

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

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Keywords

Allergen-specific subcutaneous immunotherapy · Birch · Allergic rhinitis · Cluster-SIT · RUSH-SIT · Safety

Abstract

Background: Early pollen flight and new allergens prolonging the pollen season means that the time for up-dosing of allergen-specific subcutaneous immunotherapy (SCIT) outside the pollen season becomes shorter. Hence, for patients who wish or need to be up-dosed faster, an accelerated induction regimen would provide a useful treatment option.

Methods: An accelerated up-dosing regimen (0.1–0.3–0.5 mL at weekly intervals) was compared to conventional up-dosing (0.05–0.1–0.2–0.3–0.4–0.5 mL at weekly intervals) using an allergoid birch pollen SCIT preparation. After up-dosing, the maintenance dose (0.5 mL) was given 3 times at bi-weekly intervals. The multicenter study was performed according to an open randomized, parallel-group design.

Results: A total of 123 birch pollen-allergic patients (81 adults and 42 adolescents) presenting with rhinitis or rhinoconjunctivitis with or without mild asthma (FEV₁ >70%) were randomized to either the conventional registered up-dosing or an accelerated regimen. In total, 96.7 and 98.4% successfully reached the maintenance dose for the conventional and accelerated regimen, respectively, without relevant dif-

ferences between adults and adolescents. Both regimens were safe and well tolerated. Furthermore, significant increases (similar in size) in specific IgG and IgG₄ after 3 months of treatment were observed in both groups, independent of age. **Conclusion:** The accelerated SCIT regimen was revealed to be as safe as the conventional regimen, and the immunological effects of both regimens are similar. Accordingly, the accelerated regimen may be used to up-dose patients of adult as well adolescent age within 2 weeks.

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Introduction

Studies have shown that clinical efficacy is retained using modified allergen extracts at higher doses and that modified preparations are considered safer than non-modified allergen extracts [1–4].

For the birch pollen extract under evaluation, modification allows the maintenance dose to be reached in 5 weeks instead of the 15 weeks for nonmodified extracts. Currently, it is recommended starting and finishing the

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up-dosing of subcutaneous immunotherapy (SCIT) before the start of the pollen season. However, with the trend towards earlier pollen flight, a short up-dosing phase is desirable and even mandatory for patients with multiple allergies and a narrow window of pollen-free time. In addition, a short up-dosing makes the start of the SCIT more comfortable for the patients as they can reduce the number of weekly visits to the doctor, which can have a positive effect on therapy compliance.

This study was designed to evaluate if the up-dosing phase for a modified birch pollen preparation can be reduced from 5 to 2 weeks in adults and adolescents. The safety of an accelerated up-dosing regimen (a maximum dose reached in 3 injections during 2 weeks) was compared to the conventional regimen (a maximum dose reached in 6 injections during 5 weeks). This study focuses on the up-dosing phase, since, after reaching the maintenance dose (0.5 mL), it is assumed that there is no difference anymore regarding safety.

Materials and Methods

Patients

In total, 143 patients were screened and 123 patients (59 females and 64 males with a mean age of 26.6 ± 11.50 years [range 12–59 years]), including 42 adolescents (aged 12–17 years), with rhinitis or rhinoconjunctivitis, with or without mild asthma ($FEV_1 > 70\%$) related to birch pollen were recruited. A positive skin prick test was required in combination with birch-specific IgE > 0.7 U/mL or a positive nasal provocation test for birch pollen. Written informed consent was obtained from all patients. The study protocol was approved by the relevant ethics committee.

Study Design

An open, randomized, parallel-group, multicenter, phase IV study was conducted between September 2013 and February 2014 at 8 study sites in Poland. Patients were randomized to the accelerated or conventional regimen (1:1) with birch pollen SCIT. A standardized suspension (20,000 AUM/mL) of glutaraldehyde-modified extract from birch (*Betula verrucosa*) pollen adsorbed onto aluminium hydroxide was used for SCIT (PURETHAL® Birch, HAL Allergy BV, Leiden, The Netherlands). The accelerated regimen consisted of 3 weekly doses of 0.1, 0.3, and 0.5 mL, followed by a maintenance treatment of 0.5 mL, 3 times at biweekly 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 a maintenance treatment of 0.5 mL, 3 times at biweekly intervals. If a local reaction with a wheal > 5 cm or if a grade I systemic reaction occurred within 24 h following injection, the next injection was the same as the previous dosage. If a wheal > 12 cm occurred, the next injection was 1 dose lower than the previous one. In the case of a systemic reaction greater than grade I, the patient was regarded as not having successfully reached the maintenance dose.

The primary outcome parameter was the proportion of patients successfully reaching the maintenance dose, provided that

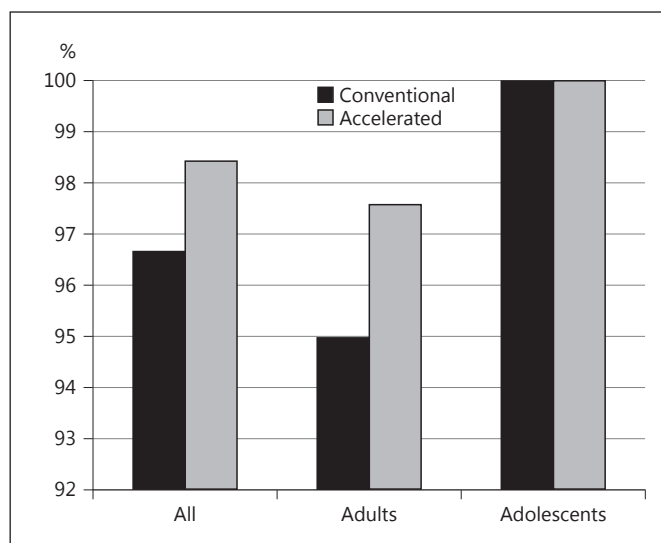


Fig. 1. Proportions (%) of patients (ITT population) reaching the maintenance dose.

no treatment-related systemic reactions greater than grade I (within 24 h) occurred and/or no more than 2 additional injections were required. Therefore, early and late (within 30 min and 24 h after injection, respectively) local and systemic reactions were recorded. All adverse reactions were recorded throughout the trial, and an assessment of vital signs and a physical examination were performed 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.

A noninferiority approach was chosen to compare the success rates between both treatment groups, and a predefined noninferiority margin of 10% was used.

Results

The intention-to-treat (ITT) population consisted of 123 patients (accelerated regimen: $n = 62$, with 21 adolescents; conventional regimen: $n = 61$, with 21 adolescents) with similar baseline characteristics. Two patients did not complete the study, 1 (conventional regimen, adult) withdrew consent during the up-dosing, and 1 (accelerated regimen, adolescent) dropped out during the maintenance phase. The proportion of patients successfully reaching the maintenance dose was 98.4% (accelerated) versus 96.7% (conventional) (ITT population, Fig. 1). The confidence interval (-3.8 to 7.1%) of the difference (1.7%) in proportion was well above the preset noninferiority margin of -10% . Analysis according to age group revealed similar results for adults and adolescents in both treatment groups (Fig. 1).

Table 1. Treatment-emergent adverse events (TEAEs) in the safety population

	Conventional regimen			Accelerated regimen			Total (<i>n</i> = 123)
	all (<i>n</i> = 61)	adults (<i>n</i> = 40)	adolescents (<i>n</i> = 21)	all (<i>n</i> = 62)	adults (<i>n</i> = 41)	adolescents (<i>n</i> = 21)	
Patients with TEAEs	39 (62.9)	27 (67.5)	11 (52.4)	38 (62.3)	30 (73.2)	9 (42.9)	77 (62.6)
Patients with TEAEs leading to early termination of treatment	0 (0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (4.8)	1 (0.8)
Number of TEAEs	96	63	33	114	84	30	210
Intensity							
Mild	57 (59.4)	36 (57.1)	21 (63.6)	86 (75.4)	64 (76.2)	22 (73.3)	143 (68.1)
Moderate	39 (40.6)	27 (42.9)	12 (36.4)	26 (22.8)	20 (23.8)	6 (20.0)	65 (31.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	2 (6.7)	2 (1.0)
Patients with drug-related TEAEs	19 (31.1)	13 (32.5)	6 (28.6)	22 (35.5)	16 (39.0)	6 (28.6)	41 (33.3)
Number of drug-related TEAEs	61 (63.5)	39 (61.9)	22 (66.7)	85 (74.6)	62 (73.8)	23 (76.7)	146 (69.5)

Values express *n* (%), unless otherwise indicated.

Table 2. Specific immunoglobulins before and after treatment

Parameter	Conventional regimen		Accelerated regimen	
	start	end	start	end
IgE birch, kU/L	56.3±82.0	56.7±82.6	41.15±52.9	49.26±63.6
IgE Bet v 1, kU/L	52.8±87.7	51.4±71.6	37.40±48.8	46.36±60.2
IgG ₄ birch, µg/L	292.9±342.9	1,583.9±2,806.7	302.87±465.8	1,484.86±2,883.2
IgG ₄ Bet v 1, µg/L	209.3±276.7	1,173.4±2,249.8	219.73±381.9	1,156.60±2,329.6
IgG birch, µg/L	0.71±0.45	1.79±1.38	0.76±0.46	1.74±1.27
IgG Bet v 1, µg/L	0.53±0.35	1.36±1.09	0.58±0.34	1.33±0.97

Values denote mean ± SD.

The similarity between the 2 regimens is also shown by the proportion of patients receiving the 1st maintenance injection (according to the most optimal schedule), being 80.3% (injection 7) and 82.3% (injection 4) for the conventional and accelerated regimens, respectively.

The majority of patients did not show early local reactions. Only wheals ≤5 cm diameter were found with similar frequency (14–19%) in both age groups. Regarding late local reactions, 24.4% (*n* = 30) of the patients reported reactions with wheals ≤5 cm and 16.3% (*n* = 20) with wheals >5 and ≤12 cm. One late local reaction with a wheal >12 cm was observed in the (conventional) adult group. For the late local reactions, no consistent differences between age groups were found.

Concerning early systemic reactions, the vast majority of patients experienced either no symptoms or nonspecific symptoms (grade 0). None of the adolescents and only 1 adult patient had an early systemic grade I reaction. Late

systemic grade I reactions occurred in 3.3 (conventional) to 6.5% (accelerated) of the patients. No consistent differences between the adult and adolescent groups were found.

In total, 210 treatment-emergent adverse events (AEs) were reported by 77 patients (accelerated: *n* = 38, conventional: *n* = 39), 146 of which (accelerated: *n* = 85, conventional: *n* = 61) were considered treatment-related. Both the frequency and nature of treatment-emergent AEs were similar in the 2 treatment regimens (Table 1). If split up by age group, the somewhat higher number of related treatment-emergent AEs in the accelerated-regimen group were all adults; there were 16 patients with 62 related AEs in the accelerated-regimen group versus 13 patients with 39 related AEs in the conventional-regimen group (Table 1).

In 1 patient (accelerated regimen, adolescent) treatment was discontinued following a possibly related AE. The patient developed fever and stomach ache 16 days after the 2nd injection during the maintenance phase.

The next day, he was hospitalized for urticaria. After 1 week, he had recovered but the study treatment was discontinued. The AE was considered serious because it required hospitalization. Safety parameters from the physical examination and the assessment of vital signs revealed no changes during the treatment period.

IgE, IgG, and IgG₄ specific for birch and Bet v 1 were determined per patient before and after treatment in both treatment groups (Table 2). Both treatment regimens resulted in an increase in specific immunoglobulin levels; in particular, the IgG and IgG₄ levels specific for birch and Bet v 1 increased by 2–5 times in both treatment groups after the up-dosing phase and the 3 additional biweekly maintenance doses. For the accelerated and conventional regimens, the changes observed were similar.

Discussion

An accelerated regimen for up-dosing birch pollen SCIT was compared to the conventional regimen in patients with rhinitis/rhinoconjunctivitis due to birch pollen. The proportion of patients successfully reaching the maintenance dose was chosen as the primary outcome measure, reflecting both the safety and practicality of applied regimen. Noninferiority of the accelerated compared to the conventional regimen was demonstrated, confirming that up-dosing for this birch pollen allergoid can be reduced from 5 to 2 weeks. In this respect, this study supported earlier results obtained with a similar grass pollen SCIT preparation [5].

In this study, one-third of the patients were adolescents aged 12–17 years. Although their number was too small to analyze this group as a separate entity, some ob-

servations can be made. In both treatment groups, all adolescent patients successfully reached the maintenance phase (Fig. 1). In addition, when considering all treatment-emergent AEs, lower percentages were observed in the adolescent group than in the adult group; however, if restricted to the related AEs, this difference appears less pronounced. So it appears that the conventional and accelerated regimens were tolerated equally well by the adult and adolescent study population.

Similar increases in serum concentrations of specific IgG and IgG₄ against birch and Bet v 1 were observed, in agreement with accelerated and conventional SCIT products against other allergens [6–8].

In conclusion, accelerated up-dosing of allergoid birch pollen SCIT is as well tolerated and safe as conventional up-dosing, with immunological effects that are comparable in the adult and adolescent populations.

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Disclosure Statement

K. Buczyłko received remunerations as (coordinating) investigator in the study, J.F. van der Werf and D. Boot were employees of HAL Allergy when the study was performed, and R. van Ree performed contract research for HAL Allergy and is a consultant of HAL Allergy.

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