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Sublingual or subcutaneous immunotherapy for seasonal allergic rhinitis: an indirect analysis of efficacy, safety and cost

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Abstract

Rationale, aims and objectives The standard of preventive care for poorly controlled seasonal allergic rhinitis (AR) is subcutaneous immunotherapy (SCIT) with allergen extracts, administered in a physician's office. As an alternative to SCIT, sublingual immunotherapy (SLIT) is now an option for patients with seasonal AR. Oralair™, a SLIT tablet containing freeze-dried allergen extracts of five grasses [cocksfoot (*Dactylis glomerata*), meadow grass (*Poa pratensis*), rye grass (*Lolium perenne*), sweet vernal grass (*Anthoxanthum odoratum*) and timothy grass (*Phleum pratense*)], and Grazax™, a SLIT tablet containing a standardized extract of grass pollen allergen from timothy grass (*P pratenase*), are two such agents currently available in many countries. However, head-to-head comparative data are not available. In this study, an indirect comparison on efficacy, safety and cost was undertaken between Oralair™, Grazax™ and SCIT.

Methods A systematic review was conducted for double-blind placebo-controlled randomized trials evaluating Oralair™, Grazax™ or SCIT in patients with grass-induced seasonal AR. Using placebo as the common control, an indirect statistical comparison between treatments was performed using meta regression analysis with active drug as the primary independent variable. An economic analysis, which included both direct and indirect costs for the Canadian setting, was also undertaken.

Results Overall, 20 placebo-controlled trials met the study inclusion criteria. The indirect analysis suggested improved efficacy with Oralair™ over SCIT [standardized mean difference (SMD) in AR symptom control = –0.21; $P = 0.007$] and Grazax™ (SMD = –0.18; $P = 0.018$). In addition, there were no significant differences in the risk of discontinuation due to adverse events between therapies. Oralair™ was associated with cost savings against year-round SCIT ($2471), seasonal SCIT ($948) and Grazax™ ($1168) during the first year of therapy.

Conclusions Oralair™ has at least non-inferior efficacy and comparable safety against SCIT and Grazax™ at a lower annual cost.

Introduction

Seasonal allergic rhinitis (AR) is a common problem affecting between 30 and 40% of adults and children [1,2]. The prevalence of AR has also been increasing in the last 20 years [3,4]. Poorly controlled AR is one of the most common reasons for visits to the family doctor and is a risk factor for the development of asthma [5,6]. Therefore, it is a major public health care concern and has a considerable economic impact on society. In a US study done in the year 2000, prescription medications used to treat AR resulted in over $6 billion in drug costs [7]. AR has also been associated with substantial indirect costs, such as lost productivity for adults and missed school days for children. In the United States, AR is responsible for 3.5 million lost workdays and 2 million lost school days annually [8]. Therefore, effective prevention of seasonal AR will have major socio-economic benefits.

AR caused by seasonal grass pollen exposure is characterized by runny nose, sneezing and nasal itching, nasal congestion, and

includes ocular symptoms such as red/burning and itchy/watery eyes. Pharmacotherapy is used as an initial treatment and consists of antihistamines, intranasal corticosteroids and nasal decongestants. Such interventions are not always effective and over 40% of patients describe their symptom management as being poorly controlled with these treatments [9]. Therefore, safe and more effective definitive therapies are needed.

The current standard of disease-modifying care for poorly controlled symptoms is subcutaneous immunotherapy (SCIT) through the injection of customized allergen extracts in a physician's office [10,11]. Allergen SCIT is a two-phased strategy, consisting of an initial induction phase followed by a maintenance period. The treatment can last from 3 to 5 years [11,12]. The induction phase consists of weekly injections of allergen extracts, administered at escalating doses until a final target dose is reached, usually after 16 to 24 weekly doses. The maintenance phase, consisting of monthly doses, is then initiated and can be continued over the entire year, for a period of 3 to 5 years. However, some allergists use modified protocols that consist of a 3-month induction phase followed by 4 months of maintenance therapy. If successful in controlling symptoms of AR, the same protocol would be repeated during the second and third year of treatment (T. Bowen, personal communication).

SCIT is effective in providing symptom control to patients [13]. However, not all patients are suitable candidates for SCIT because some have strong aversions to injections or 'needle-phobia'. In addition, regular visits to the physician's office for drug administration place an untoward burden on the patient and have substantial indirect costs in terms of missed work days or missed school days in the case of children. Anaphylaxis, with a reported prevalence of approximately 0.13%, is also a concern during SCIT [13]. As a result, it is a not uncommon practice in Canada for some allergists to provide patients with a prescription for injectable epinephrine while on active therapy. In addition, asthmatic patients are at an increased risk of adverse reactions and possibly death following SCIT if asthma is poorly controlled [13]. Therefore, some jurisdictions do not recommend the use of SCIT in patients with asthma [13].

As an alternative to the subcutaneous (SC) route of administration, sublingual immunotherapy (SLIT) is now a safe and effective option for patients. There have been two meta-analyses of placebo-controlled randomized trials which demonstrated that both perennial and seasonal SLIT are effective in reducing seasonal AR symptoms as well as the use of rescue medications in both children and adults [14,15].

One such product is Oralair™, a five-grass pollen tablet that has recently been approved by Health Canada [16]. Each 300 index of reactivity (IR) tablet contains allergen extract composed of the following grass pollens: cocksfoot (*Dactylis glomerata* L.), sweet vernal grass (*Anthoxanthum odoratum* L.), rye grass (*Lolium perenne* L.), meadow grass (*Poa pratensis* L.) and timothy grass (*Phleum pratense* L.) [17]. Several large randomized placebo-controlled trials demonstrated that Oralair™ 300 IR administered daily for 4 months pre and then for 2 months during the allergy season reduced AR symptoms and the use of rescue medication [18–21].

There is another SLIT product (Grazax™) that is currently under review by Canadian regulatory authorities. Unlike Oralair™, which is only taken once daily for 4 months before and for 1 month during the pollen season, Grazax™ is administered once daily over the entire year [22]. Unfortunately, head-to-head clinical trial data comparing Oralair™, Grazax™ and SCIT is not available. In the absence of such data, indirect statistical methods are an accepted method in generating comparative effectiveness information. In this study, an indirect comparison on efficacy, safety and cost was undertaken between Oralair™, Grazax™ and SCIT for the prevention of AR.

Methods

Literature review and meta-analysis of randomized trials

An initial review of the clinical trial literature failed to identify randomized studies comparing Oralair™, Grazax™ and SCIT. Consequently, an indirect analysis of double-blind placebo-controlled trials was undertaken to compare efficacy, safety and cost-of-care. A computer literature search of PubMed, Embase and the Cochrane Database was conducted from January 1980 to December 2012 for placebo-controlled randomized trials evaluating Oralair™, Grazax™ or SCIT in patients with seasonal AR. Search terms consisted of '{seasonal AR}, and {Oralair™} or {Grazax™} or {SLIT} or {SC immunotherapy} and {randomized clinical trial}'. The intent of the literature review was to identify trials with a common control (i.e. placebo) that could be used for an indirect comparison [23,24].

Once eligible trials were identified, the following data were extracted: baseline patient characteristics, data collection methods, definition of primary and secondary outcomes, duration of immunotherapy, trial duration, use of rescue medication, changes in patient quality of life, patient compliance, where the trial was done (i.e. controlled chamber versus outdoors), geographic region and number of withdrawals caused by adverse effects.

Effect sizes for continuous dependent variables (e.g. AR symptom control) in each study were expressed as standardized mean differences (SMD) – (Cohen's *d*), which measure the effect size between the experimental and control groups. This is a standard method that measures the degree of benefit for a therapy after the placebo effect has been accounted for. SMD are calculated from the ratio of the treatment effect (mean difference in treatment group minus difference in placebo group) to the pooled standard deviation of these differences. SMD do not have units and the outcome for the magnitude of benefit is expressed as an effect size according to the following criteria: <0.2 is usually considered as trivial, >0.2–0.5 as small, >0.5–0.8 as moderate and >0.8–1.2 as important [25].

Binary outcomes (e.g. drug discontinuation rates) were combined using a random effects model in cases of significant heterogeneity [26]. Random effects meta-analysis assumes that the effect of the intervention varies across studies. When significant between-study variation is present, the 95% confidence interval (CI) for the summary measure tends to be larger with a random-effects model. Treatment effects from individual trials were also presented as forest plots.

Statistical heterogeneity between studies was assessed by both the Q-statistic and the I^2 test statistic [27]. Briefly, the I^2 statistic measures the proportion of variance across studies due to

heterogeneity. It is considered to be a superior measure of study heterogeneity than the Q-statistic because the latter is often underpowered when evaluating homogeneity in meta-analyses. The *P*-values associated with the Q-statistic (chi-square with k-1 degrees of freedom, where K is the number of studies) were also reported. In situations where the Q-statistic was statistically significant or the I^2 statistic was greater than 25%, a random-effects meta-analysis model was used, as opposed to a fixed-effects model. Publication bias was assessed through an evaluation of funnel plots and by the method proposed by Egger, which provides a significant *P*-value when publication bias may be present [28,29].

Indirect statistical comparisons between drugs

Indirect statistical assessments for safety and efficacy between Oralair™, SCIT and Grazax™ were performed using two approaches. The first indirect method was a meta regression analysis on the primary clinical outcomes and on adverse event rates reported in the trials. A meta regression analysis is an appropriate method for conducting an indirect comparison in cases where trials evaluating the drugs of interest used a common comparator. Therefore, indirect comparisons between Oralair™ relative to either SCIT and Grazax™ were performed with those trials that had a placebo control group. Active drug (i.e. Oralair™ versus SCIT or Grazax™) was the independent variable in the regression model. Other independent variables considered in the model included year of study publication, geographic region where the trial was conducted, trial duration, duration of immunotherapy, number of asthmatic patients enrolled in the trial, number of allergens and patient type (adults versus children). All of the analyses were performed using Stata, V 11.0 (Stata Corp., College Station, TX, USA).

Indirect treatment comparisons were also performed using the univariate method of Bucher and colleagues, which partly maintains the benefits of randomization on the effect size [24,30]. It is important to make a distinction between the two methods for indirectly comparing the immunotherapies. In the meta regression approach, the evaluation is performed between each immunotherapy versus a common control (i.e. placebo) and the effect measure is expressed as a relative difference between drugs. In contrast, the method of Bucher *et al*. uses a common comparator (e.g. placebo) to statistically link the two competing treatments. As a result, the generated outcome is an absolute difference between Oralair™ versus SCIT and Grazax™, with associated *P*-values for statistical significance.

Economic analysis

An economic analysis was conducted from the societal perspective, which considered both direct and indirect costs such as time off from work and patient travel. There were four treatment regimens compared in the economic analysis. These consisted of:

1 Oralair™: 300 IR daily under the tongue: 4 months preseason and then for 2 months in-season. The same regimen would be used in years 2 and 3.

2 Grazax™: 75 000 standardized quality index (SQ-T) daily under the tongue and taken over the entire year (as per product monograph). The same regimen would be used in years 2 and 3.

3 SCIT Regimen 1 (year-round): One injection weekly × 6 months, then monthly for the remainder of the first year. Monthly dosing would be used in years 2 and 3.

4 SCIT Regimen 2 (seasonal): One injection weekly × 3 months preseason, then monthly for 4 months during the pollen season. The same regimen would be used in years 2 and 3.

The economic analysis considered costs for drug acquisition, the pharmacy dispensing fee, reimbursement for physician services (i.e. for drug injections) as well as secondary therapy when the primary agent has to be discontinued because of intolerance. The rates of primary therapy discontinuation were obtained from the meta-analysis of randomized trials. Secondary therapy recommendations in cases where the primary agent had to be discontinued were obtained via interview from two Canadian allergists. The physicians indicated that Oralair™ would be used in cases where SCIT had to be stopped because of intolerable adverse events. In contrast, SCIT would be used in cases where intolerance would occur with SLIT. This analysis assumed that one would not return to medical therapy because the choice to embark on immunotherapy implied previous failure of the same. Other direct costs included in the analysis consisted of annual prescription for injectable epinephrine in case of anaphylactic reactions in patients receiving SCIT as well as the cost of treating such a reaction. For the latter, the Ontario Health Care system will reimburse physicians $75.00 for every hour spent treating a case of anaphylaxis secondary to SCIT. Therefore, the cost of anaphylaxis was determined as the product between the reported event rate (i.e. 0.13%) and $75.00 [13].

Indirect costs consisting of patient travel (using public transit at $3.00 per ride) to receive their SC injection and time off from work (i.e. lost productivity, assuming 2 hours to visit the physician for the injection) were also included. Lost productivity was estimated using the method of Posnett and Jan for cases where production loss is for a short time interval [31]. Specifically, the full wage rate was used to quantify time off from work for SCIT, because an employer would not hire another worker in a situation where an employee is away from the job for a short period of time (i.e. a few hours). The average wage of $23.56 per hour as reported by Statistics Canada (March, 2012) was used to quantify the loss in productivity for each visit to the physician [32]. For SLIT, only the first dose has to be administered in the physician's office [17].

The economic analysis evaluated the first year of therapy (to account for the induction phase of year-round SCIT), followed by an analysis of years 2 and 3 combined. Costs were not discounted because of the short time periods involved and no mark-up on the cost of injections was assumed. Drug costs for SCIT products were obtained from the manufacturers. Drug costs for Oralair™ also included a 10% mark-up on oral drugs as well as an $8.20 pharmacy dispensing fee for pharmacists. At the time of this analysis, Grazax™ had not been approved for use in Canada, but was under Health Canada review. Therefore, the daily cost of the product in the UK (i.e. $4.83 per day) was used in the analysis, primarily for illustrative purposes [22]. Physician fees for service were obtained from the Schedule of Benefits: Physician Services under the Health Insurance Act, Ontario Ministry of Health, 2012. All costs were reported in 2012 Canadian dollars. As the analysis was a cost minimization, which had minimal variability, a sensitivity analysis was not conducted. In addition, costs were not discounted because of the short time periods.

Results

Identification of placebo-controlled randomized clinical trials

Overall, 258 citations were reviewed for eligibility. Studies were excluded from the analysis for several reasons: studies having no placebo control, fewer than 25 patients per group, evaluating treatments for other allergies, enrolling only asthmatic patients, publication of duplicate reports or the study end points did not include an assessment of AR symptom control. A total of 20 placebo-controlled trials met the inclusion criteria and underwent a more in-depth assessment in the following distribution: Oralair™ – five trials; Grazax™ – eight trials; SCIT – seven trials (Table 1).

All of the trials were double-blinded and placebo-controlled, with sample sizes per study arm ranging from 28 to 514 (Table 1). Overall, 15 of 20 studies (75%) enrolled adults only, two exclusively children and the remaining evaluated a mix of patient types. Approximately 17% of the patients enrolled in the 20 studies were asthmatic, with a median of 5 allergens (range 1 to 13) in the evaluated experimental product (two of the SCIT trials evaluated were monotherapy products). With respect to the region of patient recruitment, 15 of 20 studies (75%) were European, three were conducted in North America and the remaining two were global trials. Overall, the median duration of preseasonal therapy was 2.1 months and the total duration of therapy was 5.3 months (Table 1).

Meta-analysis of placebo-controlled trials

The 20 placebo-controlled trials provided a total of 21 complete treatment arms suitable for a meta-analysis on AR symptom control and treatment discontinuations due to adverse events. However, an evaluation of rescue medication to control symptoms of AR could not be undertaken because the trials did not consistently report the standard deviation or the standard errors associated with such end points.

The AR symptom control data were initially pooled for all trials regardless of the drug used. The findings revealed that patients treated with immunotherapy for seasonal AR had significant reductions in symptoms compared with placebo (Fig. 1). To measure the magnitude of benefit, the placebo-controlled trials for Oralair™ were statistically pooled. The findings revealed that Oralair™ reduced the symptoms of AR by approximately 0.47 units ($P < 0.001$ on a validated symptom scale relative to placebo (Fig. 2). For comparison, Grazax™ and SCIT had pooled reductions of 0.34 and 0.30, respectively (Figs 3 & 4).

Indirect comparative effectiveness analysis

The meta regression approach

The primary requirement for a cost minimization analysis evaluating active interventions is that all clinically relevant outcomes be comparable between treatments. For each of the treatments, the pooled SMDs relative to placebo in AR symptom reductions were as follows:

- Oralair™ (pooled estimate from seven trial arms): SMD = –0.47; 95% CI = (–0.56 to –0.38); $P < 0.001$
- Grazax™ (pooled estimate from seven trial arms): SMD = –0.34; 95% CI = (–0.47 to –0.21); $P < 0.001$
- SCIT (pooled estimate from seven trial arms): SMD = –0.30; 95% CI = (–0.39 to –0.20); $P = 0.001$

The above SMDs imply that the three interventions provide at least comparable benefits with respect to AR symptom reductions. Keeping in mind the caveats associated with indirect comparisons, a meta regression model with 'active drug' (Oralair™ versus Grazax™ or SCIT) was developed to compare symptom control and safety differences between treatments. The indirect comparison detected a significant difference between Oralair™ and both Grazax™ and SCIT in AR symptom reductions (Table 2). The analysis indicated that after controlling the study year and duration of therapy, patients treated with Oralair™ had significantly better symptom control than the two other active treatments. The regression model also evaluated the effect of trial characteristics such geographic region (North American versus Europe versus global trial), the type of patients enrolled, the number of asthmatic patients in each trial, the number of allergens and the duration of preseasonal therapy. None of these factors were significantly associated with the study end points.

The meta-analysis was continued with a comparison of safety data between the three treatments in terms of relative risk (RR). Overall, patients treated with any immunotherapy were more likely (RR = 2.64, $P < 0.001$) to have treatment discontinuation relative to placebo (Fig. 5). For each of the interventions, the pooled RR for treatment discontinuations relative to placebo was: Oralair™ (pooled estimate from six trial arms) RR = 4.88; 95% CI = (2.49 to 9.58), Grazax™ (pooled estimate from eight trial arms): RR = 1.90; 95% CI = (1.21 to 3.00) and SCIT (pooled estimate from seven trial arms): RR = 3.16; 95% CI = (1.40 to 7.10).

The risk of drug discontinuations due to adverse events was then compared between treatments. The indirect analysis did not identify significant differences in the risk of discontinuation due to adverse events between the three therapies (Table 2). For the subsequent economic analysis where point estimates for discontinuation rates were required, the rates of treatment discontinuations reported in each of individual study arms were statistically pooled. The point estimates for discontinuation rates due to Oralair™, Grazax™ and SCIT were 5.6% (95% CI: 3.8 to 7.3%), 3.5% (95% CI: 1.7 to 5.2%) and 2.7% (95% CI: 1.3 to 4.2%), respectively.

Comparing safety and effectiveness using the method of Bucher *et al.*[24]

The indirect method developed by Bucher and colleagues is one of the most commonly used approaches for performing indirect comparisons of randomized trials [26]. It was used for the indirect assessment of Oralair™ versus Grazax™ and SCIT, with respect to differences in AR symptom scores and drug discontinuations due to adverse events. As was previously implied by the meta regression analysis, there was evidence to suggest that Oralair™ was more effective in reducing AR symptoms than Grazax™ and SCIT. However, only the difference between Grazax™ reached statistical significance using the method of Bucher *et al*. (Table 3). There was also no statistically significant difference in the risk of treatment discontinuations between Oralair™ and SCIT. However, the findings did suggest that patients treated with Oralair™ are

Table 1 Placebo-controlled trials evaluating Oralair, Grazax and SCIT for the treatment of allergic rhinitis

First author, year of publication	Comparator (versus placebo)	Sample sizes (ITT)	Mean age, years (SD or range)	Patient group (adults/children)	Number of allergens	Length of preseasonal treatment, approx. months	Treatment duration, approx. months
Oralair™	100 IR SL daily	O – 157	O – 29.3 (6.90)	Adults	5	4	5
Didier A, 2007 [21] (4-arm trial.		P – 156	P – 29.1 (7.60)				
The 100 IR study arm was excluded)	100 to 300 IR SL as updosing, then 300 IR SL daily	O – 155	O – 28.7 (7.34)	Adults	5	4	5
		P – 156	P – 29.1 (7.60)				
	100 to 500 IR SL as updosing, then 500 IR SL daily	O – 160	O – 30.4 (7.45)	Adults	5	4	5
		P – 156	P – 29.1 (7.60)				
Mösges R, 2007 [33]	updosing with drops to 300 IR SL daily	O – 48	O + P (18–50)	Adults	5	3.5	9
		P – 53					
Horak F, 2009 [16]	300 IR SL daily	O – 45	O – 27.5 (6.58)	Adults	5	0.23	4
		P – 44	P – 27.1 (5.81)				
Wahn U, 2009 [34] & Halken S, 2010 [19]	100 to 300 IR SL as updosing, then 300 IR SL daily	O – 139	O – 10.5 (3.34)	Children	5	3.8	5.3
		P – 139	P – 11.2 (3.07)				
Didier A, 2011 [20] (3-arm trial)	300 IR SL daily	O – 207	O – 30.4 (7.57)	Adults	5	2	3.5
– 2-month lead-in		P – 219	P – 30.2 (8.56)				
– 4-month lead-in	300 IR SL daily	O – 207	O – 30.9 (8.25)	Adults	5	4	5.5
		P – 219	P – 30.2 (8.56)				
Grazax™	75 000 SQ SL daily	G – 74	G – 36.5 (10.6)	Adults	1	2.8	4.6
Dahl R, 2006[5,6,35]		P – 40	P – 34.1 (9.9)				
Durham SR, 2006 [9]	75 000 SQ SL daily	G – 153	G – 36 (18–66)	Adults	1	1.9	4.2
		P –150	P – 36 (18–64)				
Dahl R, 2006[5,6,35] (3-year study)	75 000 SQ SL daily	G – 316	G – 33.8 (9.6)	Adults	1	3.7	6
– year 1		P – 318	P – 34.5 (10.0)				
Dahl R, 2008 [36]	75 000 SQ SL daily	G – 189	G – 35.4 (9.77)	Adults	1	0	22
– year 2		P – 162	P – 35.9 (9.61)				
Durham SR, 2010 [37]	75 000 SQ SL daily	G – 170	G – 35.7 (9.87)	Adults	1	0	34
– year 3		P – 138	P – 36.4 (9.86)				
Bufe A, 2009 [38]	75 000 SQ SL daily	G – 126	G – 10.0 (2.9)	Children	1	4	6.7
		P – 127	P – 10.1 (3.1)				
Blaiss M, 2011 [39]	75 000 SQ SL daily	G – 175	G – 12.1 (6–17)	Children/adolescents	1	3.7	5.3
		P – 169	P – 12.6 (5–185)				
Nelson HS, 2011 [40]	75 000 SQ SL daily	G – 213	G – 35.96 (18–63)	Adults	1	3.7	5.3
		P – 225	P – 35.9 (18–61)				
SCIT	updosed SCIT lead-in	SCIT – 45	SCIT – 27.6 (18–53)	Adults + children	7	1.6	1.6
Zenner HP, 1997 [41]		P – 41	P – 29.4 (16–49)				
Frew AJ, 2006 [42]	updosed SCIT lead-in	SCIT – 104	SCIT – 36.9 (9.0)	Adults	1	2	7 to 8
– low dose		P – 103	P – 37.9 (9.1)				
Frew AJ, 2006 [42]	updosed SCIT lead-in	SCIT – 203	SCIT – 38.3 (9.1)	Adults	1	2	7 to 8
– high dose		P – 103	P – 37.9 (9.1)				
Drachenberg KJ [43], 2001	SCIT lead-in	SCIT – 81	SCIT – 29.6 (8.4)	Adults	13	1 to 2	1 to 2
		P – 60	P – 27.4 (7.8)				
DuBuske LM, 2011 [44]	updosed SCIT lead-in	SCIT – 514	SCIT – 36 (11)	Adults	13	1 to 2	1 to 2
		P – 514	P – 35 (11)				
Corrigan CJ, 2005 [45]	updosed SCIT lead-in	SCIT – 77	SCIT – 35 (18–58)	Adults	6	1.7	4
		P – 77	P – 34 (18–60)				
Jutel M, 2005 [46]	updosed SCIT lead-in; then continued at increasing intervals	SCIT – 29	SCIT – 25	Adults	5	2.3	20
		P – 28	P – 24.5				
Pfaar O, 2012 [47]	updosed SCIT lead-in; then continued weekly × 5	SCIT – 135	SCIT – 32.9 (13.8)	Adults + children	5	1.4	1.4
– a 2-year study		P – 60	P – 33.8 (13.3)				

All of the trials were double-blinded and placebo-controlled.

G, Grazax; IR, index of reactivity; ITT, intention to treat; O, Oralair; P, placebo; SCIT, subcutaneous immunotherapy; SL, sublingual; SQ, standardized quality.

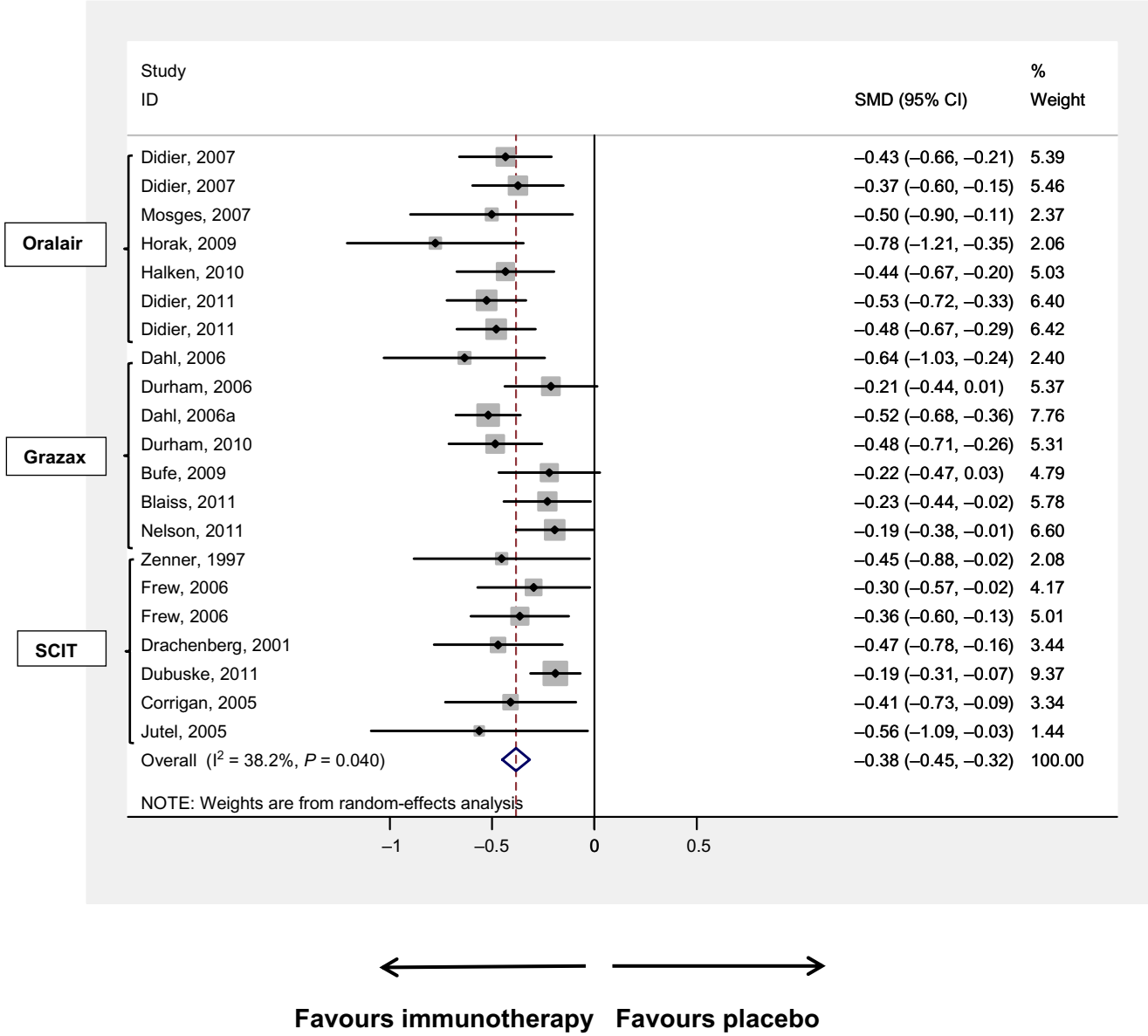

Figure 1 Random-effects meta-analysis on reductions in allergic rhinitis symptom score for all three immunotherapies combined. The pooled mean reduction in the symptom score was significantly different between immunotherapy and placebo; $P < 0.001$. Test for heterogeneity: $Chi^2 = 32.4$, d.f. = 20, $P = 0.04$, $I^2 = 38.2\%$

more likely to stop treatment because of adverse events than patients treated with Grazax™ (RR = 2.58, $P = 0.035$). The discrepancies between indirect methods were due to the fact that, unlike the meta regression modelling approach, the method of Bucher *et al*. is a univariate analysis, which does not adjust for differences in study characteristics that would influence the primary outcome.

Testing of publication bias

The potential for publication bias was also assessed. From the placebo-controlled immunotherapy trials, asymmetry in the funnel plot was detected (figure not shown) and the *P*-value from the Egger test ($P = 0.035$) indicated the possibility of publication bias. The funnel plot indicated a potential relationship between study size and effect size, where smaller studies tended to have a larger effect size. This observation may be related to differences in study inclusion criteria or the ability to minimize patient dropouts in studies of smaller sample sizes.

Economic evaluation

Resource utilization

The first step in the economic analysis was to estimate health care resource use for the interventions over the first year of

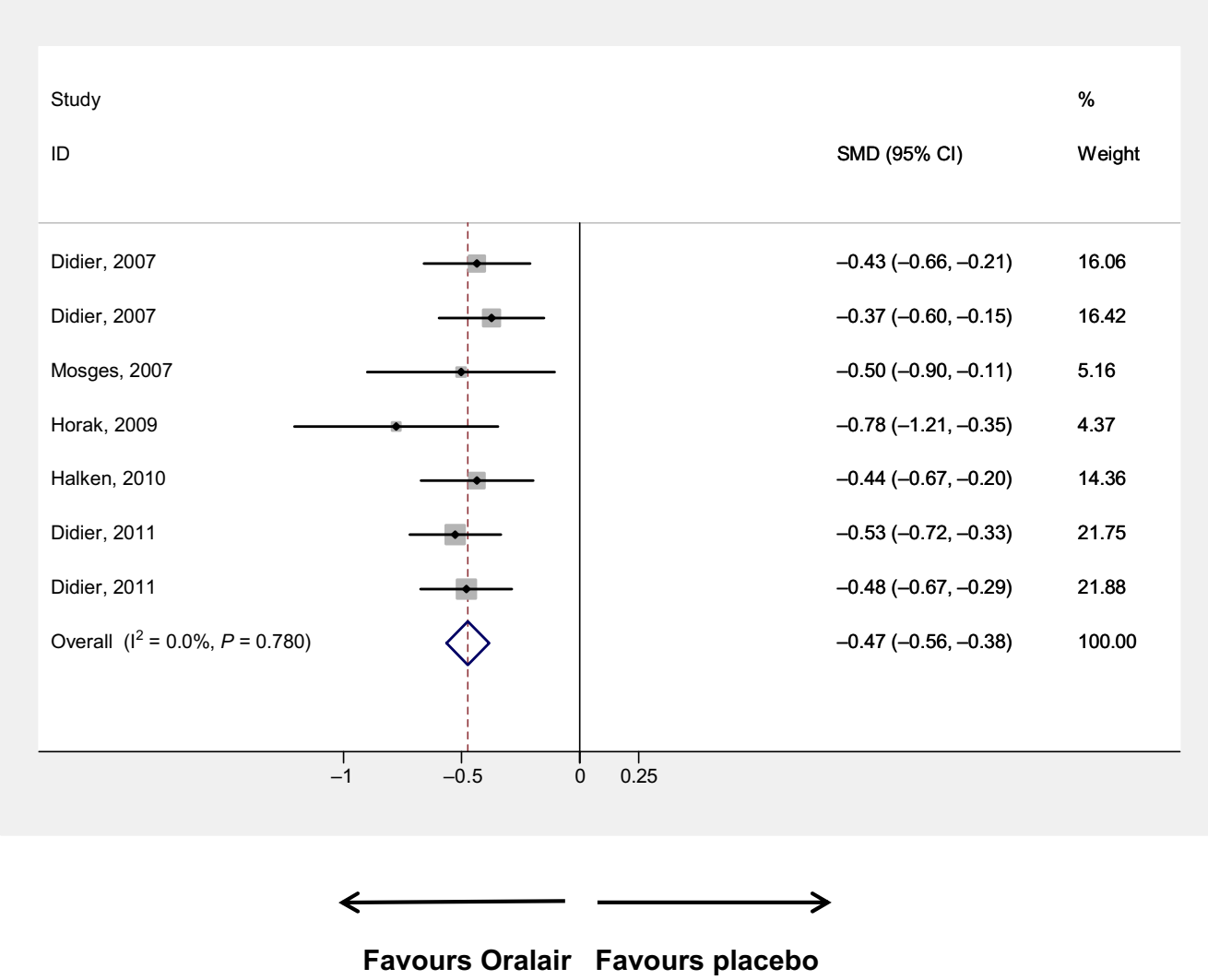

Figure 2 Fixed-effects meta-analysis on reductions in allergic rhinitis symptom score with Oralair.
The pooled mean reduction in the symptom score was significantly different between Oralair and placebo; $P < 0.001$. Test for heterogeneity: $Chi^2 = 3.2$, d.f. = 6, $P = 0.78$, $I^2 = 0.0\%$

therapy and then for years 2 and 3 combined. From the meta-analysis and expert opinion, a 300 IR daily dose of Oralair™ was used and compared with 0.5 mL year-round doses and seasonal SCIT regimens. Under the supported assumption of comparative safety and efficacy from the indirect analysis, the economic parameters that were relevant consisted of drug acquisition cost, pharmacy dispensing fees, reimbursement for physician services, annual prescriptions for epinephrine for patients receiving SCIT, treatment of anaphylaxis, secondary pharmacotherapy in cases of initial drug intolerance and all indirect costs. These estimates along with the associated unit costs were used to conduct the economic analysis.

As Oralair™ and Grazax™ are sublingual agents, they only require an initial visit at the physician's office. Therefore, regular visits to the physician's office are eliminated, leading to the avoidance of considerable indirect resource use and costs such as lost productivity, school absenteeism and travel costs to the physician's office for drug administration. Comparing Oralair™ to Grazax™, the former would require fewer months of therapy (i.e. 6 versus 12 months), which would translate into additional economic advantages. However, the magnitude of these economic advantages cannot be fully be evaluated because Grazax™ is not as yet approved by Health Canada and a Canadian price is unavailable.

Cost comparison

Using the resource use data collected from expert opinion and monthly drug costs, a cost comparison was conducted for the first year of therapy. A secondary analysis was then conducted for years 2 and 3. In addition to drug costs, both analyses considered physician visits for SC injections, annual prescriptions for injectable epinephrine (for SC products only), treatment of

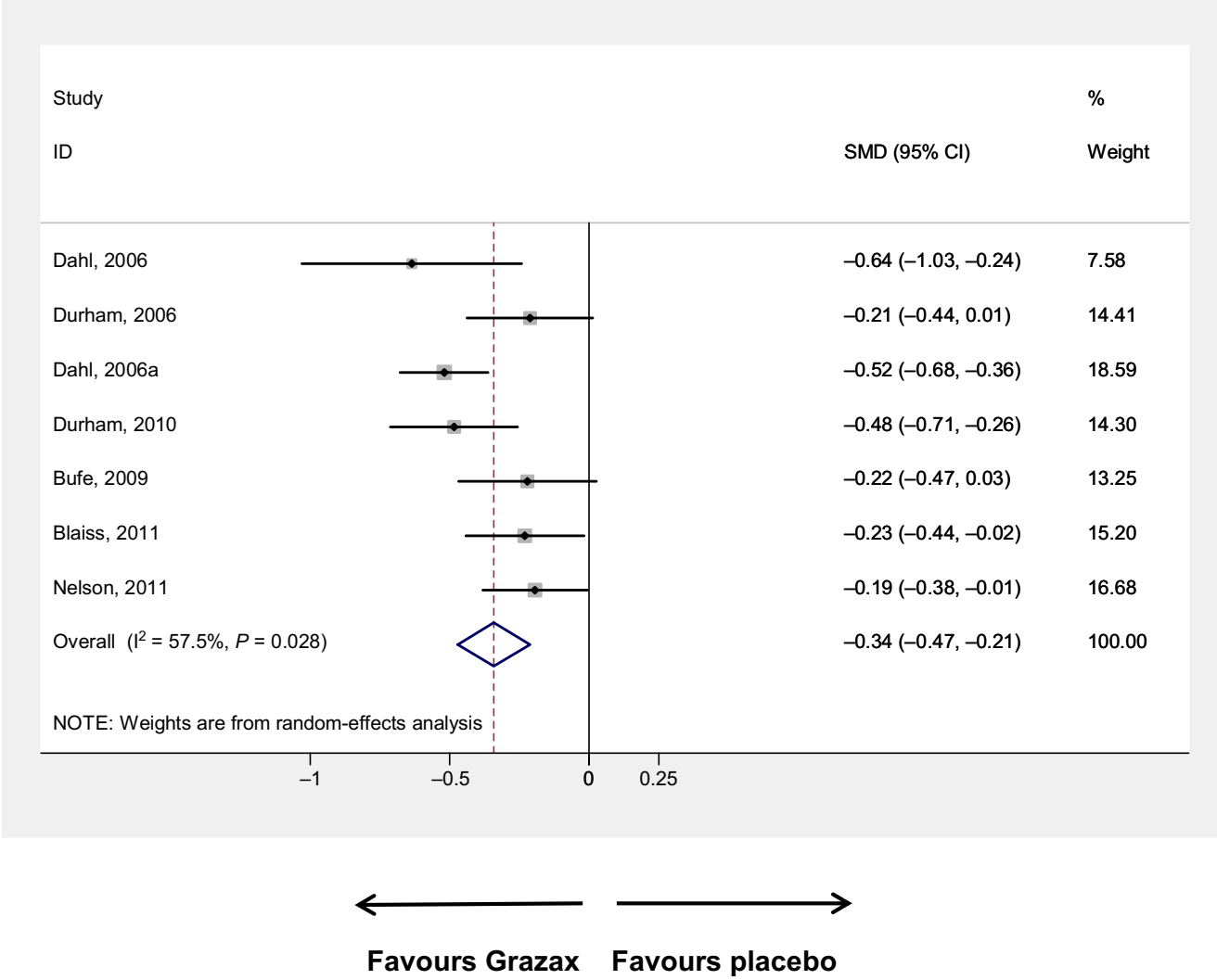

Figure 3 Random-effects meta-analysis on reductions in allergic rhinitis symptom score with Grazax.
The pooled mean reduction in the symptom score was significantly different between Grazax and placebo; $P < 0.001$. Test for heterogeneity: $Chi^2 = 14.1$, d.f. = 6, $P = 0.0.028$, $I^2 = 57.5\%$

anaphylaxis, secondary pharmacotherapy costs where the initial treatment had to be permanently discontinued in the first month because of adverse events, as well as indirect costs (i.e. patient travel and lost productivity).

Oralair™ was associated with substantial cost savings, particularly against year-round and seasonal SCIT (Table 4 and Table 5). These findings are relevant because SCIT (both annual and seasonal) is the most commonly used treatment for medically refractory seasonal AR in Canada. In addition, physicians providing clinical advice throughout this study indicated that many Canadian allergists, to a variable degree, mark up each SCIT vaccine and charge it to the patients or to their insurance company (as would a pharmacy). Therefore, the base case findings are conservative. These results, along with equal or possibly improved efficacy (as suggested by the meta regression analysis) indicate that Oralair™ should result in cost savings to society and a potential to improvement in patient care.

Discussion

An indirect comparison of placebo-controlled randomized trials was conducted to test the hypothesis that Oralair™ has comparable safety and efficacy to SCIT and Grazax™. The findings indicated that Oralair™ may be superior or at least non-inferior to both SCIT and Grazax™ for AR symptom control. These benefits were obtained with a modest risk of drug discontinuations due to adverse events (although not statistically significant). The meta-analysis also suggested that Oralair™ was well tolerated, with discontinuation rates being approximately 5.6%.

There have been two indirect analyses comparing SLIT to SCIT published in the academic literature in the past 12 months [48,49]. Both studies concluded that SCIT may be more effective than SLIT in controlling AR symptoms [48,49]. However, the findings of these studies are not comparable to the current investigation because they included all types of SLIT products and methods of

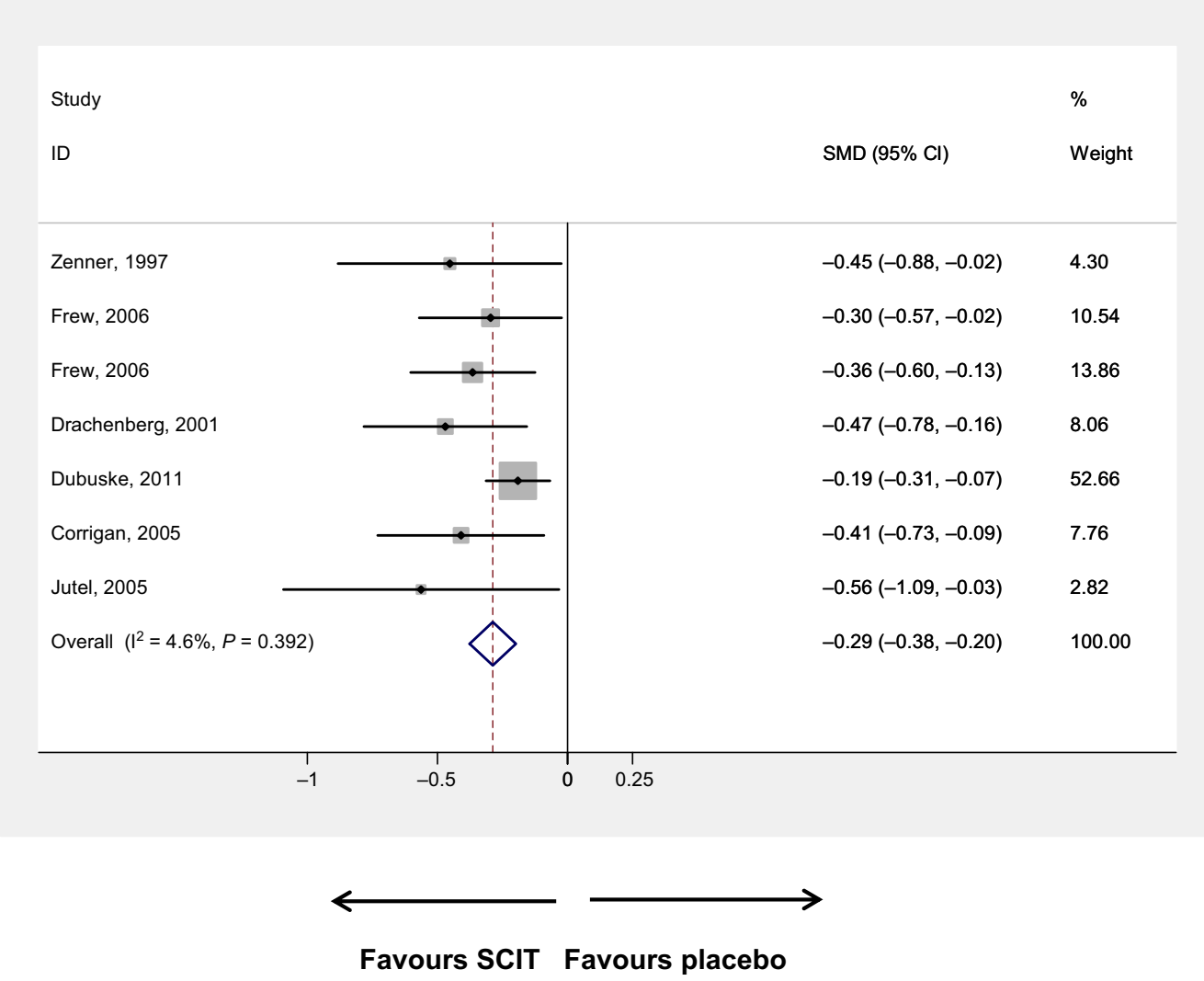

Figure 4 Fixed-effects meta-analysis on reductions in allergic rhinitis symptom score with subcutaneous immunotherapy (SCIT). The pooled mean reduction in the symptom score was significantly different between SCIT and placebo; $P < 0.001$. Test for heterogeneity: $Chi^2 = 6.3$, d.f. = 6, $P = 0.39$, $I^2 = 4.6\%$

delivery (e.g. drops) in their analysis. In contrast, the current study was specific to Oralair™ and Grazax™ as alternatives to SCIT. Therefore, the question that we sought to answer was different than the two other indirect analyses. Notwithstanding, a well-designed randomized trial comparing Oralair™ and Grazax™ to SCIT is warranted.

Of additional interest to drug policy decision-makers are the results of the economic analysis. Oralair™ in place of year-round and seasonal SCIT would be associated with an overall cost savings from the societal perspective. The two most prominent factors in the overall cost savings with Oralair™ over SCIT were the reductions in indirect costs and for physician visits for drug administration. Interviews with clinicians also revealed that marking up the cost of a dose of SCIT is common practice by some Canadian physicians. Therefore, the potential costs savings offered by Oralair™ are conservative because they do not include the SCIT mark-ups.

There has been one recent economic analysis comparing Oralair™ with Grazax™ and SCIT that was conducted in Germany from insurant's perspective, which included public and private health insurance payments and co-payments by insurants [50]. The investigators developed a Markov process to model the costs and quality-adjusted life years (QALYs) gained with each treatment over a 9-year time horizon. In the base case analysis, it generated more QALYs at a lower overall cost relative to the alternatives. It was concluded that Oralair™ was a cost-effective and cost-saving alternative to Grazax™ and SCIT in Germany [50]. However in a study conducted in Italy, Oralair™ was found to be cost ineffective in patients with mild allergic rhinitis [51].

Many new drugs approved in Canada seeking formulary entry have increased efficacy, but at a substantial incremental cost relative to the current standard of care. Oralair™ provides formulary decision-makers with a unique situation. It is a drug that can be orally administered, thereby avoiding regular visits to the

Table 2 Summary of indirect statistical comparisons using meta regression analysis

Outcome	IT (O, G,SCIT) versus placebo	(95% CI)	*P*-value
Difference in symptom score	SMD		
All drugs versus placebo	–0.38	(–0.45 to –0.32)	<0.001
Difference between drugs*			
(Oralair versus Grazax)	–0.18	(–0.32 to –0.035)	0.018
(Oralair versus SCIT)	–0.21	(–0.36 to –0.066)	0.007
Year of publication†	–0.023	(–0.59 to –0.39)	0.025
Total duration of IT‡	–0.007	(–0.016 to 0.002)	0.11
Drug D/C	RR		
All drugs versus placebo	2.64	(1.88 to 3.72)	<0.001
RR of D/C for each drugs§			
(Oralair versus placebo)	4.86	(2.41 to 9.79)	<0.001
(Grazax versus placebo)	1.90	(1.21 to 3.00)	0.006
(SCIT versus placebo)	3.16	(1.40 to 7.10)	0.005

*In the meta regression model, differences in efficacy between Oralair and the two alternatives were also adjusted by the duration of IT therapy and year of study publication. None of the other variables evaluated in the model (e.g. type of patients evaluated, prevalence of asthma, and number of allergens) made a significant impact on the overall symptom score.

†The variable year of publication was centered. The findings suggest that older studies were more likely to report a larger magnitude of benefit compared to more recent trials.

‡Even though this variable did not reach statistical significance, it still accounted for 12% of the heterogeneity observed in the data.

§Adjusted by the duration of therapy with each agent. The indirect comparison of RR for drug D/C between Oralair and both Grazax and SCIT failed to reach statistical significance (i.e. $P = 0.058$ and P 0.39 respectively).

CI, confidence interval; D/C, discontinuations due to adverse events; G, Grazax; IT, immunotherapies; O, Oralair; RR, relative risk; SCIT, subcutaneous immunotherapy; SMD, standardized mean difference.

physician's office and the unpleasantness of an injection. In addition, it may provide additional efficacy to patients and reduced costs to the Canadian system. Indeed, this situation is rare with new pharmaceuticals and should make Oralair™ an economically attractive addition to Canadian drug formularies.

There are a number of limitations in both the indirect analysis and the economic evaluation that need to be addressed. The findings of the indirect comparison suggesting a measure of improved efficacy with Oralair™ must be taken with some reserve. The only definitive way to establish clinical superiority between two treatments is through a randomized trial with adequate statistical power. It must also be acknowledged that all meta-analyses are affected by the quality of the studies analysed. For that reason, the review was limited to prospective double-blind randomized trials with sufficient sample size. The indirect analysis was not a true non-inferiority study because a pre-specified '*non inferiority margin*' in efficacy between the drugs has not been established by regulatory authorities. Differences in the use of rescue medication between treatments could not be compared due to the lack of consistent data. Some of the trials provided more than two treatment arms for the meta regression analysis. This may violate the independence assumption of regression modelling, and could lead to a slight narrowing of the 95% CI. Lastly, the SCIT regimens evaluated in the meta regression analysis were not the exact treatments that are currently used in all of Canada. This could compromise the generalisability of the indirect comparisons. At the time of the analysis, Grazax™ was not approved for use in Canada. As a result, the daily cost of Grazax™ in the UK was used as a proxy for this study. This cost may not be pertinent to the Canadian setting; however, it was used as the best estimate at the time of the analysis. The economic analysis focused only on direct and indirect costs and did not consider treatment preferences and the health state utilities associated with the various treatment alternatives. Such parameters may vary, particularly due to potential differences in efficacy, route of administration (i.e. SC versus sublingual) and tolerance between drugs.

Conclusions

An indirect comparison of double-placebo-controlled trials using meta regression techniques suggested that Oralair™ has at least non-inferior efficacy and comparable safety against SCIT and Grazax™ and is associated with cost savings. Therefore, in instances where physicians recommend immunotherapy for the treatment of seasonal AR, Oralair™ can be considered due to its economic advantages and at least similar efficacy against SCIT and Grazax™.

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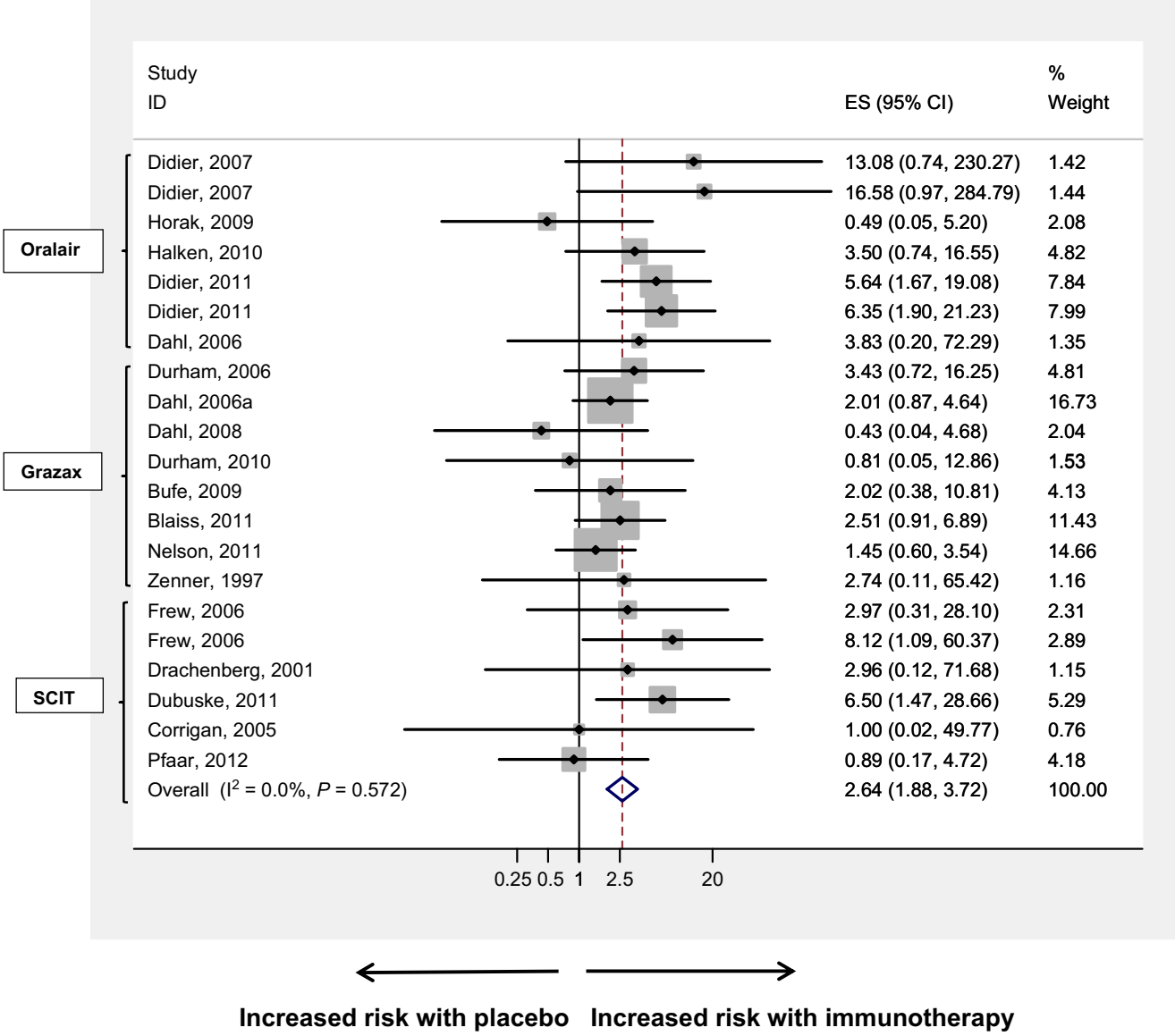

Figure 5 Fixed-effects meta-analysis on the risk of treatment discontinuations with immunotherapy treatments relative to placebo. The pooled relative risk of drug discontinuations due to adverse events was significantly different between immunotherapy and placebo; $P < 0.001$. Test for heterogeneity: $Chi^2 = 18.2$, d.f. = 20, $P = 0.57$, $I^2 = 0.0\%$.

Table 3 Summary of indirect statistical comparisons using the method of Bucher *et al.*[24]

Comparison	Mean difference	(95% CI)	*P*-value
Oralair™ versus Grazax™			
Symptom score	–0.13	(–0.29 to 0.025)	N/S
Drug D/C (expressed as a RR)	2.58	(1.14 to 5.80)	0.035
Oralair™ versus SCIT			
Symptom score	–0.18	(–0.31 to –0.047)	0.033
Drug D/C (expressed as a RR)	1.55	(0.54 to 4.44)	N/S

CI, confidence interval; D/C, discontinuations due to adverse events; N/S, not statistically significant; RR, relative risk; SCIT, subcutaneous immunotherapy; SMD, standardized mean difference.

Table 4 Cost per patient for the first year of therapy

Resource item	Oralair™	SCIT year-round	SCIT seasonal	Grazax™
Direct costs, $				
Drug cost	767	395	2010	1939
Pharmacy dispensing fee*	16.40	0.00	0.00	16.40
Assessment by allergist and first administration*	149	149	149	149
Physician visits for injections†	0.00	933	482	0.00
Prescription for Epipen® for patients receiving SCIT	0.00	88.00	88.00	0.00
Treatment of anaphylaxis	0.00	0.10	0.10	0.00
Secondary pharmacotherapy‡	11.07	17.27	17.27	6.92
Indirect costs, $				
Lost productivity in hours, secondary to receiving the drug	47.12	1508	801	47.12
Travel costs, secondary to having to receive the drug	12.00	384	204	12.00
TOTAL COST§	**1003**	**3474**	**1951**	**2171**
Cost impact (savings) with Oralair™		**(2471)**	**(948)**	**(1168)**

*Physicians stated they would provide patients with at least 4 months of drug supply per prescription.
†The first dose of oral therapy needs to be given in the physician's office.
‡In cases of intolerable side effects developing in the first month of injectable therapy, it was assumed that Oralair would be offered for the remaining 5 months. In the case of intolerance with oral therapy, an injectable option would be offered for 6 months.
§The totals values may not be exact because of rounding errors.
SCIT, subcutaneous immunotherapy.

Table 5 Cost per patient for years 2 and 3 of therapy (combined)

Resource item	Oralair™	SCIT year-round	SCIT seasonal	Grazax™
Direct costs, $				
Drug cost	1535	296	420	3879
Pharmacy dispensing fee*	32.80	0.00	0.00	32.80
Assessment by allergist and first administration†	298	298	298	298
Physician visits for injections	0.00	662	963	0.00
Prescription for Epipen® for patients receiving SCIT	0.00	176.00	176	0.00
Treatment of anaphylaxis	0.00	0.10	0.10	0.00
Indirect costs, $				
Lost productivity in hours, secondary to receiving the drug	94.24	1131	1602	94.24
Travel costs, secondary to having to receive the drug	24.00	288	408	24.00
TOTAL COST‡	**1983.84**	**2852**	**3867**	**4327**
Cost impact (savings) with Oralair™		**(868)**	**(1883)**	**(2344)**

*Physicians stated they would provide patients with at least 5 months of drug supply per prescription.
†The first dose of oral therapy needs to be given in the physician's office.
‡The totals values may not be exact because of rounding errors.
SCIT, subcutaneous immunotherapy.

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