

Accelerated Up-Dosing of Subcutaneous Immunotherapy with a Registered Allergoid Grass Pollen Preparation

Oliver Pfaar^a Esther van Twuijver^c Heike Hecker^b Johan Diderik Boot^c
Ronald van Ree^d Ludger Klimek^a

^aCenter for Rhinology and Allergology Wiesbaden, Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Mannheim, and ^bHAL Allergie GmbH, Düsseldorf, Germany; ^cHAL Allergy B.V., Leiden, and

^dDepartment of Experimental Immunology and Department of Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Key Words

(Allergen)-specific subcutaneous immunotherapy • Allergic rhinitis • Cluster-specific immunotherapy • Rush-specific immunotherapy • Safety

Abstract

Background: Climatic changes causing early pollen flight and new allergens prolonging the pollen season render up-dosing of allergen-specific subcutaneous immunotherapy (SCIT) outside the pollen season considerably more difficult. In addition, for patients with multiple pollen allergies, patients coming near the beginning of pollen season, and patients who wish to up-dose faster, an accelerated induction regimen would be helpful. **Methods:** In an open, randomized, parallel group, multicenter safety trial, an accelerated up-dosing regimen (0.1–0.3–0.5 ml in weekly intervals) was compared to conventional up-dosing (0.05–0.1–0.2–0.3–0.4–0.5 ml in weekly intervals) with an allergoid grass pollen SCIT preparation. After up-dosing, the maintenance dose was given in monthly intervals. **Results:** A total of 146 adult patients with rhinitis or rhinoconjunctivitis with or without mild asthma (FEV₁ >70%) due to grass pollen were randomized to either the conventional registered up-dosing or an accelerated regimen. In both groups (accelerated regimen, n = 69; conventional regimen, n = 75), a high proportion of

patients (92.75 and 92.0%, respectively) successfully reached the maintenance dose without safety concerns. Furthermore, significant increases in specific IgG and IgG₄ after 4 months of treatment were observed in both groups. **Conclusion:** The accelerated SCIT regimen was found to be as safe as the conventional regimen and might be used to up-dose patients within 2 weeks. Moreover, the immunological effects of both up-dosing regimens were comparable.

Copyright © 2012 S. Karger AG, Basel

Introduction

Subcutaneous immunotherapy (SCIT) currently represents the standard immunotherapy modality; however, it carries the discomfort associated with injections, requires frequent physician visits, and may be limited by adverse reactions [1, 2]. These issues have partly been addressed by modifying allergenic components in allergen extracts, allowing the administration of higher doses without increasing the incidence of adverse reactions [3,

The results of this study were presented in part as poster presentations at the XXXth Congress of the European Academy of Allergy and Clinical Immunology (EAACI) in Istanbul, Turkey, in June 2011.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2012 S. Karger AG, Basel
1018–2438/13/1604–0420\$38.00/0

Accessible online at:
www.karger.com/iaa

Correspondence to: PD Dr. Oliver Pfaar
Center for Rhinology and Allergology Wiesbaden
Department of Otorhinolaryngology, Head and Neck Surgery
University Hospital Mannheim, An den Quellen 10, DE–65183 Wiesbaden (Germany)
E-Mail oliver.pfaar@allergiezentrum.org

4]. In addition, with the modified extract under evaluation, the maintenance dose is reached in a shorter time period compared to nonmodified extracts, i.e. 5 weeks instead of 15 weeks. It is recommended to start and finish the up-dosing of SCIT before the start of the pollen season [5]. This has become increasingly difficult due to climatic changes causing early pollen flight and new allergens prolonging the pollen season. For patients with multiple pollen allergies, or patients wishing to start just before the pollen season or to up-dose faster, further reduction of the time to reach the maintenance dose is essential. Accelerated schedules of allergen-specific immunotherapy such as 'rush' or 'cluster' protocols aim to achieve the maintenance dose of immunotherapy more rapidly than conventional schedules. The safety of accelerated protocols has been shown in previous studies evaluating SCIT [6–12]. In addition, accelerated up-dosing may induce clinical and immunologic improvements sooner [10–12].

The current trial with an allergoid grass pollen SCIT evaluated the safety and immunological effects of an accelerated regimen (maximum dose in 2 weeks, 3 injections) compared to the registered conventional regimen (maximum dose in 5 weeks, 6 injections).

Materials and Methods

Patients

In total, 156 patients were screened and 146 patients (75 females and 71 males, mean age 34 ± 12 years; range 18–70 years) with rhinitis or rhinoconjunctivitis and with or without mild asthma ($FEV_1 > 70\%$) for at least 2 years related to grass pollen were recruited. A positive skin prick test, specific IgE > 0.7 U/ml, or a positive nasal provocation test for grass pollen was required. Written informed consent was obtained from all subjects. The study protocol was approved by the relevant Ethics Committees.

Study Design

An open, randomized, parallel group, multicenter, phase IV study was conducted between February and August 2010, in 11 study sites in Germany. One hundred forty-six patients were randomized to the accelerated or conventional regimen (1:1) with grass pollen SCIT. A standardized suspension (20,000 AUM/ml) of glutaraldehyde-modified extract from 10 grass pollens adsorbed onto aluminiumhydroxide was used for SCIT (PURETHAL® Grasses; HAL Allergy B.V., Leiden, The Netherlands, containing 26.3 µg/ml Phl p 5, measured by ELISA in the extract prior to modification and adsorption on aluminium hydroxide). The accelerated regimen consisted of 3 weekly doses of 0.1, 0.3, and 0.5 ml, followed by maintenance treatment of 0.5 ml, 3 times in monthly intervals. The conventional regimen consisted of 6 weekly doses of 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 ml, followed by maintenance treatment of 3 times 0.5 ml in 14-day intervals with a final injection after 4 weeks. If a local reaction with a wheal > 5 cm or a grade I systemic reaction occurred [5], the next injection

would be the same as the previous dosage. If a wheal > 12 cm occurred, the next injection would be one dose lower than the previous. In case of a systemic reaction $> \text{grade I}$ the patient would be regarded as not having successfully reached the maintenance dose. Patients were not allowed to use antihistamines 48 h before every injection.

The primary outcome parameter was the proportion of patients successfully reaching the maintenance dose, provided that no treatment-related systemic reactions $> \text{grade I}$ (within 24 h) occurred and/or not more than 2 additional injections were required. Therefore, early and late local and systemic reactions were recorded. Throughout the trial all adverse reactions were recorded. Other safety parameters (routine laboratory parameters, vital signs, ECG, physical examination) were measured at screening and at the end of treatment. As a secondary outcome parameter serum-specific immunoglobulins were determined before and at the end of treatment.

Results

The intention-to-treat (ITT) population consisted of 144 patients (accelerated, $n = 69$; conventional, $n = 75$), and the per protocol (PP) population comprised 97 patients (accelerated, $n = 47$; conventional, $n = 50$) with similar baseline characteristics. The proportion of patients successfully reaching the maintenance dose was 92.75 versus 92.00% in the ITT population (table 1). The difference in proportion is below the non-inferiority margin of 15%. A mean of 3.3 injections in the accelerated regimen and 6.1 in the conventional regimen was required to reach the maintenance dose.

The study was performed during the birch pollen season and a co-allergy at the time of up-dosing may increase the adverse event rate. Therefore, a subgroup analysis of patients with a birch co-allergy was performed. In the accelerated group 40.6% and in the conventional group 44.0% had a co-allergy to birch pollen. In the accelerated group 92.9% and in the conventional 97.0% of patients with birch co-allergy successfully reached the maintenance dose compared to 92.7 and 88.1%, respectively, in patients without birch co-allergy (table 1; fig. 1). No statistical differences were observed.

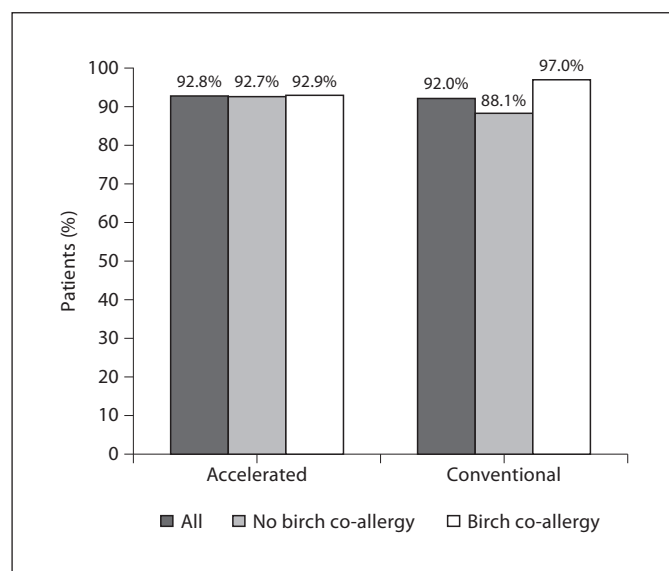
The occurrence of local and systemic reactions did not differ between the accelerated and conventional regimens; no systemic reactions of grade II or higher were observed (table 2). In total, 237 treatment-emergent adverse events (TEAEs) were reported by 78 subjects (accelerated, $n = 38$; conventional, $n = 40$), of which 164 (accelerated, $n = 86$; conventional, $n = 78$) were considered medication related. Both the number of subjects experiencing TEAEs and the frequency and nature of TEAEs were similar for both treatment regimens. Safety param-

Table 1. Proportion of patients successfully reaching the maintenance dose

Regimen	ITT		PP	
	patients reaching the maintenance dose (95% CI), %	difference (95% CI)	patients reaching the maintenance dose (95% CI), %	difference (95% CI)
All				
Accelerated	92.75 (83.89 to 97.61)	0.75	100.00 (92.45 to 100.00)	2.00
Conventional	92.00 (83.40 to 97.01)	(-7.91 to 100.00)	98.00 (89.35 to 99.95)	(-1.88 to 100.00)
No birch co-allergy				
Accelerated	92.70 (80.08 to 98.46)	4.60	100.00 (87.23 to 100.00)	3.70
Conventional	88.10 (74.37 to 96.02)	(-8.04 to 100.00)	96.30 (81.03 to 99.91)	(-3.42 to 100.00)
Birch co-allergy				
Accelerated	92.90 (76.50 to 99.12)	-4.11	100.00 (83.16 to 100.00)	No difference
Conventional	97.00 (84.24 to 99.92)	(-15.30 to 100.00)	100.00 (85.18 to 100.00)	

Table 2. Number and percentage of patients with local and systemic reactions

Reaction		Accelerated (n = 69)	Conventional (n = 75)
Local reactions	No reactions	30 (43.5%)	33 (44.0%)
	0–5 cm	19 (27.5%)	24 (32.0%)
	>5 cm	20 (29.0%)	18 (24.0%)
Systemic reactions	No reactions	62 (89.9%)	68 (90.7%)
	Grade 1	7 (10.1%)	7 (9.3%)

**Fig. 1.** Percentage of patients successfully reaching the maintenance dose.

eters like routine laboratory parameters, vital signs, ECG, and physical examination revealed no abnormalities related to the study medication.

IgE, IgG, and IgG₄ specific for phleum and phl p 5b were determined per patient before and after treatment for both treatment groups (table 3). Both treatment regimens resulted in an increase in specific immunoglobulin levels; particularly IgG and IgG₄ levels specific for phleum and phl p 5b increased ranging from 9 to 21 times in both treatment groups. No statistically significant differences were detected between the accelerated and conventional regimens.

Discussion

The safety of a grass pollen SCIT in an accelerated regimen was compared to the conventional regimen in patients with rhinitis/rhinoconjunctivitis due to grass pollen. The proportion of patients successfully reaching the maintenance dose was chosen as a primary outcome measure representing both the safety and the practicality of the preparation. Non-inferiority of the accelerated compared to the conventional regimen was demonstrated, indicating that up-dosing for this grass pollen allergoid can be reduced from 5 to 2 weeks.

This acceleration of up-dosing is relevant since it limits the number of weekly visits to the doctor, which may positively affect the compliance of patients. The advantage of this accelerated scheme versus the more traditional 'rush' or 'cluster' protocols is that it does not require multiple injections per day resulting in a length-

Table 3. Specific immunoglobulins before and after treatment

Parameter	Accelerated			Conventional		
	pre-treatment	post-treatment	post/pre ratio	pre-treatment	post-treatment	post/pre ratio
IgE phl, kUA/l	12 ± 16	20 ± 24	1.7	17 ± 24	22 ± 28	1.3
IgE phl p 5b, kUA/l	7 ± 12	14 ± 22	2.0	10 ± 19	15 ± 24	1.5
IgG phl p 5b, µg/l	471 ± 385	1,290 ± 1,322	2.7	603 ± 658	2,045 ± 2,159	3.4
IgG ₄ phl, µg/l	108 ± 158	1,004 ± 2,033	9.3	192 ± 356	1,684 ± 3,601	8.8
IgG ₄ phl p 5b, µg/l	37 ± 79	805 ± 1,789	21.8	112 ± 334	1,355 ± 2,795	12.1

Pre- and post-treatment values are presented as means ± standard deviation. phl = Phleum.

ened stay in the hospital. In addition, international guidelines recommend up-dosing of SCIT before the start of the pollen season. This has become increasingly difficult due to early pollen flight and new allergens prolonging the pollen season (presumably caused by climatic changes) resulting in a narrow time interval for up-dosing [13, 14].

In daily practice patients often have a co-allergy to birch (42.4% of the patients in the current study). Up-dosing with grass pollen SCIT is often initiated during the birch pollen season, a potential risk for increased adverse reactions. However, in patients with birch co-allergy 92.9% reached the maintenance dose in the accelerated regimen and 97.0% reached it in the conventional regimen. This suggests that treatment with an allergoid grass pollen SCIT in patients with a birch co-allergy during the birch pollen season is feasible without any major problems.

Evaluation of the immunologic response showed that the accelerated treatment regimen induced increases in IgG and IgG₄ levels specific for phleum and phl p 5b comparable to the conventional regimen, which is in accordance with previously published data on accelerated regimens with unmodified extracts [11, 15]. However, further investigations of possible long-term differences in clinical and immunological effects of accelerated and conventional schedules with modified extracts ('allergoids') in a direct head-to-head comparison are warranted.

A potential risk of accelerated immunotherapy is an increase in adverse reactions, particularly systemic ones [16]. In our study, the pattern and intensity of adverse reactions was similar for the accelerated and conventional treatments; mild systemic reactions were seen in only 10.1% of patients in the accelerated regimen and in 9.3% in the conventional regimen.

In conclusion, accelerated up-dosing with an allergoid grass pollen SCIT is as well tolerated and safe as conventional up-dosing, with comparable immunological effects.

Acknowledgements

This study was funded by HAL Allergy, Leiden, The Netherlands. We thank the following investigators for their participation in the study: F.J. Botor, M.C. Cichy, G. Sahin, S. Wicht, A. Glowania, C.V. Thorn, C. Umbreit, A. Hardt, B. Hauswald, B.H. Schuster, J.-M. Nebel, T. Bieber, A.S. Buchner, L.-K. Ehler, J. Hanf-land, D. Wilsmann-Theis, K. Woellner, C.C. Termeer, H.-C. Blum, B. Butsch-von der Heydt, S.K. Kehm, H. Wrede, U.T. Thieme, S. Zielen, M. Dreßler, M. Kirwil, S. Schilling, H. Scholz, M. Sebastian, A. Meyer, and S. Volberg. We acknowledge Pierrel Research Germany GmbH for assistance in conducting the study and for statistical analysis.

Trial-registration: EudraCT No. 2009-015012-18.

Disclosure Statement

O. Pfaar and L. Klimek have received research grants from: ALK-Abello, Denmark; Allergopharma, Germany; Stallergenes, France; HAL, The Netherlands; Artu Biologicals, The Netherlands; Allergy-Therapeutics/Bencard, UK/Germany; Hartington, Spain; Lofarma, Italy; Novartis/Leti, Germany/Spain; Glaxo-Smith-Kline, UK/Germany; Essex-Pharma, Germany; Cytos, Switzerland; Curalogic, Denmark; Roxall, Germany, and Biomay, Austria. They have also served as advisors and on the speakers' bureaus for some of the aforementioned pharmaceutical companies. O. Pfaar is a consultant of HAL Allergy, The Netherlands, and has received travel grants from HAL Allergy, The Netherlands/Germany, and Allergopharma, Germany. E. van Twuijver and D. Boot are employees of HAL Allergy. H. Hecker was an employee of HAL Allergy when this study was performed. R. van Ree has performed contract research for HAL Allergy and Stallergenes and is a consultant for HAL Allergy.

References

- 1 Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al: Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update [in collaboration with the World Health Organization, GA(2)LEN and Allergen]. *Allergy* 2008;63(suppl 86):8–160.
- 2 Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S: Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007; CD001936.
- 3 Bousquet J, Michel FB: Safety considerations in assessing the role of immunotherapy in allergic disorders. *Drug Saf* 1994;10:5–17.
- 4 Grammer LC, Shaughnessy MA, Patterson R: Modified forms of allergen immunotherapy. *J Allergy Clin Immunol* 1985;76:397–401.
- 5 Alvarez-Cuesta E, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E: Standards for practical allergen-specific immunotherapy. *Allergy* 2006;61(suppl 82):1–20.
- 6 Hansen I, Hormann K, Stuck BA, Schneider-Gene S, Mosges R, Klimek L: Cluster-immunotherapy in seasonal allergic rhinitis: safety aspects of induction therapy with depot allergoids (Purethal) (in German). *Laryngo-rhinootologie* 2003;82:558–563.
- 7 Penas A, Bosque M, Cruz M, Garcia M: Observational study of the safety of an accelerated subcutaneous immunotherapy regimen in a pediatric population. *Allergy* 2011; 66(suppl 94):207.
- 8 Pfaar O, Klimek L, Fischer I, Sieber J, Amoroso S, Moreno AC et al: Safety of two cluster schedules for subcutaneous immunotherapy in allergic rhinitis or asthma patients sensitized to inhalant allergens. *Int Arch Allergy Immunol* 2009;150:102–108.
- 9 Pfaar O, Leitzbach S, Hormann K, Klimek L: Cluster protocols in SCIT: enough evidence for practical use? *Curr Opin Allergy Clin Immunol* 2010;10:188–193.
- 10 Subiza J, Feliu A, Subiza JL, Uhlig J, Fernandez-Caldas E: Cluster immunotherapy with a glutaraldehyde-modified mixture of grasses results in an improvement in specific nasal provocation tests in less than 2.5 months of treatment. *Clin Exp Allergy* 2008;38:987–994.
- 11 Tabar AI, Echechipia S, Garcia BE, Olaguibel JM, Lizaso MT, Gomez B et al: Double-blind comparative study of cluster and conventional immunotherapy schedules with *Dermatophagoides pteronyssinus*. *J Allergy Clin Immunol* 2005;116:109–118.
- 12 Zhang L, Wang C, Han D, Wang X, Zhao Y, Liu J: Comparative study of cluster and conventional immunotherapy schedules with *dermatophagoides pteronyssinus* in the treatment of persistent allergic rhinitis. *Int Arch Allergy Immunol* 2009;148:161–169.
- 13 Ariano R, Canonica GW, Passalacqua G: Possible role of climate changes in variations in pollen seasons and allergic sensitizations during 27 years. *Ann Allergy Asthma Immunol* 2010;104:215–222.
- 14 de Weger LA, Hiemstra PS: The effect of climate change on pollen allergy in the Netherlands (in Dutch). *Ned Tijdschr Geneesk* 2009;153:A1410.
- 15 Schubert R, Eickmeier O, Garn H, Baer PC, Mueller T, Schulze J, et al: Safety and immunogenicity of a cluster specific immunotherapy in children with bronchial asthma and mite allergy. *Int Arch Allergy Immunol* 2009;148:251–260.
- 16 Møllerup MT, Hahn GW, Poulsen LK, Malling H: Safety of allergen-specific immunotherapy: relation between dosage regimen, allergen extract, disease and systemic side-effects during induction treatment. *Clin Exp Allergy* 2000;30:1423–1429.