

Safety of a rush immunotherapy build-up schedule with depigmented polymerized allergen extracts

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ABSTRACT

Conventional subcutaneous immunotherapy (SCIT) for allergy treatment needs several injections over several weeks to reach the maintenance dose. Shorter up-dosing regimens are desired but limited by the potential of side effects. This study was designed to compare the safety of Depigoid (Laboratorios LETI, Spain)—SCIT 1 day versus 3 weeks up-dosing in patients with Type 1 allergy caused by clinically relevant sensitization against tree pollen, grass pollen, and house-dust mites. A total of 303 patients with confirmed allergic rhinitis/conjunctivitis were included. A rush build-up schedule administering 0.2 mL and then 0.3 mL of the concentrate at day 1 followed by 0.5 mL at day 28 was compared with a conventional 4-week build-up schedule. The number of patients reaching the maintenance phase without systemic reactions or major deviation from treatment schedule were compared. Of the rush 91.8% and in the conventional group 90.9% reached the maintenance phase without dose modification. Neither the proportions of patients with systemic reactions (5.8% rush versus 2% conventional) nor the proportions of patients with local reactions differed significantly between the two regimens (24% rush versus 11% conventional). There was no difference with respect to the applied allergen group. The proposed rush build-up schedule for the immunotherapy treatment with depigmented allergoids without premedication is safe and not inferior to the conventional schedule.

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Key words: Allergoid, allergy, conjunctivitis, depigmented extracts, immunotherapy, rhinitis, safety

The prevalence of sensitization against aeroallergens has increased substantially in the past decades.^{1,2} Subcutaneous immunotherapy (SCIT) is one treatment that modifies the course of allergy.³ A positive impact on symptoms, medication requirement, and improvement of quality of life are well documented with SCIT.^{3,4}

Conventional SCIT requires numerous injections to reach the maintenance dose. Inconvenience is thought to be a major factor affecting compliance^{5,6} and acceptability should therefore be increased by shorter up-dosing schedules and a faster onset of symptom relief. For this reason rush immunotherapy and cluster schedules have been developed, reaching the maintenance dose within shorter treatment periods.^{7–11} However, a relatively high prevalence of systemic reactions due to rush schedules was reported in some studies.^{7,8,12}

Another approach for shorter up-dosing schedules is the use of allergoids. Depigoid (Laboratorios LETI, Spain) is chemically modified, first, by mild acid hydrolysis followed by dialysis to remove nonallergenic material such as pigments (depigmentation) and then, second, by polymerization with glutaraldehyde to form an allergoid.¹³ Depigoid has reduced allergenicity (IgE binding) but appears to preserve immunogenicity.^{14–17} Clinical efficacy and safety was shown in several studies, a pretreatment with antihistamines and corticosteroids was not required.^{7,18–26} Up-dosing schedules for allergoids are rapid compared with unmodified allergen extracts, and the maintenance dose can be reached after a few injections.

The objective of this prospective study was to compare the safety of a rush up-dosing schedule where the maintenance dose is reached at day 1, with a “conventional” build-up schedule using depigmented glutaraldehyde polymerized grass pollen, tree pollen, and house-dust mite extracts. The main outcome parameter was the percentage of patients reaching the maintenance phase without any systemic reactions after the respective build-up schedules.

METHODS

Patients

Three hundred thirty-three male and female patients aged 18–60 years were enrolled. Written informed

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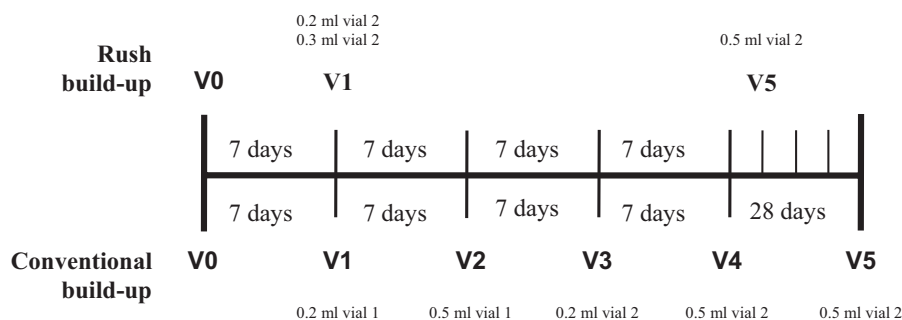


Figure 1. Flowchart showing treatment schedules.

consent was given before entry in the study. For inclusion, patients had to have rhinitis and/or conjunctivitis without uncontrolled asthma caused by allergy to tree pollen, grass pollen, or house-dust mites. IgE-mediated sensitization was confirmed by patients history and skin and blood tests (wheal diameter, ≥ 3 mm; specific IgE, $\geq$ class 1 [Pharmacia CAP, Freiburg, Germany]). Forced expiratory volume at 1 second or peak expiratory flow had to be $>70\%$ of predicted normal value. Pregnant or lactating women and women of childbearing age not using sufficient contraceptive protection were excluded. Patients who had participated in another clinical trial within the last 3 months, smokers with underlying bronchopathy, alcohol/drug abusers, employees at the investigational site, and relatives or spouses of the investigator were also excluded. All contraindications toward specific immunotherapy had to be respected.

Study Design, Assignment, and Intervention

This randomized multicenter, parallel group study was performed in 13 centers in Germany. For the build-up phase, patients were randomized to one of two treatment groups in the ratio of 2:1 receiving either a Depigoid rush schedule (group A) or a conventional Depigoid schedule (group B) followed by an open maintenance treatment phase of up to 3 years.

Depigoid was supplied by Laboratorios LETI, Spain. The purified raw material was extracted in PBS followed by dialysis in 3-kDa flatbed ultrafiltration membranes (Pellicon; Millipore, Madrid, Spain) to eliminate the bulk of unbound low molecular weight components. The next step of depigmentation consisted of a controlled acid treatment to remove the remaining proportion of adsorbed pigments and produce the inactivation of the enzymic activity. The resulting depigmented allergen preparations were used to be treated with glutaraldehyde, obtaining a high molecular weight derivative with a $>99\%$ reduction in IgE binding capacity.²⁷ The concentrate (vial 2) contained 100 depigmented polymerized (DPP)/mL (1 DPP is the result of depigmenting and polymerizing 1 HEPT [histamine equivalent prick test] of allergenic extract) for sensi-

tization against house-dust mites, or 1000 DPP/mL for sensitization against pollen. The respective major allergen equivalents before depigmentation corresponding with 1 mL of the maintenance concentrate were 60 μg of Bet v1, 17.3 μg of Der p1, 10.5 μg of Der p2, 12 μg of Der f1, 70.8 μg of Phl p1, and 147.7 μg of Phl p5 measured by scanning densitometry²⁸ and adjusted for protein content.

In group A (rush schedule), the initial screening visit was followed by two treatment visits (up-dosing visit) and 4 weeks apart (visits 1 and 5). The build-up phase (Fig. 1) consisted of two injections (0.2 and 0.3 mL) of the maintenance concentrate (vial 2) given with a 30-minute interval. Four weeks later, the maintenance dose (0.5 mL of the concentrate—vial 2) was administered.

Patients in group B (conventional schedule) had visits 1, 2, 3, 4 (up-dosing), and 8 weeks (visits 1–5) after the screening visit. The build-up phase consisted of four injections in weekly intervals: 0.2 and 0.5 mL of an initial 1:10 v/v dilution (vial 1), and 0.2 and 0.5 mL of the maintenance concentrate (vial 2).

In addition to recording medical history and physical examination, skin-prick tests, total IgE, serum-specific IgE (tree pollen, grass pollen, and house-dust mites), and laboratory investigations were performed during the screening visit. Lung function (forced expiratory volume at 1 second or peak expiratory flow) was measured before each injection and had to be $>80\%$ of the predicted value. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki. The protocol was approved by the local ethics committees for each center.

Allergic Side Effects and Adverse Events

Local reactions were evaluated according to size, itching, and pain. The largest diameter of the swelling was measured; a diameter of <5 cm was considered as mild, of ≥ 5 –10 cm was considered as moderate, and of >10 cm was considered as severe local reaction. Itching as well as pain was documented as mild, moderate, or severe.

Systemic reactions were graded following the Deutsche Gesellschaft für Allergologie und klinische Immu-

Table 1 Systemic reactions according to Deutsche Gesellschaft für Allergologie und klinische Immunologie

DGAKI Grade	Symptoms
1. Mild	General skin redness, urticaria, pruritus (especially palmar and plantar), rhinitis, rhinoconjunctivitis, unspecific symptoms such as headache, and restlessness
2. Moderate	Circulation disturbances such as changes in blood pressure or heart rate, mild dyspnea or mild bronchial obstruction, tenesmus, and anxiety
3. Severe	Shock (severe hypotension and paleness), severe bronchial obstruction, unconsciousness, and urge incontinence
4. Life threatening	Full anaphylactic shock

nologie criteria (Table 1). It differs slightly from the European Academy of Allergy and Clinical Immunology classification in that grade 1 reactions in Deutsche Gesellschaft für Allergologie und klinische Immunologie would be grade 1 or 2 in the Academy of Allergy and Clinical Immunology classification.²⁹ The intensity and severity of systemic reactions were graded using a visual analog scale from 0 (none) to 10 (very severe).

The causal relationship between adverse events (AEs) and the study medication was assessed by the investigator as “not, unlikely, likely, or definitely related.” For patients showing signs of AEs or clinically relevant deviations from laboratory values, a post-study visit was performed within a month.

Global Assessment of Treatment

At the final visit both investigator and patient were asked to give an overall assessment of the treatment by answering the following question: My overall impression of the safety of the trial medication is excellent (no side effects at all), good (some minor local side effects), moderate (major local side effects or mild systemic side effects), poor (major systemic side effects), or unacceptable (anaphylactic reaction).

Statistical Analysis

For the analysis of this study, the noninferiority approach was chosen. This approach was as described for clinical trials comparing different modes of therapy.^{30,31} Analytical practicability and appropriateness of this approach are shown in literature.^{32–34} The primary criterion of this study was the percentage of patients reaching the maintenance phase without any relevant systemic reaction (*e.g.*, systemic reactions or adverse events that at least were likely related to study medication or caused repetition of doses).

In a hierarchic test procedure (global α -level of 2.5%) the percentage of patients reaching the maintenance phase according to the primary criterion was compared between the two treatment groups. For this comparison, the difference between the build-up schedules and the according one-sided 97.5% confidence interval

(CI) for this difference was calculated. The procedure was performed using the standard normal approximation according to Blackwelder.³⁵ Noninferiority of the rush build-up phase concerning the given noninferiority margin (NIM) could be concluded if the CI for the difference between the respective percentages lay completely above this NIM.

The following system of hypotheses was tested:

$$H_0: \pi_{\text{rush}} - \pi_{\text{conventional}} \leq X_{\text{NIM}}$$

versus

$$H_1: \pi_{\text{rush}} - \pi_{\text{conventional}} > X_{\text{NIM}}$$

whereby X_{NIM} denoted the noninferiority margin and π_{rush} and $\pi_{\text{conventional}}$ denoted the percentage of patients reaching the maintenance phase. The value for the NIM X_{NIM} was increased from –15 to 0% in steps of 1%. The NIM of –15% was chosen, because similar margins were used in several other clinical trials before or were recommended by authorities.³²

Secondary parameters were

Severity of systemic reactions.

Percentage of patients with systemic reactions.

Percentage of patients with local reactions.

Physicians' and patients' overall assessments.

Adverse events were documented and causality assessment was made.

A subgroup analysis was performed for each allergen treatment group, *i.e.*, grass pollen, tree pollen, or house-dust mites. Severity of systemic reactions was analyzed using the Hodges-Lehmann estimator and the two-sided 95% CI according to Moses. The comparison of treatment groups concerning percentages of patients with systemic and local reactions, respectively, was done by Fisher's exact test. For the evaluation of overall assessment of physicians and patients the Wilcoxon rank-sum test was performed.

Sample Size

Sample size calculation was based on the percentage of patients reaching the maintenance treatment phase.

Table 2 Demography and medical history (ITT)

Treatment group	ITT (n = 303)	
	Rush Schedule (n = 206)	Conventional Schedule (n = 97)
Demography		
Mean age $\pm$ SD (yr)	34.54 ($\pm$ 11.79)	35.13 ($\pm$ 11.19)
Men/women (n)	103/103	46/51
Mean height $\pm$ SD (m)	173.86 ($\pm$ 9.44)	173.8 ($\pm$ 9.41)
Mean weight $\pm$ SD (kg)	74.02 ($\pm$ 14.94)	73.84 ($\pm$ 12.98)
Mean body mass index $\pm$ SD (kg/m ²)	24.33 ($\pm$ 3.62)	24.43 ($\pm$ 3.85)
Subgroups		
Grass pollen	84	40
Positive skin-prick test/specific IgE of >1	84	40
Tree pollen	75	38
Positive skin-prick test/specific IgE of >1	75	38
House-dust mites	47	19
Positive skin-prick test/specific IgE of >1	47	19
Medical history		
Rhinitis	11	5
Conjunctivitis	0	1
Both	194	91
Nonspecific symptoms	1	0

ITT = intent-to-treat.

Investigating 100 subjects in the conventional treatment group and 200 subjects in the rush treatment group, the lower limit of the observed one-sided 97.5% CI was expected to exceed -15% with 90% power when the standard percentage, percentage of patients reaching the maintenance treatment phase after the conventional build-up phase ($\pi_{\text{conventional}}$), is 0.95 and the test expected percentage, percentage of patients reaching the maintenance treatment phase after the rush build-up phase (π_{rush}), is 0.9. Results were based on 1000 simulations using the Newcombe-Wilson score method to construct the CI.

Populations

The statistical analysis of the presented results was performed in the intent-to-treat (ITT) collective, which comprised all patients receiving the study medication at least for the build-up phase.

RESULTS

Study Population and Compliance

The safety population comprised 307 patients. Because of concomitant treatment with substances interfering with the immune system, four patients were classified as not eligible and were excluded from the population. The ensuing ITT population comprised 303 patients for whom the results are presented. Study compliance was high, because 277 of 303 patients

(91.42%) completed the build-up phase according to study protocol.

Baseline Characteristics

Demographic variables, distribution of patients between subgroups, and medical history of patients are shown in Table 2. No relevant differences were found between treatment groups. One hundred ninety-four patients in the rush treatment arm and 91 patients in the conventional group had allergic rhinitis and conjunctivitis. Eleven patients in the rush and five in the conventional treatment group suffered only from rhinitis. One patient of the conventional treatment group reported conjunctivitis as a single symptom.

In the rush treatment arm 84 patients received Depigoid Grass Mix, 75 patients received Depigoid Tree Mix, and 47 patients received Depigoid Mite Mix, respectively. In the conventional treatment arm 40 patients received Depigoid Grass Mix, 38 patients received Depigoid Tree Mix, and 19 patients received Depigoid Mite Mix.

Safety

Patients Reaching Maintenance Phase. A 91.8% ($n = 206$) of patients receiving rush and 90.9% ($n = 97$) of patients receiving conventional treatment reached the maintenance phase without dose modification or systemic reactions (Table 3). Overall, for the percentage of

Table 3 Comparison of percentages of patients reaching the maintenance phase, percentages of patients with systemic reactions, and percentages of patients with local reactions between treatment and subgroups comparison of intent-to-treat

	Rush Schedule (%)	Conventional Schedule (%)	Lower Confidence Limit (%)	<i>p</i> Value
Patients reaching maintenance phase				
All	91.75	90.91	−5.863	
Grass pollen	89.41	92.67	−13.720	
Tree pollen	94.74	87.18	−3.968	
HDM	91.49	94.74	−16.360	
Patients with systemic reactions				
All	5.83	2.01		0.239
Grass pollen	5.88	2.44		0.663
Tree pollen	5.26	2.56		0.663
HDM	6.38	0.0		0.550
Patients with local reactions				
All	31.73	20.20		0.114
Grass pollen	44.71	29.27		0.121
Tree pollen	32.89	28.27		0.831
HDM	23.40	10.53		0.484

HDM = house dust mite.

patients reaching the maintenance phase after the rush treatment schedule non-inferiority was shown for a lower confidence limit of −5.863%. The subgroup treated with tree pollen extract revealed a lower confidence limit of −3.968%. For neither overall nor single subgroup of the rush treatment schedule was superiority over the conventional treatment schedule shown according to the one-sided Fisher's exact test.

Systemic Reactions. Overall, 5.77% of the patients in the rush and 2.02% of the patients in the conventional treatment schedule suffered from systemic reactions (Table 4). This difference was not statistically significant ($p = 0.239$).

The severity and nature of systemic reactions are shown in Tables 4 and 5. Grade 1 systemic reactions occurred in 14 patients receiving rush treatment and in 5 patients treated with the conventional regimen.

A grade 2 systemic reaction occurred in one patient (0.48%) treated with the rush regimen. For conventional treatment no systemic reactions of grade 2 occurred. No patient showed a reaction of grade 3 or 4.

Local Reactions. In the rush treatment group 31.73% of patients developed local reactions compared with 25.77% in the conventional group (Table 3). However, for patients overall and in the subgroups no significant differences between treatment schedules were found ($p > 0.05$).

Global Assessment. Table 6 shows the physicians' and patients' judgments of treatment. The majority of phy-

Table 4 Comparison of grades of systemic reactions between treatment groups (ITT)

Subgroup	Rush Schedule (%)	Conventional Schedule (%)	<i>p</i> Value
All			0.405
No reaction	94.23	97.98	
Mild	5.29	2.02	
Moderate	0.48	0.0	
Grass pollen			0.663
No reaction	94.12	97.56	
Mild	5.88	2.44	
Moderate	0.0	0.0	
Tree pollen			0.663
No reaction	94.74	97.44	
Mild	5.26	2.63	
Moderate	0.0	0.0	
House-dust mites			1.0
No reaction	93.62	100.0	
Mild	4.26	0.0	
Moderate	2.12	0.0	

Mild, grade 1; moderate, grade 2 (according to Deutsche Gesellschaft für Allergologie und klinische Immunologie).
ITT = intent-to-treat.

sicians assessed the treatment as "excellent" or "good" (rush, 94.2%; conventional, 92.8%). Only few (rush, 2.43%; conventional, 2.06%) judged the treatment as "moderate," none assessed it as "poor" or "unaccept-

Table 5 Description of systemic reactions between treatment groups (ITT) throughout the course of the study (V1–V5; multiple answers were permitted)

Reaction Type	Rush Schedule <i>n</i> Reactions (<i>n</i> = 206)	Conventional Schedule <i>n</i> Reactions (<i>n</i> = 97)
Grade 1		
General skin redness	1	0
Urticaria	2	1
Pruritus	3	5
Rhinoconjunctivitis	10	2
Nonspecific symptoms	6	1
Reactions developed by <i>n</i> patients	14	5
Grade 2		
Bronchial obstruction	1	0
Tenesmus	1	0
Anxiety	1	0
Reactions developed by <i>n</i> patients	1	0

ITT = intent-to-treat.

able.” A similar distribution of percentages was found in the patients’ assessment. The comparison of the two treatment schedules over all patients showed no significant difference in the assessment of physicians and patients.

Adverse Events. Each undesired reaction occurring during the course of the study but not allocated to the categories systemic or local reaction by the investigator was classified as AE. A 22.8% of patients in the rush treatment schedule versus 35.5% of patients in the conventional treatment schedule reported 111 AEs. The difference is statistically significant ($p = 0.027$). AEs related to the rush schedule were 2× asthma and 1× pruritus, and related to the conventional schedule were 1× eczema, 2× pruritus, 1× urticaria, 1× fatigue, and 1× peripheral edema. Most treatment-related AEs (61.8%) were mild; only 2.7% were of severe intensity. One serious AE occurred during the entire study period documented as immediate severe bronchospasm during rush treatment schedule. Most frequent treatment-emergent adverse event symptoms were nasopharyngitis in 6.6% of patients and local reactions in 4.0% of patients.

Withdrawals. Only seven patients discontinued the study prematurely because of AEs. Four patients under rush treatment withdrew because of local reactions, pregnancy, intervertebral disk prolapse, and severe

bronchial obstruction. Three patients withdrew their consent in the conventional treatment schedule because of asthma, nasopharyngitis, and fatigue. The laboratory tests revealed no pathological findings.

DISCUSSION

This prospective clinical trial was designed to evaluate the safety of Depigoid SCIT in a rush compared with a conventional up-dosing schedule. In a former observation on 1068 patients this rush schedule was assessed to be safe.

In our study, the percentage of patients reaching maintenance phase without any relevant systemic reactions after rush build-up schedule (91.8%) did not differ significantly from the percentage after the conventional build-up schedule for Depigoid (90.9%; $p = 0.405$). Also, within subgroups treated with different allergen source material, no statistical differences were found ($p > 0.05$). The lower confidence limit suggests that with a probability of 97.5% the difference between the two build-up schedules is below 5.863%. Therefore, the noninferiority of the rush build-up schedule could be concluded for confidence limits lower than −5.863% over all patients. Patients receiving a tree pollen extract showed a lower confidence limit compared with the overall results. The lower confidence limit was −3.968%, indicating a potentially smaller difference between the treatment schedules below 3.968%.

Although the percentages of patients with systemic reactions were found to be numerically higher in the rush treatment group compared with the conventional treatment (over all patients and in the three subgroups), the differences were not statistically significant. This indicates that treatment with the rush build-up schedule does not carry a higher statistical risk of systemic reactions compared with the conventional Depigoid build-up schedule.

Studies evaluating the safety of rush schedules with nonmodified aeroallergen extracts reported a higher prevalence of systemic reactions compared with conventional up-dosing protocols.⁸ Because of the reduced IgE reactivity, modified allergen extracts in general show lower systemic and local reactions.²³ Although there are no direct comparisons between modified and nonmodified allergen extracts, the published studies, such as the present report, suggest a high safety profile for allergoids. In a large multicenter study of unmodified, standardized allergen extracts of grass pollen, a rate of grade 3 systemic reactions (urticaria or asthma) of up to 4.4% was reported.³⁶ Systemic reactions were reported in 2.1 and 2.9% of two large U.S. series.³⁷ In a rush protocol of ragweed immunotherapy using unmodified allergen extracts, a rate of anaphylaxis of 25.6% was reported in those patients not cotreated with omalizumab (and 2.6% for those receiving rush SCIT and anti-IgE

Table 6 Comparison of global assessment of physicians' and patients' (ITT) *p* values for significant differences between treatment (sub-)groups

	Physicians		Patients	
	Rush Schedule (%)	Conventional Schedule (%)	Rush Schedule (%)	Conventional Schedule (%)
Excellent	52.91	56.70	53.88	52.58
Good	41.26	36.08	37.86	38.14
Moderate	2.43	2.06	2.91	4.12
Poor	0.0	0.0	0.49	0.0
Unacceptable	0.0	0.0	0.0	0.0
All <i>p</i> Value	0.426		0.818	

ITT = *intent-to-treat*.

therapy).³⁸ In clinical practice, 33 fatalities associated with allergen immunotherapy were reported in the United States between 1985 and 2001.³⁷ To date, no cases of anaphylaxis and no fatalities are reported in >200,000 patients treated with depigmented-polymerized extracts, although continued postmarketing surveillance is essential.

Another important issue is the patient's acceptance and compliance. A long duration and slow onset of efficacy of conventional immunotherapy schedules with nonmodified extracts may have a negative impact on compliance. In contrast, trials using rush schedules generally show a good acceptance of treatment resulting in high compliance, even though undesired reactions occurred during therapy with nonmodified extracts.^{9,10}

The global assessment of treatment for both the rush and the conventional Depigoid build-up schedules was very good in the present study. The majority of physicians (rush, 94.2%; conventional, 92.8%) and patients (rush, 91.7%; conventional, 90.7%) assessed the treatment as excellent or good, indicating a very high level of acceptance. Because the global assessment of the two treatment schedules did not differ between physicians and patients, these findings support, in addition to the other results, the noninferiority of the rush build-up schedule compared with the conventional build-up schedule.

Although this study was purely designed to show the safety of the rush build-up regimen, its efficacy has been shown in two clinical studies under environmental challenge chamber conditions.^{39,40} Patients were treated with a 1-day up-dosing regimen followed by five injections in 1–2 weekly intervals. In the first study, compared with placebo, a 14% reduction of nasal symptoms due to grass pollen exposure was reported ($p < 0.08$). Seventy-one percent of the actively treated patients and 42% of placebo-treated patients developed a >30% reduction of nasal symptoms.

Physicians and patients show high treatment satisfaction, which we suggest would result in a high compliance in practice. In conclusion, this rush protocol offers an attractive treatment schedule, especially for patients with long distances to the doctors office or time limits.

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