SUBLINGUAL OR SUBCUTANEOUS IMMUNOTHERAPY FOR SEASONAL ALLERGIC RHINITIS: AN INDIRECT ANALYSIS OF EFFICACY, SAFETY AND COST

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ABSTRACT

Background: The current standard of care for poorly controlled seasonal allergic rhinitis (AR) symptoms is subcutaneous immunotherapy (SCIT) with allergen extracts, administered in a physician's office. As an alternative to SCIT administration, sublingual immunotherapy (SLIT) is now an option for patients. Oralair™ and Grastek™ are two SLIT agents currently available in many countries**.** However, direct head to head comparative data between the three options are not available. In this study, an indirect comparison on efficacy, safety and cost was undertaken between Oralair™**,** Grastek™ and SCIT.

Methods: A systematic review of major databases was conducted from January 1980 to December 2012 for double blind placebo controlled randomized trials evaluating Oralair™, Grastek™ 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. Other variables considered in the regression 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 vs. children). A Canadian cost comparison, which included costs for drug therapy, pharmacy fees, physician visits and indirect costs (i.e. patient travel and lost productivity) was also undertaken.

Results: Overall, 20 placebo-controlled trials met the inclusion criteria for indirect analysis. The indirect analysis suggested a possibility for improved efficacy with Oralair™ over SCIT (standardized mean difference [SMD] in AR symptom control = - 0.21; p = 0.007) and Grastek™ (SMD = - 0.18; p = 0.018). In addition, the meta regression analysis did not identify significant differences in the risk of discontinuation due adverse events between the three therapies. Oralair™ was also associated with cost savings against year round SCIT ($2,471), seasonal SCIT ($948) and Grastek™ ($1,168) during the first year of therapy.

Conclusions: Through an indirect comparison of placebo controlled trials, the evaluation suggested that Oralair™ has at least non-inferior efficacy and comparable safety against SCIT and Grastek™ at a lower annual cost.

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OBJECTIVES

- To perform a systematic review of placebo controlled randomized trials evaluating Oralair™, Grastek™ and subcutaneous immunotherapy (SCIT) in patients with grass-induced seasonal allergic rhinitis (AR).
- To indirectly compare the safety and efficacy of Oralair™ to Grastek™ and SCIT for the management of grass-induced seasonal AR.
- To compare the direct and indirect costs of Oralair™ to Grastek™ and SCIT over a three-year time horizon

COMPARATORS

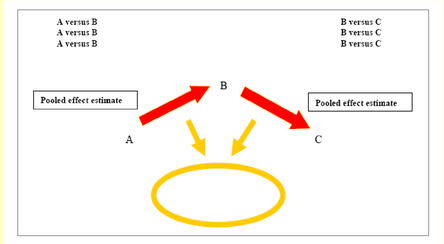
- Oralair™: 300 IR daily under the tongue: 4 months pre-allergy season and then for 2 months co seasonally . The same regimen was used in years 2 and 3.
- Grastek™**:** 75000 SQ-T daily under the tongue and taken over the entire year. The same regimen was used in years 2 and 3.
- SCIT Regimen 1 (year round): One injection weekly x 6 months, then monthly for the remainder of the first year. Monthly dosing would be used in years 2 and 3.
- SCIT Regimen 2 (seasonal): One injection weekly x 3 months preseason, then monthly for 4 months during pollen season. The same regimen would be used in years 2 and 3.

METHODS

- A systematic literature review of major databases was conducted from January 1980 to April 2012 for placebo controlled randomized trials evaluating Oralair™, Grastek™ or SCIT in patients with seasonal AR.
- Clinical trials were statistically pooled using fixed or random effects meta analysis as indicated by tests for heterogeneity.
- Statistical heterogeneity between studies was assessed by both the Q-statistic and the I^2 test statistic.
- Treatment effects from individual trials were then presented as standardized mean differences (SMD) in AR symptom control.
- Publication bias was assessed by the method proposed by Egger et al.

Methods of Indirect Comparison

What do we mean by indirect comparisons?



- The indirect comparisons were performed using two distinct methods: *Meta regression and the method of Bucher et al., (1997).*

Meta regression modeling:

- The dependent variable was the SMD or relative risk (RR) of the event. The independent variable is "treatment" (Oralair, Grastek™ or SCIT)
- We then test to see if the variable "drug" has a significant effect on the SMD in AR symptom control or the RR for treatment discontinuation (D/C).

The Method of Bucher et al. (1997)

- The indirect comparison of A and B is adjusted according to the results of the direct comparisons with a common intervention – C.

Formulas for the Butcher et al. Method

- *lnRR'AB = lnRRAC – lnRRBC*

The standard error would be:

- *$SE(lnRR'AB) = \sqrt{[SE(lnRRAC)2 + SE(lnRRBC)2]}$.*

ECONOMIC ANALYSIS

- An economic analysis was conducted from the societal perspective, which considered both direct and indirect costs.
- The 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.
- Indirect costs consisting of patient travel to receive their SCIT injection and time off work (i.e. lost productivity, assuming 2 hours to visit the physician for the injection) were also included.
- At the time of the analysis, a Canadian price for Grastek™ was unavailable. Therefore, the UK price of $4.83 per day was used.

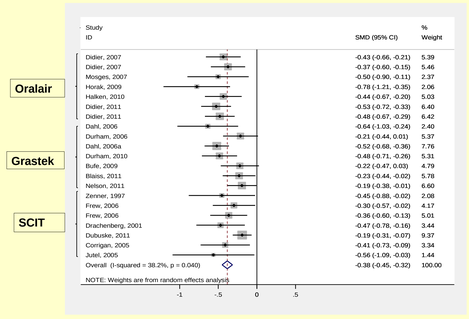
RESULTS

- 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; Grastek™ - eight trials; SCIT - seven trials.
- All of the trials were double blinded and placebo controlled, with sample sizes per study arm ranging from 28 to 514.

Pooled Results

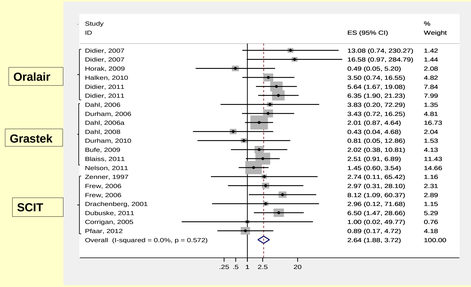
- Oralair™ (pooled estimate from seven trial arms): SMD for AR symptom control = -0.47; 95%CI = (- 0.56 to -0.38); p < 0.001
- Grastek™ (pooled estimate from seven trial arms): SMD = -0.34; 95%CI = (- 0.47 to - 0.21); p < 0.001
- SCIT (pooled estimate from seven trial arms): SMD = -0.30; 95%CI = (- 0.39 to - 0.20); p = 0.001

Figure 1. Random effects meta analysis on reductions in AR symptom score for all three immunotherapies combined.



The pooled mean reduction in the symptom score was significantly different between immunotherapy vs. placebo; p < 0.001. Test for heterogeneity: Chi² = 32.4, df = 20, p = 0.04, I²=38.2%

Figure 2. 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 vs. placebo; p < 0.001. Test for heterogeneity: Chi² = 18.2, df=20, p = 0.57, I²=0.0%.

Table 1. Indirect statistical comparisons using the method of Bucher et al., (1997).

Comparison	Mean Difference	(95%CI)	P-Value
Oralair™ vs. Grastek™			
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™ vs. 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

RESULTS

Table 2. Indirect statistical comparisons using meta regression analysis.

Outcome	IT (O, G,SCIT) vs. Placebo	(95%CI)	P-Value
Difference in Symptom Score	SMD		
All drugs vs. placebo	-0.38	(-0.45 to -0.32)	< 0.001
Difference between drugs			
(Oralair vs. Grastek)	-0.18	(-0.32 to -0.035)	0.018
(Oralair vs. 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			
All drugs vs. placebo	RR 2.64	(1.88 to 3.72)	< 0.001
RR of D/C for each drugs			
(Oralair vs. placebo)	4.86	(2.41 to 9.79)	< 0.001
(Grastek vs. placebo)	1.90	(1.21 to 3.00)	0.006
(SCIT vs. placebo)	3.16	(1.40 to 7.10)	0.005

Abbreviations: IM = immunotherapies, O = Oralair, G = Grastek, SCIT = subcutaneous immunotherapy P = placebo, SMD = standardized mean difference, RR = relative risk, D/C = discontinuations due to adverse events.

Table 4. Cost per patient for the first year of therapy.

Resource item	Oralair™	SCIT Year Round	SCIT Seasonal	Grastek™
Direct Costs:				
Drug cost	$767	$395	$2010	$1,939
Pharmacy dispensing fee	$16.40	$0.00	$0.00	$16.40
Assessment by allergist and first administration[1]	$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	$1,508	$801	$47.12
Travel costs for drug injections	$12.00	$384	$204	$12.00
TOTAL COST[4]	**$1003**	**$3,474**	**$1,951**	**$2,171**
Cost impact (savings) with Oralair™		**($2,471)**	**($948)**	**($1,168)**

Table 5. Cost per patient for years two and three of therapy (combined).

Resource item	Oralair™	SCIT Year Round	SCIT Seasonal	Grastek™
Direct Costs:				
Drug cost	$1,535	$296	$420	$3,879
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	$1,131	$1,602	$94.24
Travel costs, secondary to having to receive the drug	$24.00	$288	$408	$24.00
TOTAL COST	**$1,983.84**	**$2,852**	**$3,867**	**$4,327**
Cost impact (savings) with Oralair™		**($868)**	**($1,883)**	**($2,344)**

CONCLUSIONS

- Through an indirect comparison of placebo controlled, the evaluation suggested that Oralair™ has non-inferior efficacy and safety against SCIT and Grastek™ and at a substantially lower annual cost.

References: Available upon request to the primary author.