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 prior to SLIT administration[7,8]. The primary aim of this study was to assess the safety of grass pollen sublingual immunotherapy in patients with severe seasonal allergic rhinitis who have co-existing stable and mild asthma. The secondary aim was to determine whether asthma control improved post grass pollen sublingual immunotherapy.

**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 Oralair" or Grazax". Asthma was diagnosed based on clinical history and lung function testing in a specialist asthma center. Patientsâ   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[9-11]. Asthma control was categorised as controlled, partially controlled, and uncontrolled using the GINA 2014 assessment tool[12]. 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 analyzed using patientsâ   pharmacotherapy step based on GINA 2014 (GINA Step 1-Step 5) before and after SLIT[12]. Individual data was plotted reflecting change from baseline asthma control status after at least 6 months of SLIT.

Each patientâ  s 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 patientâ  s asthma control improved by 1 category; partially-controlled to controlled or uncontrolled to partially-controlled. Results for change in a patientâ  s 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 is +2. Data was analyzed using Minitab v.17. Wilcoxon signed rank test, and McNemar test was used to compare nasal symptoms and asthma control before and after SLIT. A p value of less than 0.05 was considered statistically significant.

**Results**

Patient demographics are summarized in Table 1. Average age was 36 years. The range of baseline FEV1 was 80-130% 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 asthma control before and after at least 6 months SLIT. 0 indicates no change in asthma control; - 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 patientsâ   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=0.059). Four patients required a step up in their asthma pharmacotherapy.

**Discussion**

This study demonstrates that grass pollen sublingual immunotherapy (SLIT) is safe in patients with controlled mild asthma while producing a 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 sensitization in the blood is highlighted. The 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 the 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.[13] This increase in bronchial hyper responsiveness is similarly noted in perennial allergic rhinitis e.g. house-dust mite atopic, where there are seasonal fluctuations in mite prevalence due to weather variations and temperature changes. Perennial allergic rhinitis is currently treated with either SCIT or SLIT 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.[2,14] Commonly patients notice mild local reactions (e.g. perioral tingling, dyspepsia) during the first 2 weeks, which disappear with continued administration. If necessary, increased antihistamines can be dispensed 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[2]. All placebo-controlled studies demonstrated a high strength of evidence in SLIT for the control of asthma symptoms. One of the studies included was Durham et alâ s multinational European study which documented a 39% reduction in 79 patients on daily grass pollen SLITâ s weighted asthma combined score when compared to placebo over the entire grass pollen seasons[15]. 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[1]. 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[16]. 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 add-on therapy for uncontrolled asthmatics with concomitant symptomatic allergic rhinitis. GINA also advises that potential benefits of SLIT must be weighed up against the risk of adverse effects, inconvenience and the cost of prolonged therapy e.g. 3 years in our centre[12]. Our study is limited by our small cohort and the heterogeneity of our study population. This is mainly due to allergen-specific immunotherapy being a developing area in Irish allergy and asthma management. As current licensing also excludes SLIT from being used in patients with severe and uncontrolled asthma, we were limited to using SLIT in mild asthmatics. Furthermore this 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 comparison of this papersâ results with other similar trials. Professional societies like ARIA and BSACI are currently working on formalising in-vitro potency tests, dosing and treatment schedules to facilitate comparable research into the efficacy of SLIT.

The importance of our findings is consistent with WHOs 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[7]. 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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