

Original article

Cost-effectiveness of specific immunotherapy with Grazax in allergic rhinitis co-existing with asthma

Background: In the United Kingdom, approximately 10.8 million people suffer from asthma, placing an economic burden on the society of more than £2 billion per year. For allergic asthma, treatment options consist of allergen avoidance, symptomatic treatment and allergen-specific immunotherapy (SIT). Only SIT addresses the underlying cause of the disease, reducing symptoms and offering the potential for long-term improvement. Grazax – the first tablet-based SIT – is indicated for the treatment of patients with grass pollen-induced rhinoconjunctivitis, including those with co-existing asthma.

Objective: To assess the cost-effectiveness of Grazax in patients with rhinoconjunctivitis and co-existing asthma.

Methods: A prospective pharmacoeconomic analysis was carried out as part of a multinational clinical trial assessing the efficacy of Grazax ($n = 79$) compared with placebo ($n = 72$). Both groups had access to symptomatic medication; thus the placebo group represented current standard care. Pooled data on health resource use, productivity loss because of absence from work and quality of life (Quality Adjusted Life Years, QALYs) were collected in the trial. Reduced productivity at work was estimated from the literature. A societal perspective was adopted with a 9-year time horizon. The NHS price of Grazax of £2.25 per tablet was used.

Results: The QALY gain was significantly higher for patients treated with Grazax than the placebo group receiving symptomatic medication alone (0.197 discounted QALYs gained 9 years into the future – equal to an extra 72 days of perfect health over 9 years). The levels of resource use and productivity loss were higher for the placebo group. As a result, the cost per QALY gained with Grazax was £4319, which is highly cost-effective. Price sensitivity analyses demonstrated that Grazax remained cost-effective up to a tablet price of £5.07.

Conclusion: SIT with Grazax is a cost-effective strategy compared with standard management of patients with rhinoconjunctivitis and co-existing asthma.

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Key words: allergen-specific; asthma; cost-effectiveness; grass pollen allergy; immunotherapy; QALY; Rhinoconjunctivitis; tablet.

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Study design: Prospective health economic evaluation

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The prevalence of asthma is increasing worldwide (1) and in the United Kingdom alone it is estimated that 10.8 million people suffer from asthma, of which 2.2 million experience inadequate symptom control with their current treatment options (2).

A strong epidemiologic relationship has been documented between asthma and allergic rhinitis (3–5). The two conditions may be manifestations of the same syndrome – the chronic allergic respiratory syndrome (5). As a consequence, the majority of patients with asthma have rhinitis and rhinitis is a major independent risk factor for asthma (4, 5).

Allergic problems are responsible for 12.5 million general practitioner (GP) consultations per year and 183 000 bed days in the UK. In total, the costs amount to more than one billion pounds per year with primary care

prescribing contributing with £700 million (6). The economic burden of asthma alone is estimated at around £889 million per year, in terms of direct healthcare costs for the National Health Service (NHS). In addition, £1200 million are lost due to work days missed (7). The impact of asthma also extends beyond economic outcomes, and has effects on family life, lifestyle, well being and perceived health status (8).

Standard clinical guidelines in the UK for treatment of allergic asthma consist of allergen avoidance and symptomatic treatment, such as bronchodilators and topical corticosteroids, offering only short-term symptom relief (9). Allergen-specific immunotherapy (SIT) is the only treatment capable of targeting the underlying cause of the allergic disease, with the potential to produce long-term remission (10). SIT in patients with asthma has been

shown to reduce asthma symptom and medication scores and asthma-related events, such as acute ward visits and hospitalizations (11). Until now, SIT has only been available in the UK as preseasonal treatment administered by subcutaneous injections.

Grazax (ALK-Abelló) is a new, registered and licensed, tablet-based SIT indicated for the treatment of grass pollen-induced rhinoconjunctivitis, including patients with co-existing allergic asthma. It is the first registered sublingual SIT product on the market in the UK and has a safety profile allowing home administration. Each tablet contains standardized allergen extract of Timothy grass pollen (*Phleum pratense*).

For optimal clinical effect in the first grass pollen season, treatment, is initiated at least 4 months prior to the expected start of the grass pollen season. Patients are then advised to take one Grazax tablet per day for three consecutive years, after which it is expected that they will have built up a sustained immunological tolerance towards grass pollen.

Objectives

The objective of the present study was to assess the cost-effectiveness of Grazax in the UK, in patients suffering from rhinoconjunctivitis with co-existing asthma.

Design and population

The pharmacoeconomic analysis was designed as a cost-utility analysis and a societal perspective was adopted, meaning that all costs relevant to society were included. Data were collected prospectively alongside a randomized, parallel-group, double-blind, placebo-controlled trial carried out during the 2005 pollen season. The trial investigated the efficacy of Grazax in 634 patients with grass pollen-induced rhinoconjunctivitis with or without asthma. Patients were recruited from the UK, Germany, the Netherlands, Denmark, Sweden, Spain, Austria and Italy (12).

The focus of this article is on the 151 patients who had a clinical history of asthma at study start. Seventy-nine patients were randomized to receive Grazax and 72 to receive placebo. Both arms were permitted to use clearly defined symptomatic medication for asthma (salbutamol and fluticasone) and rhinitis (desloratadine and budesonide). Consequently, the placebo arm represented standard care in the current analysis. The implications of this are discussed in detail in the discussion section and dispensing of medication for symptomatic use described in detail in Dahl et al. (12). To ensure sufficient power, pooled data from all countries were used in the calculations. The Quality of Life (QoL) scores from UK patients ($n = 95$) were not statistically different from the entire patient population ($n = 642$) (t -test $P = 0.534$).

Resource use and cost data

The resource-use data were recorded in weekly diaries during the pollen season and included emergency physician visits, acute ward visits, hospitalization and hours missed from work due to grass pollen-induced rhinoconjunctivitis and asthma. Data on reduced productivity at work were estimated from published literature (13).

Protocol-driven costs associated with undertaking the trial *per se* were not included in the analysis (14). The annual number of physician visits for a patient not treated with SIT was estimated to be 2.4 visits in the UK, based on a recent European survey (15).

Unit costs (Table 1) were based on official tariffs (16, 17), as well as average gross wages from the national statistics bureau in the UK. The NHS price of Grazax of £2.25 per tablet, or £821.25 per annum, was used in the cost-effectiveness analysis.

Quality of life

If economic analyses are to be useful to decision makers, the reported outcomes should be in a form comparable across disease areas. For this purpose, the Quality Adjusted Life Year (QALY) is used. It combines the two dimensions of health: life expectancy and QoL (14). Thus, medical interventions can be compared regardless of whether they increase life expectancy, QoL – or both. A QALY represents the patient's QoL on a scale from 0 (dead) to 1 (perfect health). However, negative values are also possible and these are to be interpreted as health states considered by the respondents to be worse than death. The QoL used for QALY calculations was measured with the EuroQol-5D (EQ-5D) questionnaire, which describes QoL using five domains – mobility, self-care, usual activities, pain/discomfort and anxiety/depression (14). The EQ-5D questionnaires were completed by patients on a weekly basis and the health profiles described were assigned QALY weights based on the preferences of a random sample of 3395 British adults (14).

Table 1. Unit costs applied in the analysis (2005-prices, £)

	Unit cost (£)	Source
General practitioner (per surgery visit)	24.00	Curtis et al. (16)
Allergy specialist (per clinic visit)	28.00	Curtis et al. (16)
Accident and emergency (per visit)	204.00	NHS reference costs index (17)
Desloratadine, 10 mg (per tablet)	0.23	http://www.drugtariff.com
Budesonide, 50 mcg (per inhalation)	0.04	http://www.drugtariff.com
Salbutamol, 200 mcg (per inhalation)	0.09	http://www.drugtariff.com
Fluticasone, 250 mcg (per dose)	0.32	http://www.drugtariff.com
Grazax (per tablet)	2.25	ALK-Abelló
Productivity loss (average salary/h)	12.12	National Statistics (http://www.statistics.gov.uk)

Duration of the analysis

Pharmacoeconomic analyses should represent 'real life', particularly with respect to the time horizon considered (14). The overall aim of SIT is a long-lasting immunomodulation resulting in a maintained effect after termination of therapy. Grazax has shown long-term and progressive effect on immunologic parameters and significant efficacy over 2 years of treatment (18). The active ingredient in Grazax (*P. pratense*) is the same as that used in studies by Durham et al. and Mosbech and Østerballe, where the maintained effect of injection SIT was investigated (10, 19). The concept of continuous treatment is also similar. The studies differ in route of administration (subcutaneous vs sublingual), but a long-term effect has been documented for both types of administration (10, 19, 20).

Therefore, it is assumed that 3 years of Grazax treatment will result in a long-term effect similar to subcutaneous SIT with the same allergen, i.e., 3 years of SIT treatment with Grazax will yield a further 6 years of sustained effect, making the total time horizon of the analysis 9 years. Furthermore, previous studies have demonstrated increasing efficacy with each year of SIT over a treatment period of 3 years during which sustained immunological tolerance develops (21). However, in order to keep a conservative view, the prospective clinical trial data from the first year of treatment was linearly extrapolated to a 9-year time horizon (Fig. 1).

Discounting

In accordance with National Institute of Health and Clinical Excellence (NICE) guidance, future costs and QALYs were discounted at a rate of 3.5% per year (22).

Statistics

Because of the skewed nature of medication use and QoL data that did not fit a standard distribution and to the size of the data set, a nonparametric test (Mann–Whitney) was applied to compare resource use and QALYs in the two groups. The Mann–Whitney *U* test assesses whether

the medians between two samples of observations are the same, i.e., the null hypothesis is that the two samples are drawn from a single population and therefore the medians do not differ.

Results

QALYs

The mean QALY value for the subgroup of asthma patients was 0.9391 (SD = 0.1040) in the Grazax group ($n = 68$) and 0.9141 (SD = 0.1608) in the placebo group ($n = 63$). The medians observed in the two groups were different ($P < 0.05$) and the mean difference was 0.0250 additional QALYs in favour of the Grazax group. When extrapolating the 0.0250 QALYs gained 9 years into the future at a 3.5% discount rate, this amounts to an extra 0.197 QALYs, equivalent to an extra 72 days of perfect health for patients treated with Grazax when compared with those receiving standard care.

Resource use

None of the patients with rhinoconjunctivitis and co-existing asthma in the two groups were admitted to hospital. The amount of time missed from work in the placebo group was three times higher than in the Grazax group ($P < 0.10$). The differences in mean symptomatic medication use were all in favour of Grazax. The hypothesis of equal distribution of the two treatment arms was rejected for salbutamol and desloratadine ($P < 0.05$, two-tailed) (Table 2). Hence, the benefit of Grazax over standard care was confirmed for the use of salbutamol and desloratadine, while the use of budesonide and fluticasone although lower was not significant in the Grazax arm.

Cost-effectiveness

The comparison of the two treatment strategies for asthma patients was based on their relative cost-effectiveness. This was measured as the incremental cost-

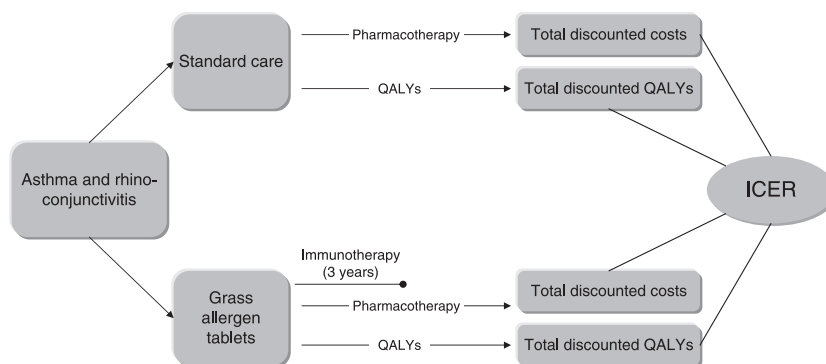


Figure 1. Outline of the pharmacoeconomic analysis. ICER, incremental cost-effectiveness ratio.

Table 2. Mean resource use by patient in the Grazax and the standard care groups during the pollen season

Resource use item	Grazax			Standard care			Difference
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD	<i>P</i> -value (two-tailed)
<i>Visits</i>							
Physician visits	–	1 visit ¹	–	–	2.4 visit ²	–	Not relevant
Extra GP/specialist visit	68	0.176 visit	0.517	63	0.127 visit	0.421	0.518
Acute ward visits	68	0.059 visit	0.237	63	0.016 visit	0.126	0.202
<i>Symptomatic medication</i>							
Desloratadine	79	13.22 tablets	22.57	72	15.88 tablets	16.88	0.045*
Budesonide	79	15.68 inhalations	31.56	72	22.43 inhalations	45.23	0.166
<i>Asthma medication</i>							
Salbutamol	79	9.08 inhalations	26.55	72	9.43 inhalations	16.79	0.040*
Fluticasone	79	3.77 inhalations	14.28	72	8.29 inhalations	24.90	0.156
<i>Production loss</i>							
Hours missed from work	68	2.12 h	9.60	63	6.27 h	20.05	0.178
Hours at work with reduced productivity ³	–	4.73 h	–	–	14.01 h	–	Not relevant

SD, standard deviation.

*Difference is significant (Mann–Whitney *U* test, *P* < 0.05, two-tailed).¹One standard visit is assumed for the Grazax group, since intake of the first tablet should be made under medical supervision.²EFA (8).³Based on Lamb et al. (13), who found a ratio of 2.24 between hours missed from work and reduced productivity at work in favour of the last.

Table 3. Cost-effectiveness values for allergic rhinitis and asthma patients (9 year, 3.5% discount rate, including productivity loss, 2005 price level, £)

	Total costs per average patient (£)	Incremental costs (£)	Health Benefits (QALYs) gained	Incremental QALY gain	ICER* (£)
Symptomatic medication	2578		7.198		
Grazax	3429	851	7.395	0.20	4,319

*Incremental cost-effectiveness ratio.

effectiveness ratio (ICER) of Grazax compared with standard care. The ICER determines the cost-effectiveness of a drug in comparison to a viable alternative and is calculated in the following way:

$$\text{ICER} = \frac{\text{Cost}_{\text{Grazax}} - \text{Cost}_{\text{standard care}}}{\text{QALY}_{\text{Grazax}} - \text{QALY}_{\text{standard care}}} = \frac{\Delta \text{Cost}}{\Delta \text{QALY}}$$

The equation measures the difference in costs between two alternatives divided by the difference in QALYs.

According to NICE, a drug that generates 1 QALY for less than £20 000 compared with an alternative is considered cost-effective and therefore, reimbursement is efficient use of NHS resources (20). This cost-effectiveness threshold is used by NICE to restrict or reject the recommendations of new drugs (23, 24).

In the present analysis, the cost-effectiveness of Grazax was calculated for the NHS price of £2.25 per tablet. By including productivity loss in the analysis, the ICER per QALY gained using Grazax, was calculated as £4319, i.e., this is the cost of an additional year of perfect health (Table 3).

Sensitivity analysis

Reduced productivity at work resulting from poorly controlled seasonal asthma and rhinoconjunctivitis was estimated from the literature and was not measured directly in the trial. Therefore, a sensitivity analysis was undertaken to exclude the influence of reduced productivity upon the cost-effectiveness result. This resulted in an increase in the cost per QALY gained to £8816.

The base-case analysis was based on a 9-year time horizon. The choice of time horizon has important implications for the overall cost-effectiveness result. Therefore, a sensitivity analysis was performed, where the total time horizon of the analysis was changed to 7 years, i.e., 4 years of sustained benefit after completion of 3 years of SIT as has been documented by Durham et al. (10). This increased the cost per QALY gained to £7272 or to £11 769 if also excluding the costs because of the reduced productivity.

Additional price sensitivity analysis was carried out for a range of annual costs of Grazax between £1000 and £3000 (Fig. 2). Grazax remains cost-effective up to an annual cost of £1850. This is equal to a tablet price of £5.07, which is substantially above the current NHS price of £2.25 per tablet.

Conclusions

In the present analysis, the placebo arm of the trial was used as a proxy for standard care. This was possible as patients in the placebo arm used symptomatic medication as required, which equates to 'real life' standard care for the majority of patients in the UK treated for seasonal allergic

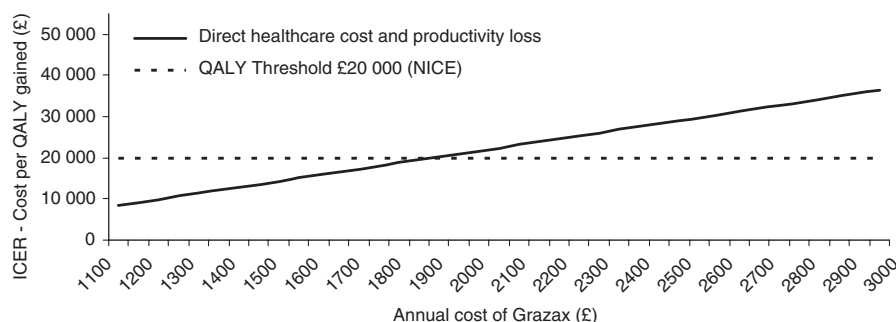


Figure 2. Incremental cost-effectiveness ratios for Grazax.

symptoms. If the patients had been treated with prophylactic medication this could have resulted in an increase in the use of symptomatic medication. Assuming that prophylactic medication, has a positive influence on QoL, this could underestimate QoL in the standard care arm of the analysis. On the other hand, the placebo effect has not been addressed. Assuming that there is an effect of placebo, this could overestimate QoL in the standard care arm as this effect would not be present in 'real life' standard care.

The use of Grazax in the present analysis was found to be very cost-effective with a cost per QALY gained at £4319. The sensitivity analyses did not alter this conclusion although the result depends on both the duration of the sustained effect of Grazax and the inclusion of reduced productivity at work. However, even with a more conservative model – 4 years of sustained effect and no influence of Grazax treatment on productivity at work – the cost per QALY gained at £11 769, still remains comfortably below the NICE cost-effectiveness threshold of £20 000.

By comparison, studies investigating the cost-effectiveness of asthma control have found the cost per QALY gained for inhaled corticosteroids in adults with mild-to-moderate asthma to be between £7600 and £13 700 (25, 26).

It can be concluded that treatment with Grazax in patients suffering from allergic rhinitis with co-existing asthma is cost-effective in the UK for a tablet price up to £5. From a socio-economic standpoint, specific immunotherapy with Grazax represents efficient use of NHS resources and should therefore be integrated into the care pathway of patients with moderate-to-severe grass pollen-induced asthma and rhinoconjunctivitis in the UK.

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