Drugs 2006; 66 (7): 931-938
0012-6667/06/0007-0931/$44.95/0

Ultra-Short-Course Seasonal Allergy Vaccine (Pollinex® Quattro)

Paul L. McCormack and *Antona J. Wagstaff*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ This novel ultra-short-course seasonal allergy vaccine, containing glutaraldehyde-modified allergens and the adjuvants 3-deacylated monophosphoryl lipid A (MPL®) and L-tyrosine, requires a preseasonal course of only four injections to be effective in the treatment of seasonal allergic rhinitis.

▲ In patients with seasonal allergic rhinitis and/or allergic asthma, a four-injection vaccination course with either the grass pollen or tree pollen allergy vaccine significantly reduced skin prick sensitivity reactions, significantly elevated allergen-specific IgG levels and significantly reduced the seasonally induced boost of IgE.

▲ Preseasonal vaccination of adult patients with either grass pollen or tree pollen allergy vaccine significantly reduced the median combined symptom/medication score compared with placebo.

▲ Similarly, preseasonal vaccination of children and adolescents with allergies to grass pollen or tree pollen significantly reduced the global symptom and medication use scores compared with the previous pollen season.

▲ Postmarketing surveillance indicated that after a course of vaccination, 82% of patients experienced reduced symptoms and 62% reduced their rescue medication use compared with the previous season.

▲ The allergy vaccine was generally well tolerated. Local reactions, mainly injection-site redness and swelling, were more common than systemic reactions. There were no serious adverse events.

Features and properties of ultra-short-course seasonal allergy vaccine (Pollinex® Quattro)	
Indication	
Allergen-specific seasonal allergy (seasonal allergic rhinitis, allergic conjunctivitis or allergic asthma)	
Mechanism of action	
Allergy vaccine	
Vaccine components	
Glutaraldehyde-modified allergen extract (allergoid)	
Allergoids in separate formulations include grass pollen (cultivated rye plus 12 temperate-zone grasses: meadow, meadow foxtail, meadow fescue, crested dogstail, cocksfoot, rye, sweet vernal, bent, timothy, soft brome, false oat and Yorkshire fog), tree pollen (birch or birch/alder/hazel), mugwort, plantain, fat hen, parietaria, olive and ragweed	
3-Deacylated monophosphoryl lipid A (MPL®) adjuvant (50 μg/mL)	
L-tyrosine (2% w/v) adjuvant and depot base for adsorbed allergoid and MPL®	
Dosage and administration	
Dosage in clinical trials	1.0 mL containing 300, 800 or 2000 standardised units [SU] of allergoid
Route of administration	Subcutaneous injection
Frequency of administration	Three doses of increasing strength vaccine at 1- to 2-week intervals (300, 800 and 2000 SU) and a fourth dose (2000SU) after an additional 1–4 weeks
Adverse events	
Most common	Local (redness and swelling, itching and pain) and systemic (e.g. rhinoconjunctivitis)

Type I allergic disease to common aeroallergens, such as pollen, mold spores and dust mite residue, is highly prevalent, affecting up to 10–20% of the population in many developed countries.[1,2] Seasonal allergic rhinitis (hayfever) is most commonly caused by allergy to pollen from trees, grasses or weeds, while perennial allergic rhinitis is most commonly associated with allergy to dust mite residue, mould spores or animal dander.[1] While the symptoms of allergic rhinitis (frequently including ocular symptoms) are often mild, they may progress over time and lead to more serious conditions, such as asthma.[3,4]

Allergy vaccination (i.e. immunotherapy with gradually increasing quantities of specific allergen in order to reduce symptoms to that allergen upon subsequent exposure) is effective in the treatment of allergic rhinitis or conjunctivitis and allergic asthma.[1,5,6] Unlike standard pharmacotherapy with agents such as antihistamines, bronchodilators, corticosteroids, cromones or anticholinergics, allergy vaccination modifies the underlying disease process,[5,6] rather than just treating the symptoms, and appears to reduce the progression from seasonal allergic rhinitis to asthma.[4]

Treatment guidelines for seasonal allergic rhinitis recommend a stepped-care approach involving allergen avoidance, pharmacotherapy and allergy vaccination.[1,3] The recommended therapies are generally oral or topical nasal/ocular second-generation antihistamines or topical cromones for mild symptoms, and a topical nasal corticosteroid for moderate symptoms or mild symptoms not controlled with antihistamines. More severe symptoms should be treated with a combination of antihistamines and nasal corticosteroids. Additional symptomatic medications should be added as required. Allergy vaccination is currently recommended for consideration in patients with severe symptoms that are difficult to control.[1,3]

The mechanisms of allergy vaccination are becoming better understood, although they are clearly complex and interactive.[7] Cytokine evidence indicates a shift from a more T-helper type 2 (T_h2)-like to a more T_h type 1 (T_h1)-like population of allergen-specific T cells; [5,6] T_h2 are associated with elevated interleukin (IL)-4 and IL-5, while T_h1 are associated with elevated interferon-γ (IFNγ). There is a down-regulation in the production of allergen-specific IgE and an elevation in the IgG response, particularly IgG4. CD4+CD25+ allergen-specific regulatory T cells (T_{reg}) are induced and can down-regulate the T_h2 and eventually the T_h1 responses.[8] The cytokines IL-10 and transforming growth factor-β from T_{reg} are associated with the production of allergen-specific IgG4 and IgA antibodies, respectively.[8] These noninflammatory, so-called blocking antibodies may act by preventing the interaction between allergen and mast cell-bound IgE.

Although allergy vaccination has been used for nearly a century, it is only recently that mechanisms have been sufficiently understood to permit rational design to lead to more effective and safer products and more acceptable injection schedules.[5,6] The safety of the treatment has always been of some concern, particularly with traditional long courses of treatment with unmodified extracts. The introduction of depot adjuvants and chemically modified allergens (allergoids), which have a much reduced reactivity with IgE antibodies, has led to safer and shorter injection regimens.[6,9] In addition, the quality control of the standardised extracts now used has reduced further the likelihood of any severe reaction.[9,10] The appropriate use of allergy vaccination by trained physicians has also contributed to reduced reports of serious reactions.[5]

A novel seasonal allergy vaccine (Pollinex® Quattro)[1] containing a new adjuvant, 3-deacylated monophosphoryl lipid A (MPL®), has been shown to require a preseasonal course of only four injections to be effective in treating seasonal allergies. The MPL® adjuvant derived from the lipopolysaccharide of *Salmonella minnesota* R595 induces a T_h1-like immune response, and promotes the induction of allergen-specific IgG antibodies.[11,12] The ultra-short-course allergy vaccine is produced with different allergens to treat different

1 The use of trade names is for product identification purposes only and does not imply endorsement.

specific allergies, for example grass pollen allergy, tree pollen allergy or allergy to pollen from weeds, such as ragweed or mugwort. The allergen extract in the vaccine is treated with glutaraldehyde to reduce allergenicity without reducing the immunogenicity of the resultant allergoid. The vaccine contains the natural amino acid L-tyrosine as a depot base, to adsorb both the allergoid and MPL®, as well as acting as an adjuvant.[9,13]

This review summarises the published data on the clinical efficacy and tolerability of the ultra-short-course allergy vaccine, which focus on the grass pollen and tree pollen vaccines. In addition, immunological changes associated with clinical benefit are described.

1. Immunological Changes

The immunological changes associated with the use of the ultra-short-course seasonal allergy vaccine in humans have been assessed in a number of studies predominantly involving the grass pollen and tree pollen formulations.

- Allergy vaccination induced a significant allergen-specific IgG antibody response. In the clinical trials of the grass pollen and three-tree pollen allergy vaccines (see section 2), serum levels of pollen-specific IgG were significantly ($p < 0.01$) higher in actively treated patients than in placebo recipients 2 weeks after therapy, in the middle of the assessment period and at the end of the grass pollen season, but not at baseline before treatment.[14,15]
- The allergy vaccine also suppressed the seasonal rise in allergen-specific IgE. At the evaluation point in the middle of the pollen season, grass-pollen-allergen-specific IgE levels in placebo recipients were significantly ($p = 0.002$) elevated compared with the active vaccine treatment group. The IgG/IgE ratio was significantly ($p < 0.01$) higher for the active treatment group versus placebo at all time points after treatment.[14]
- Allergy vaccination appeared to reduce the level of IgE-related B-cell activation. Treatment with a four-injection course of three-tree pollen allergy vaccine in patients with tree-pollen-specific allergic seasonal rhinoconjunctivitis decreased the expression of CD23, CD54 and HLA-DR-II on patients' peripheral blood B cells (CD19+) compared with placebo prior to the third injection and after the end of therapy.[16] These markers are considered to be involved in the regulation of IgE. The levels of these surface markers were increased after the pollen season in both the active treatment and placebo groups. Expression of the B-cell activation marker CD86 was decreased during treatment in both the active treatment and placebo groups. However, the clinical relevance of the reduced B-cell activation observed during immunotherapy is not known.[16]
- The ultra-short-course allergy vaccine induced allergen-specific IgG4 and IgG1 antibody responses. In a subset of patients from the grass pollen vaccine efficacy trial who were tested for antibodies directed against timothy grass pollen allergens, active treatment ($n = 11$), but not placebo ($n = 9$), was associated with a strong induction of IgG1 (208% increase vs 46% for placebo; $p < 0.001$) and/or IgG4 (428% vs 51%; $p < 0.01$) directed predominantly against the rPhl p 5 recombinant timothy grass pollen allergen.[12]
- The IgG antibody response induced by allergy vaccination appeared to consist of allergen-specific blocking antibodies. Preincubation of a timothy grass pollen allergen extract (rPhl p 5) with sera from actively treated patients reduced the subsequent induction by the allergen preparation of histamine release from basophils derived from an allergic individual.[12] Allergen preincubated with patients' sera obtained at baseline induced the release of 30–50% of total basophil histamine, while allergen preincubated with patients' sera obtained after active treatment induced the release of 0–5% of basophil histamine. Preincubation of allergen with sera from placebo-treated patients had no effect on basophil histamine release.[12]
- IgE antibody, which displayed a blunted increase in the active treatment group compared with placebo at the start of the pollen season in this study, was also mainly directed against the timothy grass rPhl p 5 allergen.[12] Induction of an IgM response to timothy grass allergens was observed in 5 of the 11

actively treated patients, while 4 patients showed an IgG2 antibody response.[12]

- In children and adolescents vaccinated preseasonally (see section 2), IgE levels increased only slightly during the pollen season, whereas there were significant increases in the levels of grass- ($p < 0.001$) or tree-pollen-reactive IgG ($p = 0.003$) after treatment, which were sustained throughout the season.[17]
- Allergy vaccination increased the release of the T_h1 cytokine IFNγ and decreased the release of the T_h2 cytokines IL-4 and IL-5 from T cells stimulated by allergen challenge *in vitro*. In a randomised, double-blind, placebo-controlled study, preseasonal vaccination with birch pollen allergy vaccine ($n = 9$) significantly ($p < 0.001$) elevated IFNγ production *in vitro* compared with placebo ($n = 5$) at the intraseasonal and postseasonal assessments.[18]
- The increases in IL-4 and IL-5 production *in vitro* seen in the placebo group during the pollen season were completely inhibited in the active immunotherapy group at the intraseasonal ($p < 0.01$ for both IL-4 and IL-5) and postseasonal (IL-4, $p < 0.05$; IL-5, $p < 0.001$) assessments.[18]
- Preseasonal vaccination with grass or mugwort allergy vaccine ($n = 21$) was shown to result in enhanced *in vitro* allergoid-induced lymphocyte stimulation in 17 patients prior to the fourth injection and 2 weeks after the end of therapy compared with pretreatment levels or with untreated allergy patients.[19] At 5 months after therapy, the mean allergoid-induced lymphocyte stimulation index had decreased to pretreatment levels. The increased lymphocyte stimulation indices were greatest when challenged with allergoid in the presence of MPL® adjuvant. MPL® was shown not to produce any nonspecific effects.[19]

2. Therapeutic Efficacy

The therapeutic efficacy of the allergy vaccine in the treatment of seasonal allergic rhinitis and/or allergic asthma has been assessed in two fully published randomised, double-blind, placebo-controlled, multicentre studies in adults: one evaluating vaccine containing grass pollen allergoids (cultivated rye plus 12 temperate-zone grasses)[14] and the other evaluating vaccine containing tree pollen allergoids (birch, alder, and hazel).[15] The efficacy of the allergy vaccine containing either grass pollen or three-tree pollen allergoid has also been assessed in adolescents and children (aged 6–17 years) in a noncomparative, multicentre study.[17] In addition, the efficacy of the allergy vaccine in the management of various pollen allergies (grasses, birch, birch/alder/hazel, plantain, or mugwort) has been assessed at 1[20] and 3 years[10] in a postmarketing surveillance study.

In prospective studies, patients with seasonal allergic rhinitis[14,15,17] and/or allergic asthma[15,17] and a positive skin-prick test (wheal >3mm diameter) as well as a positive radioallergosorbent (or similar) test [score class 2 or above] to the relevant pollen were treated with a four-injection course of vaccine finishing 2–4 weeks prior to the start of the main pollen season. Patients recorded symptoms and medication use in daily diaries during 1 month of the main pollen season.[14,15,17]

In all studies, the vaccination schedule consisted of three subcutaneous 1mL injections of increasing strength vaccine (300, 800 and 2000 standardised units [SU]/mL) at weekly intervals, followed by a fourth, full-strength, injection (2000SU) after an additional 1–4 weeks.[14,15,17,20] For the grass pollen vaccine, 2000SU was approximately equivalent to 24μg of group 1 grass pollen allergen.[14]

The primary efficacy parameter in both clinical trials in adults was the median combined symptom and medication score derived from patient diary cards. Symptoms from the eye, nose and lung were scored on a 4-point scale (0 = none, 3 = severe) and rescue medication use (e.g. short-acting antihistamines, bronchodilators, topical corticosteroids and cromones) was scored by allocating one point per organ treated.[14,15] In the study in children and adolescents, efficacy parameters consisted of patient-rated, separate symptom and medication global scores using 12- and 4-point scales, respectively.[17]

- In the grass pollen vaccine trial in adults, the median daily combined symptom/medication score was significantly ($p = 0.013$) lower in patients re-

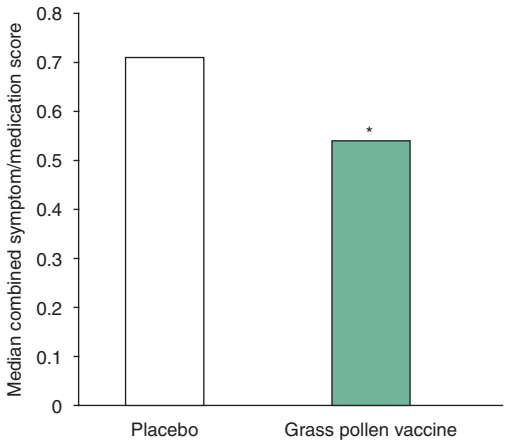

Fig. 1. Therapeutic efficacy of ultra-short-course allergy vaccine in patients with grass-pollen-specific seasonal allergic rhinitis. Median daily combined symptom/medication scores (primary endpoint) over a 1-month period during the main grass pollen season in patients who were treated preseasonally with a four-injection course of grass pollen (cultivated rye plus 12 temperate-zone grasses) allergy vaccine (n = 74) or placebo (n = 50) in a randomised, double-blind, placebo-controlled, multicentre trial.[14] * p = 0.013 vs placebo.

ceiving grass pollen allergy vaccine (n = 74) than in those receiving placebo (n = 50) [figure 1].[14] Symptom scores were significantly (p = 0.003) lower in vaccine recipients than in placebo recipients, but medication use was similar between treatment groups. Skin-prick sensitivity (total wheal areas) was significantly (p = 0.04) reduced from baseline in the active treatment group compared with placebo.[14]

- In the three-tree pollen vaccine trial in adults, the median combined symptom/medication score in patients treated with active three-tree pollen allergy vaccine (39 evaluable patients) was significantly (p = 0.028) lower than that in placebo (n = 19) recipients (figure 2).[15] After therapy, skin-prick sensitivity was significantly (p < 0.01) reduced from baseline in active vaccine recipients (n = 48), but not in placebo recipients (n = 26).[15]

- Preseasonal open-label treatment with a four-injection course of allergy vaccine in children and adolescents with seasonal allergies to grass pollen (n = 26) or tree pollen (n = 64) significantly (p < 0.01) improved the global symptom and medication use scores compared with the previous pollen season (figure 3).[17] Skin-prick test reactivity was significantly reduced after vaccination with the grass pollen (p = 0.035) or tree pollen (p < 0.001) allergy vaccines.[17]

- In the 1-year postmarketing surveillance assessment, treatment with allergy vaccine (n = 1736) reduced medication use compared with the previous pollen season in 62.2% of patients (p = 0.001), whereas medication use was increased in only 5.9% of patients.[20] Similarly, 82.4% of patients recorded a reduction in symptoms (relative to the previous season) compared with 2.3% of patients recording an increase in symptoms.[20] The timing of vaccination (early or late before the pollen season) did not affect efficacy as assessed by consumption of antiallergy medication.[20]

- In patients treated with allergy vaccine for three successive years, the proportion of patients not requiring additional antiallergic medication increased from 2.5% before therapy to 16%, 27% and 32% at 1, 2 and 3 years, respectively.[10] After the first year, 88% of patients showed an improvement in their allergy symptoms, while 94% showed improvement after 2 and 3 years of treatment.[10]

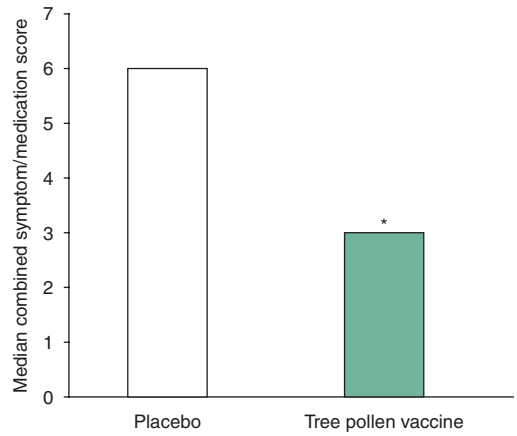

Fig. 2. Therapeutic efficacy of ultra-short-course allergy vaccine in patients with tree-pollen-specific seasonal allergic rhinitis and/or allergic asthma. Median daily combined symptom/medication scores over a 1-month period during the main tree pollen season in patients who were treated preseasonally with a four-injection course of three-tree pollen (birch/alder/hazel) allergy vaccine (n = 39) or placebo (n = 19) in a randomised, double-blind, placebo-controlled, multicentre trial.[15] * p = 0.028 vs placebo.

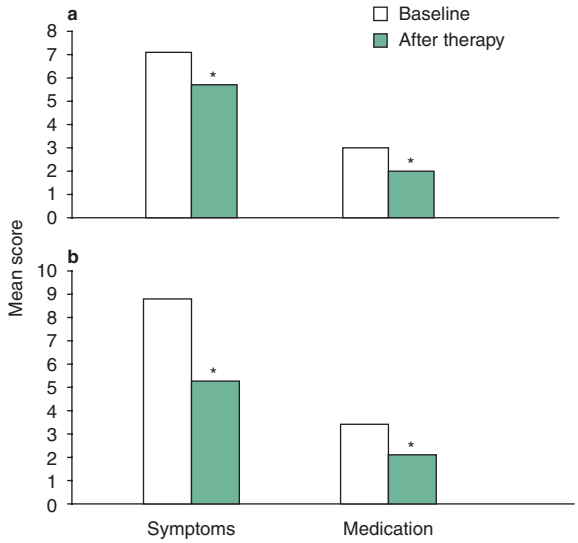

Fig. 3. Therapeutic efficacy of ultra-short-course allergy vaccine in children and adolescents with seasonal allergies to grass pollen (n = 26) or tree pollen (n = 64). Mean total symptom (eyes, nose and lung) and medication use scores during the pollen season after treatment, relative to scores for the previous season (baseline). Results from a noncomparative, multicentre study in which patients aged 6–17 years received a four-injection course of allergy vaccine containing (**a**) grass or (**b**) tree (birch/alder/hazel) pollen allergoid.[17] * $p < 0.01$ vs baseline.

3. Tolerability

- In clinical trials (see section 2 for design details), the grass pollen and tree pollen allergy vaccines were generally well tolerated,[14,15] confirming the results of preclinical toxicology and tolerability studies on the grass pollen vaccine which demonstrated that the only notable adverse event was a local inflammatory/immunostimulatory reaction at the injection site.[9]
- Systemic adverse events to the allergy vaccines (grass or tree pollen) in clinical trials occurred with similar incidences in the active treatment and placebo groups and consisted predominantly of mild rhinoconjunctivitis.[14,15,17] There were no serious or severe adverse events and no anaphylactic reactions.[14,15]
- In the grass pollen allergy vaccine trial in adults, the incidence of injection-site redness and swelling in active vaccine recipients was significantly higher than in placebo recipients (75% vs 25% of patients; $p < 0.01$).[14] Itching was similarly more frequent in the active treatment group than in the placebo group (23% vs 3%; $p < 0.01$). The between-group difference in the incidence of injection-site pain in adults (23% vs 13%) did not reach statistical significance.[14]
- In the tree pollen allergy vaccine trial in adults, the incidence of redness and swelling with a diameter of 5–10cm was 19.2% of injections in the active treatment group compared with 5.5% in the placebo group.[15]
- In children and adolescents, local reactions occurred after 34% (grass) and 23% (tree) of injections.[17] Itching was more prevalent with the grass pollen vaccine (10% vs 3%) and pain was more prevalent with the tree pollen vaccine (19% vs 4%).[17]
- In the 1-year postmarketing surveillance assessment involving 1736 patients (8512 injections), local reactions were observed in 16.9% of patients and systemic reactions in 1.6% of patients.[20] Severe reactions occurred in 14 patients, but were not of clinical concern. There were no instances of anaphylactic shock. Overall, 89.5% of patients rated their medication as good or very good.[20]

• Preliminary data from 3 years of postmarketing surveillance in 3114 patients suggest that the incidences of both local and systemic adverse events decrease over time.[10] For instance, local reactions occurred in 8.1% of patients (n = 2235) in the first year, but in only 2.7% of patients (n = 324) in the third year. During 3 years of monitoring (21 428 injections), there were no serious systemic adverse events and no instances of anaphylactic reactions.[10]

4. Dosage and Administration

Formulations of this seasonal allergy vaccine contain MPL® 50 μg/mL, L-tyrosine 2% w/v and specific glutaraldehyde-modified allergens. Vaccination may be performed at any time prior to the relevant pollen season each year. The vaccine should be administered annually for at least the first 3 years, since allergy vaccination has demonstrated persistent long-term effects after 3–4 years of treatment.[21]

The vaccination schedule used in clinical trials of the allergy vaccine in patients with seasonal allergic rhinitis consisted of three 1mL injections, at weekly intervals, of increasing strength vaccine (300, 800 and 2000 SU/mL) followed by a fourth, full-strength, dose (2000SU) after 1–4 weeks.[14,15,17,20] Injections were given subcutaneously in the upper arm.

The cumulative dose from the grass pollen vaccination course was approximately 61μg of group 1 grass pollen allergen, since 2000 SU was approximately equivalent to 24μg of group 1 grass pollen allergen.[14]

5. Ultra-Short-Course Seasonal Allergy Vaccine (Pollinex® Quattro): Current Status

The ultra-short-course seasonal allergy vaccine, containing a range of different allergoids included under the trade name Pollinex® Quattro, is available on a named-patient basis in Austria, Germany, Greece, Italy, Portugal, Spain, and the UK.

The allergy vaccine has shown clinical efficacy in significantly reducing the symptoms of grass and tree pollen allergies during the peak allergy season after a four-injection vaccination course lasting only 3 weeks prior to the start of the pollen season.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

References

1. van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. Allergy 2000 Feb; 55 (2): 116-34
2. Schädlich PK, Brecht JG. Economic evaluation of specific immunotherapy versus symptomatic treatment of allergic rhinitis in Germany. Pharmacoeconomics 2000 Jan; 17 (1): 37-52
3. Plaut M, Valentine MD. Allergic rhinitis. N Engl J Med 2005 Nov 3; 353 (18): 1934-44
4. Möller C, Dreborg S, Ferdousi HA, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002 Feb; 109 (2): 251-6
5. Hellman L, Carlsson M. Allergy vaccines: a review of developments. Clin Immunother 1996 Aug; 6: 130-42
6. Wheeler AW, Woroniecki SR. Allergy vaccines: new approaches to an old concept. Expert Opin Biol Ther 2004; 4 (9): 1473-81
7. Till SJ, Francis JN, Nouri-Aria K, et al. Mechanisms of immunotherapy. J Allergy Clin Immunol 2004 Jun; 113 (6): 1025-34
8. Akdis M, Blaser K, Akdis CA. T regulatory cells in allergy: novel concepts in the pathogenesis, prevention, and treatment of allergic diseases. J Allergy Clin Immunol 2005 Nov; 116 (5): 961-8
9. Baldrick P, Richardson D, Wheeler AW, et al. Safety evaluation of a new allergy vaccine containing the adjuvant monophosphoryl lipid A (MPL®) for the treatment of grass pollen allergy. J Appl Toxicol 2004 Aug; 24 (4): 261-8
10. Clay M, Urban E. Specific immunotherapy using pollen allergoids adjuvanted with monophosphoryl lipid A over a three year period shows good efficacy and increased tolerability [abstract no. 4]. Clin Exp Allergy 2005; 35: 1411. Plus poster presented at the Annual Conference of the British Society for Allergy and Clinical Immunology; 2005 Jul 18–21; Loughborough, UK
11. Wheeler AW, Marshall JS, Ulrich JT. A Th1-inducing adjuvant, MPL®, enhances antibody profiles in experimental animals suggesting it has the potential to improve the efficacy of allergy vaccines. Int Arch Allergy Immunol 2001 Oct; 126 (2): 135-9
12. Mothes N, Heinzkill M, Drachenberg KJ, et al. Allergen-specific immunotherapy with a monophosphoryl lipid A-adjuvanted vaccine: reduced seasonally boosted immunoglobulin E production and inhibition of basophil histamine release by ther-

apy-induced blocking antibodies. Clin Exp Allergy 2003 Sep; 33 (9): 1198-208

13. Baldrick P, Richardson D, Wheeler AW. Review of L-tyrosine confirming its safe human use as an adjuvant. J Appl Toxicol 2002; 22: 333-44

14. Drachenberg KJ, Wheeler AW, Stuebner P, et al. A well-tolerated grass pollen-specific allergy vaccine containing a novel adjuvant, monophosphoryl lipid A, reduces allergic symptoms after only four preseasonal injections. Allergy 2001 Jun; 56: 498-505

15. Drachenberg KJ, Heinzkill M, Urban E. Short-term immunotherapy with tree pollen allergoids and the adjuvant monophosphoryl lipid A: results from a multicentre, placebo-controlled, randomised, double-blind study [in German]. Allergologie 2002; 25 (9): 466-74

16. Röver AC, Reimann S, Zuberbier T, et al. Immunophenotypic characterization of peripheral B cells during short-term immunotherapy with tree pollen allergoid and the immunoadjuvant monophosphoryl lipid A. J Invest Allergol Clin Immunol 2002; 12 (4): 227-34

17. Drachenberg KJ, Heinzkill M, Urban E, et al. Efficacy and tolerability of short-term specific immunotherapy with pollen allergoids adjuvanted by monophosphoryl lipid A (MPL®) for children and adolescents. Allergol et Immunopathol 2003; 31 (5): 270-7

18. Stuck BA, Schneider-Gene S, Schäfer D, et al. Short-term preseasonal immunotherapy with birch pollen allergoid plus monophosphoryl lipid A (MPL): influence of cytokine production of peripheral T cells in patients with allergic rhinitis. Allergy Clin Immunol Int - J World Allergy Org 2004; 16 (2): 60-4

19. von Baehr V, Hermes A, von Baehr R, et al. Allergoid-specific T-cell reaction as a measure of the immunological response to specific immunotherapy (SIT) with a Th1-adjuvanted allergy vaccine. J Investig Allergol Clin Immunol 2005; 15 (4): 234-41

20. Drachenberg KJ, Pröll S, Urban E, et al. Short-term immunotherapy using an allergy vaccine adjuvanted with monophosphoryl lipid A: a post-marketing surveillance study. Int Rev Allergol Clin Immunol 2002; 8 (4): 219-23

21. Durham SR, Walker SM, Varga EM, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 1999 Aug 12; 341 (7): 468-75

Correspondence: *Paul L. McCormack,* Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz