Shortened Up-Dosing With 7 Injections of Subcutaneous Allergy Immunotherapy (Alutard SQ) Is Safe and Well Tolerated

Horn A[1], Fernández-Rivas M[2], Wolf H[3], Ghaussy N[3], Møller Kruse T[4], Koutromanou K[4], Wüstenberg E[3,5]
[1]*ENT Practice am Neckar, Drs Horn & Choudhry, Heidelberg, Germany*
[2]*Allergy Dept, Hospital Clínico San Carlos, IdISSC, ARADyAL, Madrid, Spain*
[3]*Medical Department ALK-Abelló Arzneimittel GmbH, Hamburg, Germany*
[4]*ALK Global Pharmacovigilance and Clinical Development, Hørsholm, Denmark*
[5]*ENT Clinic Medical Faculty Carl-Gustav-Carus, Technical University, Dresden, Germany*

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Allergic rhinoconjunctivitis (ARC) affects 10%-25% of the global population [1]. In Europe, it is caused mainly by allergens from grass pollen, Fagales tree pollen (hazel, alder, birch), and house dust mites (HDM) [2,3].

Allergy immunotherapy (AIT) can be applied by the subcutaneous or sublingual route and is the only treatment of ARC with the potential for long-term effect and disease modification [4,5].

In the case of subcutaneous AIT (SCIT), high doses are administered at 4 to 8-week intervals. The optimal maintenance dose is reached safely and effectively by up-dosing over several weeks [6]. The convenience and practicability of SCIT, as perceived by patients and physicians, depend largely on the number of injections needed for up-dosing [7]. Short up-dosing has previously been reported to be safe [8-10].

We performed a partly randomized, parallel-group, controlled (open-label), multicenter trial to compare the safety and tolerability profile of a 7-injection up-dosing schedule with the registered and widely used AIT product Alutard SQ (ALK, based on either 6 grasses and rye, birch, or HDM allergens) with that of the established 11-injection up-dosing schedule for grass pollen allergens. The trial was conducted in Germany and Spain from 2017 to 2018 (EudraCT 2017-000971-97).

Patients treated with grass allergen extracts were randomized 1:1 to up-dosing with 11 weekly injections (grass-11) or 7 weekly injections (grass-7). Patients treated with birch allergen extracts (tree-7) or HDM allergen extracts (HDM-7) were treated using only the 7-injection schedule (Supplementary figure 1). Because the tolerability of SCIT with grass, tree, and HDM allergens was expected to be

similar, it was considered adequate to apply the 11-injection schedule with 1 product only. The 11-injection up-dosing schedule with Alutard SQ 6 grasses and rye was chosen, as it is the most frequently used up-dosing schedule for all Alutard SQ in Germany. The baseline characteristics of patients are shown in Supplementary table 1; injection volumes and vial concentrations of the 7- and 11-injection schedules are shown in Supplementary figure 2.

The sample comprised male and female patients aged 12-65 years with moderate-to-severe ARC to grass or birch pollen or HDM despite treatment with pharmacotherapy during the previous 2 grass or birch pollen seasons or 2 years (for allergy to HDM). Patients with and without asthma were included (see supporting information for inclusion and exclusion criteria, estimation of sample size, and safety and statistical analyses).

The primary endpoint was the number of treatment-related adverse events (TRAEs).

A total of 357 patients were screened and 340 treated (see CONSORT diagram in Supplementary figure 3). The proportion of patients who discontinued was higher for the grass-7 group (15%) than for the grass-11 group (7%) and the tree-7 (2%) and HDM-7 (6%) groups.

In total, 302 (89%) patients experienced 2755 adverse events (AEs), and 269 (79%) experienced 2162 TRAEs. All AEs and TRAEs in the 4 treatment groups are displayed in the Table (see Supplementary table 2 for all AEs and TRAEs in adolescent and adult subgroups).

More TRAEs were reported in the grass-11 group than in the groups with the short up-dosing schedule (grass-11, 711; grass-7, 561; tree-7, 444; HDM-7, 446) as the primary endpoint of the trial, although no major differences in the proportion of patients who experienced TRAEs were observed between the treatment groups (grass-11, 76%; grass-7, 80%; tree-7, 76%; HDM-7, 84%) (Supplementary figure 4 A and B). Most TRAEs typically occurred within the first 30-40 days of treatment (ie, during the up-dosing phase), and most were mild (90%) or moderate (9%) in severity with a similar pattern in all treatment groups. There were no major differences in the percentage of patients experiencing TRAEs between the adolescent and adult subgroups (adolescents, 71%-86%; adults, 73%-85%) or in severity, seriousness, changes to treatment, and outcome. Fourteen patients (4%) reported 23 TRAEs that were classified as severe (grass-11, 7 patients (8%) [8 events]; grass-7, 6 patients (7%) [14 events]; tree-7, none; HDM-7, 1 patient (1%) [1 event]).

The most frequently reported TRAEs (≥5% of patients in any group) in all treatment groups were typically injection site reactions related to subcutaneous administration (Supplementary figure 5). Median onset was on the first day of treatment, typically 1-2 hours after injection, and median duration was 2-3 days.

Four systemic allergic reactions were identified in the grass-11 group (all serious) and 3 in the grass-7 group (1 serious and 2 nonserious) (details in Supplementary information, subheading Systemic allergic reaction and Supplementary table 3).

In total, 14 patients (4%) discontinued treatment due to 26 AEs, as follows: grass-11, 2 patients (2%); grass-7, 9 patients (11%); tree-7, none; HDM-7, 3 (4%). Of these, 11 (3%) experienced 20 TRAEs leading to discontinuation. More patients discontinued owing to TRAEs in the grass-7 group (7 [8%]) than in the grass-11 group (1 [1%]) and the HDM-7 group (3 [4%]). Six patients (2%) experienced 6 serious AEs (grass-11, 4; grass-7, 2; tree-7, none; HDM-7, none), of which 5 were considered treatment-related (grass-11, 4; grass-7, 1; tree-7, none; HDM-7, none) (Supplementary table 2).

Serious TRAEs, systemic allergic reactions, and severe TRAEs were seen predominantly in the grass groups, although there were no indications that grass-7 was less safe or less tolerated than grass-11.

This trial is limited by the challenges of comparing treatment schedules of different durations and the lack of corresponding comparators (11- or 16-injection up-dosing

Table. AEs and TRAEs in the 4 Treatment Groups

	Grass-11 (N=85) No. (%), Events	Grass-7 (N=85) No. (%), Events	Tree-7 (N=87) No. (%), Events	HDM-7 (N=83) No. (%), Events
All AEs	74 (87), 859	79 (93), 729	75 (86), 611	74 (89), 556
TRAEs	65 (76), 711	68 (80), 561	66 (76), 444	70 (84), 446
Severity				
Mild	63 (74), 657	64 (75), 488	66 (76), 398	69 (83), 406
Moderate	19 (22), 46	23 (27), 59	16 (18), 46	16 (19), 39
Severe	7 (8), 8	6 (7), 14	-	1 (1), 1
Serious	4 (5), 4	1 (1), 1	-	-
Dose not changed	63 (74), 666	64 (75), 493	65 (75), 431	69 (83), 416
Dose reduced	20 (24), 44	18 (21), 49	5 (6), 11	12 (14), 26
Treatment interrupted	-	1 (1), 4	1 (1), 2	-
Treatment withdrawn	1 (1), 1	7 (8), 15	-	3, (4), 4
Event leading to discontinuation	1 (1), 1	7 (8), 15	-	3, (4), 4
Treated with medication	30 (35), 95	31 (36), 98	18 (21), 63	28 (34), 76
Immediate onset (<30 min)	23 (27), 99	26 (31), 106	17 (20), 52	20 (24), 56
Delayed onset (>30 min)	64 (75), 612	68 (80), 455	65 (75), 392	67 (81), 390

Abbreviations: AE, adverse event; TRAE, treatment-related adverse event

schedule) for the tree-7 and HDM-7 groups. In addition, the trial was not powered to detect differences in systemic allergic reactions, since these reactions rarely occur.

Overall, the 7-injection up-dosing schedules were well tolerated, consistent with observations made in previous trials with a similar up-dosing period and a higher number of injections with the same product [11,12].

Our results suggest that the 7-injection up-dosing schedules for grass, tree, and HDM have an acceptable safety and tolerability profile, which is generally comparable to the 11-injection up-dosing schedule for grass in adolescents and adults (12-65 years) with moderate to severe ARC induced by the respective allergen. SCIT with Alutard SQ based on the 7-injection up-dosing schedules may improve the convenience of treatment and, thus, facilitate patients' access to the benefits of AIT.

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Conflicts of Interest

A Horn reports grants during the conduct of the study.

M Fernández-Rivas reports fees for lectures from Aimmune, ALK, Allergy Therapeutics, HAL Allergy, and Thermo Fisher Scientific and consultancy fees from Aimmune and DBV.

H Wolf, N Ghaussy, TM Kruse, SH Jacobsen, K Koutromanou, and E Wüstenberg are employed by ALK. H Wolf and E Wüstenberg report personal fees and stock/stock options outside the submitted work.

Previous Presentation

The design of the study and the results were presented in abstract and poster form at the following meetings: European Academy of Allergy and Clinical Immunology (EAACI) Congress, May 26-30, 2018, Munich, Germany; the Annual Meeting of the American Academy of Allergy Asthma and Immunology, February 22-25, 2019, San Francisco, California, USA; and at the EAACI Congress, June 01-05, 2019, Lisbon, Portugal.

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Hendrik Wolf
Medical Department/Clinical Development
ALK-Abelló Arzneimittel GmbH
Griegstrasse 75, Haus 25
D-22763 Hamburg
E-mail: hendrik.wolf@alk.net

