

Practice and safety of allergen-specific immunotherapy for allergic rhinitis in the UK national health service: A report of “real world” clinical practice

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1 | INTRODUCTION

Allergen-specific immunotherapy (SIT) alleviates symptoms, improves health-related quality of life and alters the natural course of the disease in patients suffering from allergic rhinitis. It is currently delivered in the UK National Health Service (NHS) via 2 modalities namely subcutaneous injection immunotherapy (SCIT) and sublingual immunotherapy (SLIT). The latter has a superior safety profile—ana-phylaxis is a rare occurrence. Most vaccines currently employed for SIT in the UK NHS are unlicensed and available on a named-patient basis and prescribed in secondary care by a specialist. The unlicensed status in the UK may indirectly in part stem from concerns raised by a report published by the Committee of Safety of Medicines (CSM) regarding 26 deaths relating to SCIT.¹ A similar report was also published from North America relating to 46 SCIT-associated fatalities that occurred over a 40-year period.²

There are no published data since the CSM report in 1986 regarding the safety of SIT in routine adult allergy clinical practice in the UK. The main aim of the study was to (i) survey the use of SCIT and SLIT in the UK adult allergy clinics and (ii) investigate the safety profile of both treatment modalities.

An e-questionnaire was designed and circulated for consultation amongst the members of the Standards of Care Committee (SOCC) of the British Society for Allergy and Clinical Immunology (BSACI). The membership of SOCC comprises of an experienced panel of specialists in clinical and academic allergy. The comments and feedback were considered, and the final version of the questions was agreed

by all co-authors. All authors confirmed that the questions (Appendix S1) were appropriate to capture the required information as per the aims of this study. Clinical leads for all 33 UK NHS adult allergy services registered with the BSACI were invited to participate in this online survey via an email using a link created in survey monkey (www.surveymonkey.co.uk) (Appendix S1). This retrospective data collection survey was carried out in 2013 pertaining to the period between 01.01.2010 and 31.12.2012. The data were uploaded on Microsoft Excel for statistical analysis.

2 | RESULTS

Twenty-two (67%) centres participated in this study, and 11 centres did not respond (up to 3 reminders were sent before closing the survey). All 22 centres offered SIT as either SCIT, SLIT or both. For 19 centres, questionnaires were completed by the lead clinicians and clinical colleagues for the other three. Twenty centres offered SCIT, 18 offered SLIT and 16 offered both. Eleven centres had an allergist as the lead physician. The service leads in the remaining centres were as follows: respiratory physician (n = 4), clinical immunologist (n = 4), dermatologist (n = 1), ENT specialist (n = 1) and general physician (n = 1). Only 50% of these professionals had allergy as their main continuing professional development (CPD) activity.

The mean age (of centre level data) of the patients was 36 years (SD: 4.8) [seven centres did not provide this information]. Eight centres (40%) offered SCIT to patients with moderate and severe

allergic rhinitis, 12 centres (60%) only to those with severe disease. On the other hand, 7 centres (39%) offered SLIT to patients with moderate and severe disease and 11 centres (61%) only to those with severe disease. The severity of allergic rhinitis was based on an adapted version of the modified ARIA guidelines³ (Appendix S1). Data on systemic reactions (SRs) for SCIT and SLIT were analysed using an international grading system.⁴ All SIT products except Pollinex and Grazax were prescribed on a named-patient basis. It was not within the scope of this study to capture data on (i) the number of patients who received the UK-licensed products vs those who received on a "named-patient basis" and (ii) on the number of asthmatics treated with SCIT and SLIT.

3 | SCIT

A total of 1731 patients received therapy over the 3-year period (Table 1). Grass pollen allergen vaccine was most commonly prescribed and accounted for 63% of all SCIT patients (Table 1). Tree pollen was less frequently used accounting for 19% of SCIT followed by house dust mite which accounted for 15%. Other allergen vaccines included cat, dog, horse and weeds accounting for 1.5%, 0.5%, 0.3% and 0.2%, respectively (Table 1). All centres except two obtained written informed consent prior to commencing SCIT.

There was heterogeneity with regard to the SCIT vaccines used; Allergovit (Allergopharma Joachim Ganzer KG, Germany) by 8 centres, Alutard SQ (ALK Abello, Denmark) by 17 centres, Pollinex (Allergy Therapeutics, UK) by 12 centres, Acaroid (Allergopharma Joachim Ganzer KG, Germany) by 3 centres, Depigoid (Leti pharma GmbH, Germany) by 1 centre and mixed allergen product (no name given) by 1 centre. Four centres used a single allergen product and others used at least 2 different products. Nineteen centres employed pre-medication with an antihistamine.

TABLE 1 Frequency of patients receiving SCIT, SLIT and SRs

Allergen	Number of patients	
	SCIT	SLIT
Grass	1093 (63%)	566 (76%)
Tree	334 (19%)	41 (5%)
House dust mite	251 (15%)	106 (14%)
Cat	28 (1.5%)	14 (2%)
Dog	8 (0.5%)	14 (2%)
Horse	5 (0.3%)	6 (1%)
Weed/Plantain	4 (0.2%)	0 (0%)
Unknown	8 (0.5%)	0 (0%)
Total	1731	747
SR		
Grade 1	47	1
Grade 2	33	0
Grade 3	4	0
Grade 4	2	0
Total	86	1

Eighty-six patients (5%) experienced 103 systemic reactions (SRs) of which 81% ($n = 83$) occurred in the induction phase and 19% ($n = 20$) in the maintenance phase. Furthermore, 78% ($n = 80$) of those SRs occurred with grass pollen vaccine. House dust mite and tree pollen were the next most commonly implicated at 7% ($n = 7$) for each allergen. Grades 1, 2, 3 and 4 SRs occurred in 3% ($n = 47$), 2% ($n = 33$), 0.2% ($n = 4$) and 0.1% ($n = 2$) in SCIT patients, respectively. No fatalities were recorded. Adrenaline was administered in 7 of 86 patients with SRs and 0.4% of the total SCIT patients. The severity of the SRs requiring adrenaline ranged from grade 2 ($n = 2$), grade 3 ($n = 3$) to grade 4 ($n = 2$).

Nineteen centres offered SCIT to patients with seasonal asthma. Nine centres offered SCIT to patients with both seasonal and perennial asthma. One centre did not provide information about the status of asthma in their patients. The severity of asthma was step 1 (in 9 centres) or 2 (in 9 centres) according to the BTS/SIGN asthma guidelines⁵ and only one centre enrolled patients with perennial asthma staged at step 3. Asthma was present in 11.6% ($n = 10$) of the patients who had SRs but the questionnaire did not capture the severity of asthma amongst patients affected by SRs. Thirteen (0.9%) patients withdrew from SCIT due to side-effects.

4 | SLIT

SLIT was offered to 747 patients (Table 1). There was heterogeneity with respect to the vaccines used; Grazax (ALK Abello, Denmark) by 16 centres, Oralvac (Allergy Therapeutics, UK) by 5 centres and Staloral (Stallergenes, France) by 7 centres. Six centres had used at least 2 different products. All but 5 centres had obtained written informed consent prior to commencement of SLIT. Seven centres offered SLIT to patients with moderate disease severity and the others to patients with severe disease. Pre-medication with an antihistamine was offered by 7 centres to some of the patients and 2 centres offered this to all their patients.

Frequency distribution of allergens used for SLIT was grass pollen (76%), house dust mite allergen (14%) and tree pollen (5%). Other allergens included cat, dog and horse at 2%, 2% and 1%, respectively (Table 1). Overall, 17 centres offered SLIT to patients with seasonal asthma and 10 centres offered SLIT to patients with perennial asthma. Two centres offered SLIT to patients with asthma at step 3 and 4,⁵ and all other centres had patients with asthma at either step 1 or 2 or both.⁵ One centre did not record the asthma severity.

Other than local reactions, there was only one case of grade 1 SR to grass pollen SLIT. None of patients received treatment with adrenaline, and no fatality was reported. These data highlight the superior safety profile of SLIT in comparison with SCIT stated in previous section. However, forty (5.4%) patients withdrew from SLIT due to side-effects.

This is the first UK-wide survey on the "real world clinical practice" of SIT in adult patients with allergic rhinitis. The study has shown some heterogeneity in terms of patient selection, particularly for those with concomitant perennial asthma and vaccines employed,

thus highlighting the need to standardize practice and improve the uptake of BSACI guidelines for SIT for allergic rhinitis.

This study was nationwide with respect to its geographical distribution and thus reflects the current UK practice. This study, however, did not capture data to allow comparison of clinical practice between BSACI members vs non-members and allergists versus non-allergists and organ-based specialists practising SIT. Also, it was not possible to determine from the data set if the non-responders to the e-questionnaire (23%) employed SIT to treat allergic rhinitis in their centres.

There was some heterogeneity in the vaccines used for SCIT and SLIT, and there are no comparative clinical effectiveness data available for the different products used. There was lesser heterogeneity with respect to severity of rhinitis; SCIT and SLIT were offered only to those with moderate and severe disease. SCIT and SLIT were also offered to patients with concomitant perennial (chronic) asthma which is not in keeping with the BSACI guidelines.⁶ The BSACI guideline states that chronic asthma is a relative contraindication except for those with mild intermittent symptoms requiring the occasional use of short-acting bronchodilator.⁶ The heterogeneity and deviations from BSACI guidelines may need to be addressed not only to maintain a safe clinical practice but also to achieve equity and standardization as per the NHS England document on specialized services in Allergy and Immunology.⁷ Our study also highlights the need for reviewing the recent evidence and perhaps to consider revising the guideline which was published 6 years ago.⁶ There is also need for a study to investigate the safety of SIT in patients with concomitant mild-moderate asthma.

The reported SRs to SCIT were mostly mild to moderate in severity (grades 1-2), a recognized adverse effect of this treatment. Seventy-eight per cent of SRs to SCIT occurred to grass pollen vaccine, and this is most likely to be due to higher prescription rates compared to other allergens. Although adrenaline was administered to 7 patients, 2 had relatively mild (grade-2) SRs. A limitation of the data set is that no further information was available regarding (i) whether or not these patients had seasonal and/or perennial asthma and (ii) asthma severity during the period leading up to the SR. Despite the relatively moderate sample size and deviation from BSACI recommendations by some centres (specifically with respect to inclusion of patients with chronic asthma), the data suggest SCIT is safe in allergic rhinitis.

In the Cochrane meta-analysis,⁸ 22% of patients undergoing SCIT for allergic rhinitis experienced grade II reaction versus 8% receiving placebo. In addition, 0.72% of patients (three in the SIT group) vs 0.33% (one in the placebo group) had grade IV reactions, and adrenaline was used in 3.4% of the total participants in the SCIT group. However, no fatalities were recorded. Our data also found comparable outcomes of rates and severity of SRs with only 0.4% of the SCIT patients treated with adrenaline. Fatalities reported with SCIT in the 1980s occurred almost exclusively in patients with co-existing asthma that was frequently poorly controlled. The majority of fatal events occurred in the USA, where a high concentration of the whole allergen extract is used, and multiple allergens were

administered as mixed products.⁹ In our study, despite SCIT being offered to patients with perennial asthma, there was no significant increase in rates of SRs and this may, at least in part, reflect better disease control. Whilst 1 centre offered SCIT to patients with asthma in step 3, the others only included those at step 2 or below of the BTS/SIGN guidelines.⁵ The study questionnaire did not capture information regarding the proportion of patients with concomitant chronic asthma undergoing SCIT and SLIT in each centre. Further studies are required to investigate the efficacy and safety of SIT in patients with allergic rhinitis and concomitant mild-moderate asthma.

This study has shown that the safety profile of SLIT was superior to SCIT, with only 1 grade-1 SR reported with SLIT to grass pollen and this is in keeping with observations reported in clinical trials. These data should be interpreted with caution as adverse reactions to SLIT may not have been accurately captured as the treatment is self-administered by the patient at home. However, anaphylaxis is an extremely rare complication of SLIT, but relatively minor adverse reactions have been reported in a significant proportion of cases and have been classed as local non-life-threatening and self-limiting episodes.¹⁰ Most patients develop relatively minor discomfort in the early-phase of treatment, mainly oropharyngeal symptoms that respond to antihistamines on an ad hoc or prophylactic basis and often settle with continued administration of the vaccine.¹⁰ In addition, our study also showed that a higher percentage (5.4%) of patients withdrew from the SLIT due to local side-effects.

Our findings justify the UK practice of SIT being restricted to specialist allergy centres with the relevant expertise, knowledge and experience and in a safe clinical environment with immediate access and support for the treatment of anaphylaxis.⁵ Although no fatalities were reported in this survey, there is a rare but real risk for anaphylaxis, and robust patient selection is key to a successful clinical outcome. Offering SIT in patients with severe allergic rhinitis with co-existing mild and well-controlled asthma may need to be revisited in the next iteration of the BSACI guideline.

In conclusion, this study showed considerable heterogeneity in SCIT and SLIT products employed for the treatment of allergic rhinitis in the UK adult NHS allergy services. There is deviation from BSACI guidelines with respect to offering SCIT and SLIT to patients with co-existing chronic asthma. This study therefore highlights the need to raise awareness of BSACI guidelines and to standardize the practice of SCIT and SLIT with respect to patient selection criteria. In addition, there is also a need to revisit the current BSACI recommendations regarding the restriction in the use of SIT in patients with allergic rhinitis and concomitant chronic stable mild-moderate asthma in view of the current survey findings of patients with chronic asthma receiving SCIT without major risk.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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