The benefit-risk balance of subcutaneous immunotherapy (SCIT) for seasonal allergic rhinitis (SAR)

P. Patel[1], A.M. Salapatek[1], L. DuBuske[2], K. Fischer von Weikersthal-Drachenberg[3],

AllerPharma Inc., Toronto, Canada[1], Brigham and Women's Hospital, Boston, United States[2], Allergy Therapeutics plc, Worthing, United Kingdom[3]

Introduction

Various approaches are used for the treatment of allergic rhinitis, including the avoidance of allergens, pharmacotherapy with antihistamines, leukotriene antagonists and glucocorticosteroids, and specific immunotherapy (SIT).

The use of allergen-specific subcutaneous immunotherapy (SCIT) spans nearly a century.[1]

Immunotherapy is a consideration in patients with moderate to severe symptoms that are difficult to control using other treatments.

SCIT involves the subcutaneous administration of an increasing dose of allergen with the goal of desensitizing the immune system in allergic individuals.

Objectives

We compared data describing the efficacy and safety of SCIT with selected published study data involving other pharmacological options for SAR.

Methods

Well-designed, randomized controlled studies where symptom improvement from baseline could be calculated for the active therapy compared with placebo, were identified and reviewed.

Treatment efficacy was calculated as a percentage reduction in symptomatic scores from baseline. The treatment effect of each compound was estimated by comparing the percentage reduction reported in the placebo group and the active drug group.

Efficacy data for SCIT were compared with equivalent data available for symptomatic therapy for SAR (antihistamines, topical glucocorticosteroids and leukotriene antagonists).

The safety profile of each therapy was assessed from a review of the literature.

Results

Efficacy

Table 1 summarizes the studies included in this analysis.

The largest improvements in symptom scores were seen with SCIT, ranging from 29 to 71%.

SCIT was associated with statistically significant reductions in symptoms and medication use throughout the pollen season

- several studies reported considerable reductions in symptomatic medications use e.g. 50% compared with placebo for birch pollen SIT[10] and 32%,[11] 69%[12] and 36.5%[13] for grass pollen SCIT compared with placebo.

Topical glucocorticosteroids appeared to be more clinically effective than antihistamines, with studies reporting symptom reductions of up to 50%.

Antihistamines had a rapid onset of action, but were clinically less effective than glucocorticosteroids in the reduction of symptom severity (treatment effects ranged up to 12%).

Leukotriene antagonists demonstrated a clinical benefit similar to antihistamines with a treatment effect of up to 8%.

Safety

Adverse events varied with treatment types (Table 2).

Table 2. Commonly reported adverse events [14-18]

	Adverse Events
Antihistamines	**Oral preparations:** mild sedation; dry mouth (small proportion of patients); psychomotor impairment (cetirizine 10 mg/day)
Leukotriene antogonists	**Oral preparations:** increased alanine aminotransferase, aspartate aminotransferase, bilirubin (all rare)
Glucocorticosteroids	**Nasal preparations:** epistaxis (up to 20% of patients); increased intraocular pressure and posterior subcapsular cataracts (rare case reports in adults)
Subcataneous immunotherapy	**Local adverse events:** injection site swelling, redness, pain and induration **Systemic adverse events:** dyspnoea, urticaria, hot flush, dizziness, cough, anaphylaxis (rare)

None of the treatments investigated were frequently associated with serious adverse events. Adverse events with SCIT were predominantly mild to moderate in intensity, easily managed and usually decreased in incidence as treatment progressed.

Local reactions with SCIT included itching, redness and swelling at the injection site but did not represent a clinical concern. Estimates of the frequency of such reactions varied markedly according to the definitions used and ranged from 26 - 86% of injections in one study.[19]

Systemic reactions from SCIT were rare and were of relatively lesser (conjunctivitis, rhinitis, itching, sneezing) or greater (wheezing, urticaria) clinical concern. However, more serious systemic adverse events have historically been associated with SCIT including anaphylaxis (predominantly in patients with poorly controlled severe asthma).

- recent advances, such as the use of allergoids and immunological adjuvants, have reduced the risk of SAEs with SCIT.

Side effects associated with nasal glucocorticosteroid use were predominantly local, with the most common being epistaxis in up to 20% of adults.

- systemic side effects associated with steroid therapy are rare with newer agents.

Antihistamines were generally well tolerated, with the most common adverse event for some being sedation (cetirizine). There were also rare incidences of dry mouth.

The leukotriene antagonist montelukast is reported to be well tolerated in SAR, although rare hypersensitivity reactions have been reported along with rare cases of hepatocellular injury.

Discussion

Few data exist to directly compare SCIT with symptomatic therapy in SAR.

Cross-trial comparisons are difficult because of the lack of standardization of trial endpoints and differences in patient populations between therapy types

- studies of SCIT commonly include patients with more severe disease than those in trials of symptomatic therapies.

Most studies identified a large placebo effect, which when subtracted from the treatment effect of the active compound rendered the treatment effect of many symptomatic interventions to be relatively poor.

SCIT was associated with the greatest reduction in SAR symptoms

- symptomatic benefit has been reported 7 - 12 years following a three-year course of SCIT.[20,21]

Symptomatic therapy is readily available, but may not be adequately effective in all patients.

Good administration practice and careful patient selection can minimize the risk of more serious events with SCIT.

Shorter-course SCIT regimens involving fewer injections may increase patient acceptance and adherence.

Conclusions

Specific immunotherapy is a highly effective and well tolerated treatment which can be administered safely to appropriately selected patients.

As such, the benefits of specific immunotherapy for patients with moderate to severe SAR outweigh the benefits of symptomatic treatment.

References

1. Cohen et al. J Allergy Clin Immunol 2003:111;1142-1150
2. Meltzer et al. J Allergy Clin Immunol 1996:97;617-626
3. Merk & Co. PI for Singulair. http://www.merckservices.com/portal/site/merckproductservices/singulair/
4. Meltzer et al. J Allergy Clin Immunol 2000:105;917-922
5. Schering Corporation. Prescribing information for Clarinex http://www.spfiles.com/piclarinex.pdf
6. Bernstein et al Clin Exp Allergy 2004:34;952-957
7. Bielory Ann Allergy Asthma Immunol 2008:100;272-279
8. Mandl et al. Ann Allergy Asthma Immunol 1997:79;370-378
9. Ciprandi et al. Allergy 2002:57;586-591
10. Bodtger et al. Allergy 2002:57;297-305
11. Corrigan et al. Allergy 2005:60;801-807
12. Jutel et al. J Allergy Clin Immunol 2005:116;608-613
13. Frew et al. J Allergy Clin Immunol 2006:117;319-325
14. Calderon et al. Cochrane Database Syst Rev 2007CD001936
15. Simons N Engl J Med 2004:351;2203-2217
16. Passalacqua et al. Expert Opin Investig Drugs 2006:15;1615-1625
17. Van et al. Drugs 2007:67;2717-2726
18. Nielsen et al. Am J Respir Med 2003:2;55-65
19. Tankersley et al. J Allergy Clin Immunol 2000:106;840-843
20. Eng et al. Allergy 2006:61;198-201
21. Jacobsen et al. Allergy 2007:62;943-948

Table 1. Summary of the clinical effectiveness of a variety of treatment options for seasonal allergic rhinitis

Group	Reference	Treatment	Study Design (duration, symptom measurement, number of patients)	Change from baseline in mean symptom score		
				Active drug	Placebo	Treatment effect
Antihistamines	Meltzer JACI 1996[2]	Cetirizine	2 days, total symptom complex (10), n=278	45% (n=93)	40% (n=92)	5%
	Meltzer JACI 1996[2]	Loratadine	2 days, total symptom complex (10), n=278	36% (n=92)	40% (n=92)	-4%
	Merk & Co PI for Singulair[3]	Loratadine	2 weeks, mean daytime nasal symptom score, n=1294	22% (n=599)	12% (n=351)	10%
	Meltzer JACI 2000[4]	Loratadine	2 weeks, mean nasal symptom score, n=368	18% (n=92)	13% (n=91)	5%
	Schering Corporation PI for Clarinex[5]	Desloratidine	2 weeks, mean total symptom score, n=344	30% (n=171)	18% (n=173)	12%
	Schering Corporation PI for Clarinex[5]	Desloratidine	4 weeks, mean total symptom score, n=674	33% (n=337)	27% (n=337)	6%
	Bernstein Clin Exp Allergy 2004[6]	Loratadine	28 days, total ocular symptom score, n=471	36% (n=158)	29% (n=155)	7%
Leukotriene antagonist	Merk & Co PI for Singulair[3]	Montelukast	2 weeks, mean daytime nasal symptom score, n=1294	19% (n=344)	12% (n=351)	7%
	Meltzer JACI 2000[4]	Montelukast (10 mg)	2 weeks, mean nasal symptom score, n=368	21% (n=95)	13% (n=91)	8%
	Meltzer JACI 2000[4]	Montelukast (20 mg)	2 weeks, mean nasal symptom score, n=368	18% (n=90)	13% (n=91)	5%
Corticosteroids	Bielory Ann Allergy Asthma Immunol 2008[7]	Mometasone furoate	15 days, ocular symptom, n=983	20% (n=491)	6% (n=492)	14%
	Bernstein Clin Exp Allergy 2004[6]	Fluticasone propionate	28 days, total ocular symptom score, n=471	42% (n=158)	29% (n=155)	13%
	Mandl Ann Allergy Asthma Immunol 1997[8]	Mometasone furoate	15 weeks, nasal symptoms in perennial rhinitis, n=474	61% (n=166)	35% (n=146)	26%
	Mandl Ann Allergy Asthma Immunol 1997[8]	Fluticasone propionate	15 weeks, nasal symptoms in perennial rhinitis, n=474	55% (n=162)	35% (n=146)	20%
	Ciprandi Allergy 2002[9]	Budesonide	35 days, combined nasal symptoms, n=280	47% (n=100)	15% (n=84)	32%
	Ciprandi Allergy 2002[9]	Fluticasone propionate	35 days, combined nasal symptoms, n=280	55% (n=102)	15% (n=84)	40%
SCIT	Bodtger Allergy 2002[10]	High-dose birch pollen SCIT	1 year, severity of symptoms score, n=34	35% (n=17)	(+) 36% (n=17)	71%
	Corrigan Allergy 2005[11]	Multiple (6) grass pollen allergoid	2 years, combined symptom and medication score, n=154	174AU (n=66)	337AU (n=60)	48%
	Jutel JACI 2005[12]	Multiple recombinant grass pollen allergens	2 years, combined symptom and medication score, n=62	4.92AU (n=31)	8.05 AU (n=31)	39%
	Frew JACI 2006[13]	Grass pollen	1 year, mean symptom score, n=410	3.13AU (n=169)	4.39AU (n=91)	29%

AU, arbitrary units: SCIT data were commonly reported as a change from baseline scores rather than as absolute baseline and post-therapy values.