A systematic review and economic evaluation of subcutaneous and sublingual allergen immunotherapy in adults and children with seasonal allergic rhinitis

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Scientific summary

Subcutaneous/sublingual immunotherapy in patients with seasonal allergic rhinitis

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Scientific summary

Background

Allergic rhinitis (AR) is an immunoglobulin E (IgE)-mediated inflammation of the nasal mucosa following allergen exposure. The condition is often comorbid with allergic conjunctivitis and is a risk factor for asthma. AR is more common in developed countries and the prevalence of allergic sensitisation is >50% in some age groups. The high impact of AR on health-related quality of life (QoL), as well as work or educational performance results in a significant individual and economic burden. Conventional treatment involves providing symptomatic relief; however, up to two-thirds of patients report only partial or poor symptom control.

Allergen immunotherapy involves administering gradually increasing doses of a specific allergen, or part of the allergen, to an allergic subject, with the aim of reducing sensitivity and minimising future symptomatic reaction on natural exposure to the causative agent. Recent meta-analyses have concluded that both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) are effective in reducing symptoms of AR when compared with placebo. In addition, the clinical benefits of both SCIT and SLIT appear to be sustained following cessation of treatment. There is some evidence that immunotherapy can prevent disease progression, development of new sensitisations and onset of asthma. However, it is unclear whether one route of administration is more effective than the other, and the long-term cost-effectiveness of the treatments is uncertain.

Objectives

To determine the comparative clinical effectiveness and cost-effectiveness of SCIT and SLIT for seasonal allergic rhinitis (SAR) by (1) undertaking a systematic review of randomised controlled trials (RCTs) in order to update existing Cochrane reviews on the topic; (2) undertaking an indirect comparison of SCIT with SLIT; (3) undertaking a systematic review of existing economic evaluations (EEs); and (4) conducting an independent EE.

Review methods

Major electronic databases {e.g. MEDLINE, EMBASE, The Cochrane Library [Cochrane Central Register of Controlled Trials (CENTRAL)] and the NHS Economic Evaluation Database (NHS EED)} and several internet sites, including trial registries, were searched from inception up to April 2011. There were no language restrictions. For the review of clinical effectiveness, double-blind randomised, placebo-controlled trials of SCIT or SLIT were included, as were direct comparisons of SCIT with SLIT. Studies were eligible if they included adults and/or children with a clinical diagnosis of moderate to severe SAR with or without asthma. For the review of EEs, any suitable evaluations (including analyses of cost-effectiveness, cost–benefit, cost–utility, cost–consequences and cost minimisation) or reviews of EEs were included, as were studies reporting data of potential use for informing an economic model, such as utilities or cost data. Standard systematic review methods were used for study selection, data extraction and quality assessment.

For the review of clinical effectiveness, analyses were limited to four patient-centred outcomes – symptom scores (SSs), medication scores (MSs), combined symptom and medication scores (SMS), and QoL – as well as any reported adverse events (AEs). With the exception of AEs, random-effect meta-analyses were conducted for all outcomes. Analyses were also conducted to explore the impact of a range of prespecified patient and trial characteristics on outcome measures. Adjusted indirect comparisons of SCIT versus SLIT

were conducted across all four patient-centred outcomes, using random-effects meta-regression and adjusting for covariates.

The EE was based on a systematic review and critical appraisal of existing EEs and a new cost-effectiveness model, based on estimates of QoL, and cost and resource use estimates derived from the literature and following consultation with clinical experts.

Results

Clinical effectiveness

Seventeen new RCTs of SCIT compared with placebo and 11 of SLIT compared with placebo were identified, which were published subsequent to the corresponding Cochrane reviews of these interventions. One small head-to-head trial of SCIT compared with SLIT was found. A further 23 ongoing, or not yet reported, RCTs were identified. Risk of bias assessment was hampered by inadequate reporting of all quality criteria. The majority of trials appeared to have low risk of bias when sufficient information to make a judgement was reported, with only very few instances of high risk of bias identified.

Of the 17 newly identified RCTs of SCIT (vs placebo) and 11 newly identified RCTs of SLIT (vs placebo), only five trials of each type of intervention reported data in a form suitable for meta-analysis. However, meta-analysis also included all previous relevant studies from the Cochrane reviews. Statistically significant results were found for both SCIT and SLIT, suggesting a moderate effect size in favour of the active treatment for all patient-centred outcomes (SS, MS, SMS, and QoL). This remained the case for the vast majority of subgroup analyses performed (e.g. for treatment duration, and type and amount of allergen used). A large amount of variability in how outcomes were scored meant that results had to be presented as standardised mean differences. Interpretation of these is difficult and the clinical significance of the results is uncertain.

There is less evidence for children, particularly for SCIT. One small SCIT trial found significantly lower SSs and MSs, and improved QoL, in the actively treated group (after 3 years of treatment). For SLIT, statistically significant results (based on nine studies) were found for SSs but not for MSs. The one study including a quality-of-life measure found a statistically significant difference in favour of SLIT.

Indirect comparisons of SCIT with SLIT were suggestive of SCIT being more beneficial for SSs and MSs, but this was associated with substantial residual heterogeneity. No statistically significant difference was found between the two interventions for combined SMSs or QoL, which could arguably be deemed more clinically useful outcomes. These findings were not substantially altered when participant age, treatment duration and type or amount of allergen were included as covariates.

Adverse events were common with both SCIT and SLIT, but the majority were local reactions at the point of administration and resolved spontaneously without treatment. Systemic reactions were less common, occurring in approximately 4.4% of injections for SCIT, and most were graded as mild or moderate in severity. However, 19% of systemic reactions following SCIT treatment were considered to be severe, compared with only 2% of systemic reactions following SLIT. Discontinuations due to AEs were similar between the interventions – 3% and 3.4% for SCIT and SLIT, respectively. No fatalities occurred in any of the trials.

Cost-effectiveness

Searches for EEs identified 14 EEs and two reviews of EEs. Overall, the studies found that both SCIT and SLIT were more beneficial than symptomatic treatment (ST), and in some cases also become less costly than ST over time. Where studies expressed results as incremental cost-effectiveness ratios (ICERs), both SCIT and SLIT were found to be cost-effective at thresholds of £20,000 per quality-adjusted life-year (QALY). However, there were issues around transparency and/or robustness of parameters for most studies. None of the cost–utility analyses were conducted by independent researchers.

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A preferred Markov model was constructed for adults and children but could not be adequately populated largely owing to a lack of suitable data on transition probabilities between different health states in SAR. An alternative, simpler, model was therefore constructed, which used data on quality-of-life improvement based on the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) from the direct and indirect comparison meta-analyses. Using a number of assumptions, changes in RQLQ were mapped to changes in European Quality of Life-5 Dimensions (EQ-5D), in order to express results as cost per QALY. Based on a threshold of £20,000–30,000 per QALY, results showed that immunotherapy compared with ST became cost-effective after around 6 years from the start of treatment (NHS and patient perspective; 7 years for NHS perspective only).

Subcutaneous immunotherapy was found to be cost-effective compared with SLIT after around 5 years, based on the same threshold. This is based on SCIT being both more effective and more costly than SLIT. As the difference in RQLQ was not statistically significant (the confidence interval crosses zero), there is uncertainty associated with the effectiveness estimate, which, in turn, affects the reliability of the cost-effectiveness estimate. Results overall should be seen as indicative because they are based on a very simple analysis. Sensitivity analyses were restricted to varying the time horizon and using upper and lower confidence limits for RQLQ improvement. Potential cost savings from preventing future cases of asthma were not considered in this cost-effectiveness analysis (CEA). It was not possible to undertake a CEA for children owing to a paucity of available data.

Conclusions

Based on a substantial number of RCTs, both SCIT and SLIT have been consistently shown to be significantly more effective than ST only, and this remains the case for the vast majority of subgroup analyses based on differences in population and treatment protocol. It is uncertain to what extent this statistical significance translates to clinically significant differences across the different types of outcome measures used. An indirect comparison is suggestive of SCIT being more beneficial than SLIT based on SSs and MSs, but no such difference could be shown for combined SMSs or QoL, and firm conclusions cannot be drawn. CEAs suggest that both SCIT and SLIT may become cost-effective at a threshold of £20,000–30,000 per QALY from around 6 years. However, these estimates were based on limited data and the use of a number of assumptions. Potential cost savings resulting from future cases of asthma avoided were not included in the analysis, but would likely lead to an increase in cost-effectiveness.

Recommendations for future research

Future research should focus on:

- Head-to-head RCTs comparing SCIT with SLIT, consistent with current guidelines on treatment protocols and using standardised outcome and reporting measures to enable between-study comparison. Further studies of either intervention compared with placebo are unlikely to add to the already extensive literature on this subject.
- Outcomes that (1) take into consideration that the relative effectiveness of immunotherapy compared with symptomatic medication varies depending on prevailing allergen levels and (2) could best inform EEs.
- Evaluation of long-term effectiveness from shorter courses of immunotherapy, as this places less of a burden both on the patient in terms of time and inconvenience and in terms of associated costs.
- The extent to which results of all previous primary research can be made available to independent researchers in order to inform model-based value-of-information analysis.

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