Safety of a depigmented, polymerized vaccine for the treatment of allergic rhinoconjunctivitis and allergic asthma

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ABSTRACT

Background: *Clinical efficacy of specific immunotherapy (SIT) with depigmented, polymerized allergen extracts is well documented in placebo-controlled trials, and safety data are encouraging although further data are required.*

Methods: *We enrolled 768 patients (51% men; mean age, 31 years) in this prospective multicenter study on safety and clinical effects of Depigoid (Laboratorios LETI, S.L., Madrid, Spain). Immunotherapy consisted of four injections of increasing doses of Depigoid at weekly intervals followed by monthly maintenance injections. All adverse events were documented. Moreover, nose, eye, and lung symptoms were assessed at baseline after 3 and 6 months. Results were compared with the scores of the preceding season.*

Results: *Rates for local and systemic reactions that might possibly be related to the study medication were 2.36 and 4.56/1000 injections, respectively. With 5923 injections given, 14 local reactions were reported (5 patients), and 27 systemic reactions were reported, including 20 of grade 1 (6 patients) and 7 of grade 2 (4 patients). The best safety profile was seen for patients vaccinated against house-dust mites. Reductions in nose, eye, and lung symptoms as well as in concomitant medication compared with either the preceding season (pollen-sensitized patients) or the baseline (house-dust mite–sensitized patients) were observed at the end of study.*

Conclusion: *In this large multicenter study on 768 patients with allergic rhinoconjunctivitis and allergic asthma under daily practice conditions SIT with Depigoid was well tolerated with low rates of local and systemic reactions. Furthermore, SIT resulted in considerable reductions in symptoms and concomitant medication.*

(Am J Rhinol Allergy 24, 220–225, 2010; doi: 10.2500/ajra.2010.24.3437)

Key words: Allergic asthma, allergic rhinitis, depigmented polymerized allergen extract, dust mite, pollen, specific immunotherapy (SIT)

Immediate-type allergies result from interaction of allergens with specific IgE and can result in clinical diseases such as allergic rhinoconjunctivitis and asthma. Specific immunotherapy (SIT) can not only help to reduce symptom severity and medication requirements in allergic rhinoconjunctivitis and asthma but is also able to modify the natural course of the disease.[1–4] The efficacy of SIT is thought to be dose dependent.[5,6] However, injecting allergen extracts to which a patient is sensitized carries a risk of causing allergic reactions including anaphylaxis. Thus, the concept of optimal dose is used, which is defined as the dose of allergen vaccine inducing a relevant clinical effect in most patients without causing unacceptable side effects.[7–11]

Concerning adverse effects, the application of high doses of unmodified allergen extracts, which results in rapid achievement of the maintenance dose, results in a high incidence of adverse events (AEs).[12,13] Hence, traditional build-up schedules of administration consist of slow dose increase with weekly injections over 12–16 weeks to arrive at the maintenance dose. Because of this delayed onset of clinical benefits, compliance is often reduced.[14]

Side effects of SIT appear to be related to IgE binding (allergenicity) whereas clinical efficacy depends more on interactions with T cells (immunogenicity).[15] To reduce allergenicity while maintaining immunogenicity, glutaraldehyde-modified allergen extracts (allergoids) were developed, proving to be safer than unmodified vaccines while retaining clinical efficacy.[13,16] Recently, these modified allergens were improved by a depigmentation step before polymerization.[17–19] The resulting product (Depigoid; Laboratorios LETI, S.L., Madrid, Spain) is on the market in Germany and Spain. Several clinical trials documented the fast onset of allergy protection[20] and the possibility of a rapid dose escalation[21] as well as safety and efficacy.[22–24] These clinical trials apply carefully controlled clinical protocols in experimental conditions with limited patient numbers. Hence, it is advisable to collect complementary data in large-scale, practice-oriented noninterventional studies, where the patients are treated with medicinal products (with a marketing authorization) according to the product label and the physician's normal practice routine. The objective of this large prospective multicenter trial was to investigate the tolerability, safety, and clinical effects of a depigmented, polymerized vaccine for the treatment of allergic rhinoconjunctivitis and allergic asthma over a period of approximately 6 months on 768 patients under daily practice conditions.

PATIENTS AND METHODS

Study Design and Patients

This prospective postmarketing multicenter noninterventional study on safety and clinical effects of Depigoid was conducted by 238 office-based allergologists in Germany. Between January and November 2007 a total of 768 patients (mean age, 31 years) were enrolled in the study. Demographic data are shown in Table 1. Subjects had suffered from IgE-mediated allergic diseases for 3.8 years (median) and had been treated for 2.1 years (median).

Diagnosis

At baseline, diagnosis of type I allergy was performed by skin-prick test or determination of allergen-specific IgE. Sensitizations against grasses, trees, mites, and others were detected (Fig. 1). Indications for SIT included IgE-mediated allergic rhinoconjunctivitis and allergic asthma that were diagnosed by a clinician using defined criteria.[10] Current treatment was recorded (Table 1). In a questionnaire, reasons for participation in the study, *i.e.*, for the initiation of Depigoid

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Supported by LETI (Spain)

O. Pfaar and L. Klimek have received research grants from ALK-Albello, Denmark; Allergopharma, Germany; Stallergenes, France; HAL and Artu Biologicals, the Netherlands; Bencard, Great Britain; Hartington, Spain; Lofarma, Italy; Novartis/Leti, Germany/Spain; and Roxall, Germany; and have served as advisors and on the speaker's bureau for the aforementioned pharmaceutical companies
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Table 1 **Patient characteristics (n = 768) at baseline**

	No.
Gender	
Female	369 (48.1%)
Male	394 (51.3%)
Age	
0–11 yr (81 male patients)	113 (14.1%)
12–17 yr (54 male patients)	97 (12.6%)
>17yr (255 male patients)	549 (71.5%)
Smoking status	
Yes	56 (7.3%)
No	642 (83.6%)
Former smoker	38 (4.9%)
Type of allergy	
Allergic rhinoconjunctivitis	545 (70.96%)
Allergic rhinitis	471 (61.33%)
Allergic asthma	358 (46.61%)
Atopic eczema	137 (17.84%)
Others*	22 (2.86%)
Pretreatment	
Systemic antihistamines	523 (68.10%)
Topical antihistamines	319 (41.54%)
Topical corticosteroids	215 (27.99%)
Inhaled corticosteroids	193 (25.13%)
Others	75 (9.77%)

*Totals <100% are caused by missing data in some patients. "Others" * include food allergies, insect venom allergies, and oral intolerance syndrome*

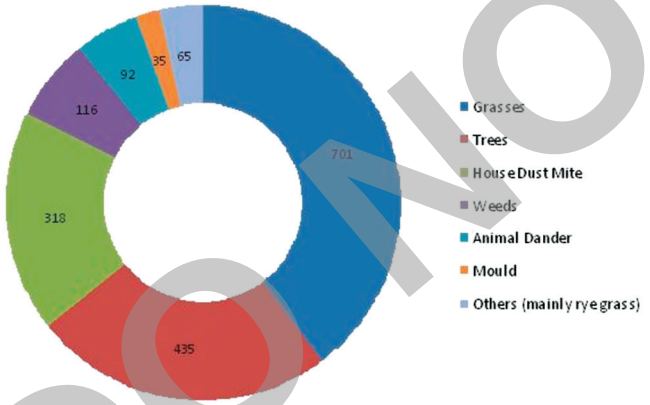

Figure 1. *Sensitization for different allergens in 768 patients. Absolute numbers are given (several sensitizations per patient are feasible). "Others" denotes predominantly rye grass.*

treatment, and symptoms during the past allergic season were reported by the patients. In addition, concomitant medication was documented.

Immunotherapy

SIT consisted of a build-up phase lasting 3 weeks with four injections of increasing doses at weekly intervals and a subsequent maintenance phase with monthly applications of 0.5 mL of the respective allergen extract for a duration of 6 months. According to the patient's history treatment with a commercial vaccine of the modified allergen extract adsorbed to aluminum hydroxide (Depigoid, Laboratorios LETI S.L., Spain) was administered as shown in Fig. 2 using Depigoid House Dust Mite mixture (50% of *Dermatophagoides pteronyssinus* and 50% of *Dermatophagoides farinae*), Depigoid *D. pteronyssinus*, and Depigoid, with the latter containing allergens of either grasses, trees,

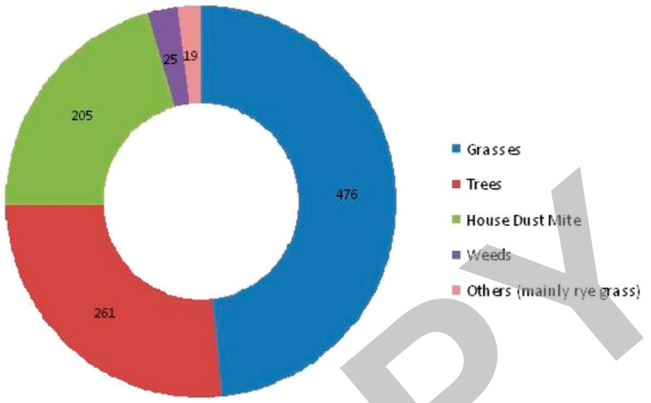

Figure 2. *Vaccination with corresponding depigmented, polymerized allergen extracts. Absolute numbers are given (several vaccinations per patient are feasible). "Others" denotes predominantly rye grass.*

weeds, or others. Because of the fact that many patients showed sensitizations against more than one antigen (Fig. 1), some subjects received more than one vaccination (Fig. 2). Administration was performed according to the summary of product characteristics.[25]

Following the recommendations of the European Academy of Allergology and Clinical Immunology,[3] all patients were monitored by a physician for 30 minutes after each injection. None of the patients received preventive pharmacologic treatment.

Evaluation

To assess safety of the applied immunotherapy, immediate and late local reactions as well as systemic reactions were documented using the criteria of the European Academy of Allergology and Clinical Immunology position paper for severity grading.[3] Also, general tolerability was rated by physicians and patients. Clinical assessment took place at baseline, after 3 (control visit) and 6 months (final visit) of treatment with Depigoid.

Nose, eye, and lung symptoms were assessed by a physician on a 4-point rating scale from 0 (absent) to 3 (severe). Definitions are as follows: mild = prevalent, but not disturbing; moderate = disturbing but not impairing or not tolerable; severe = impairing and/or not tolerable. In case of seasonal allergens (*e.g.*, pollen) final visit scores were compared with the scores of the preceding season (rated by patients by recall at baseline visit). For perennial allergens (*e.g.*, house-dust mites) baseline scores where used instead of preceding season scores. The same comparison was performed to analyze the changing use of concomitant medication.

Statistical Analysis

Data analysis was performed using descriptive statistics only. Results were presented as frequency scores in absolute numbers or as a percentage.

RESULTS

A total of 768 patients started SIT with Depigoid. Physicians reported as reasons for the initiation of Depigoid rapid updosing (90.4%), fast onset of action (64.6%), and expectation of better safety than conventional extracts (25.7%). The initial follow-up visit took place after 109 (±63) days of SIT. At this time, 79 patients discontinued because of planned short-term preseasonal treatment. An additional 33 patients dropped out of the study, with 4 patients reporting AEs (itchy throat, general discomfort, swallowing disorder, bronchitis, cough, and circulatory instability) as the reason and 29 patients with a lack of compliance. For the remaining 656 patients the mean study duration was 180.3 (±65) days and at

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Table 2 **The incidence per 1000 injections; total number of injections given is 5923 (total of 41 adverse events possibly related to the study medication were observed in or reported by 15 patients)**

Adverse Events Related to the Study Medication	No. (*n*)	Incidence per 1000 Injections
Local reactions		
Pruritus	6	1.0
Swelling	5	0.8
Redness	3	0.5
Systemic reactions (grade 1)		
General discomfort, tiredness, malaise, and nausea	5	0.8
Eyes (itching, tearing, sensation of pressure, and redness)	4	0.7
Swallowing disorder, throat irritation, and itchy throat	4	0.7
Itchy scalp, facial rash, and facial pruritus	3	0.5
Hand rash, and atopic flare-up	2	0.3
Allergic rhinitis and runny nose	2	0.3
Systemic reactions (Grade 2)		
Bronchitis and cough	4	0.7
Circulatory instability	2	0.3
Atopic dermatitis	1	0.2

the final visit 84.5% of the patients decided to continue with Depigoid after the end of the study.

Safety

General tolerability of the SIT with a depigmented, polymerized allergen extract was rated by the physicians as "very good" or "good" in 94.1% of cases. This estimation was confirmed by the patients with 93.4% rating tolerability as "very good" or "good." Documentation of AEs also supports the good safety profile of the vaccine with only 32 patients (4.2%) reporting 64 AEs, of which 41 AEs in 15 patients (1.95%) were regarded as being possibly related to the study medication. In consideration of the total number of injections given (5923), the rates for local and systemic reactions possibly related to the study medication were 2.36 and 4.56/1000 injections, respectively. The incidences for the occurrence of AEs per 1000 injections are given in Table 2.

Nine adverse reactions were reported in association with the injections in the updosing phase and 12 together related with the injections in the maintenance phase. For the remaining AEs the temporal relationship with injections was not recorded.

Local reactions including pruritus, swelling, and redness at the injection site occurred 14 times in five patients, with nine cases occurring in patients vaccinated against tree pollen (Table 3). No treatment was required.

Mild systemic reactions (grade 1) were reported by 6 patients (20 cases), with only 4 cases occurring in patients vaccinated against house-dust mites. Seven AEs in four patients were classified as moderate (grade 2 systemic reactions). One of these patients, a 25-year old woman vaccinated against grass pollen experienced an exacerbation of her preexisting atopic dermatitis and was hospitalized. Another female patient vaccinated against tree pollen suffered from bronchitis and cough (four times), and two patients experienced circulatory instabilities with a mild drop of blood pressure (Table 3). No grade 3 or 4 systemic reactions were recorded. All patients who experienced AEs recovered.

Table 3 **The incidence per patient for subjects treated with different allergens. Figures for mixtures not shown because of low numbers.**

Adverse Events Related to the *n*	HDM (*n* = 132)		Grasses (*n* = 219)		Trees (*n* = 178)	
	n	Incidence per Patient	*n*	Incidence per Patient	*n*	Incidence per Patient
Local reactions		0.015		0.005		0.051
Pruritus	1	0.008	1	0.005	3	0.017
Swelling	1	0.008	—		3	0.017
Redness	—		—		3	0.017
Systemic reactions (grade 1)		0.030		0.037		0.040
General discomfort, tiredness, malaise, and nausea	2	0.015	2	0.009	—	
Eyes (itching, tearing, sensation of pressure, and redness)	—		3	0.014	1	0.006
Swallowing disorder, throat irritation, and itchy throat	2	0.015	2	0.009	—	0.011
Itchy scalp, facial rash, and facial pruritus	—		—		3	0.017
Hand rash and atopic flare-up	—		—		2	
Allergic rhinitis and runny nose	—		1	0.005	1	0.006
Systemic reactions (grade 2)		0		0.014		0.022
Bronchitis and cough	—		—		4	0.022
Circulatory instability	—		2	0.009	—	
Atopic dermatitis	—		1	0.005	—	

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Clinical Assessment

At the end of the study improvements in comparison with the preceding season were seen for nasal symptoms in 73.3%, for eye symptoms in 66.9%, and for lung complaints in 39.7% of patients. In comparison with the preceding season, nose, eye, and lung symptoms rated as moderate or severe by the physicians showed a considerably lower frequency after SIT (Fig. 3 *A*). Similarly, separate analysis of age groups (children, adolescents, and adults) revealed a reduction of such symptoms and, thus, a positive effect of SIT (Fig. 3 *B*). The greatest improvements (66.7% and 68.9%) were seen for nose and eye problems in adolescents. Also children <12 years of age experienced a distinctive reduction (68.1%) in lung symptoms reported as moderate or severe (Fig. 3 *B*).

Further analysis for allergen subgroups revealed reductions in eye and lung symptoms reported as moderate or severe of >70% for patients who had received vaccination against house-dust mites. Patients vaccinated against seasonal allergens (grasses and trees) also experienced reductions in nose, eye, and lung symptoms of >50% (Fig. 3 *C*). Reductions in concomitant medication compared with either the preceding season (pollen-sensitized patients) or the baseline (house-dust mite–sensitized patients) were observed at the end of study (Fig. 4).

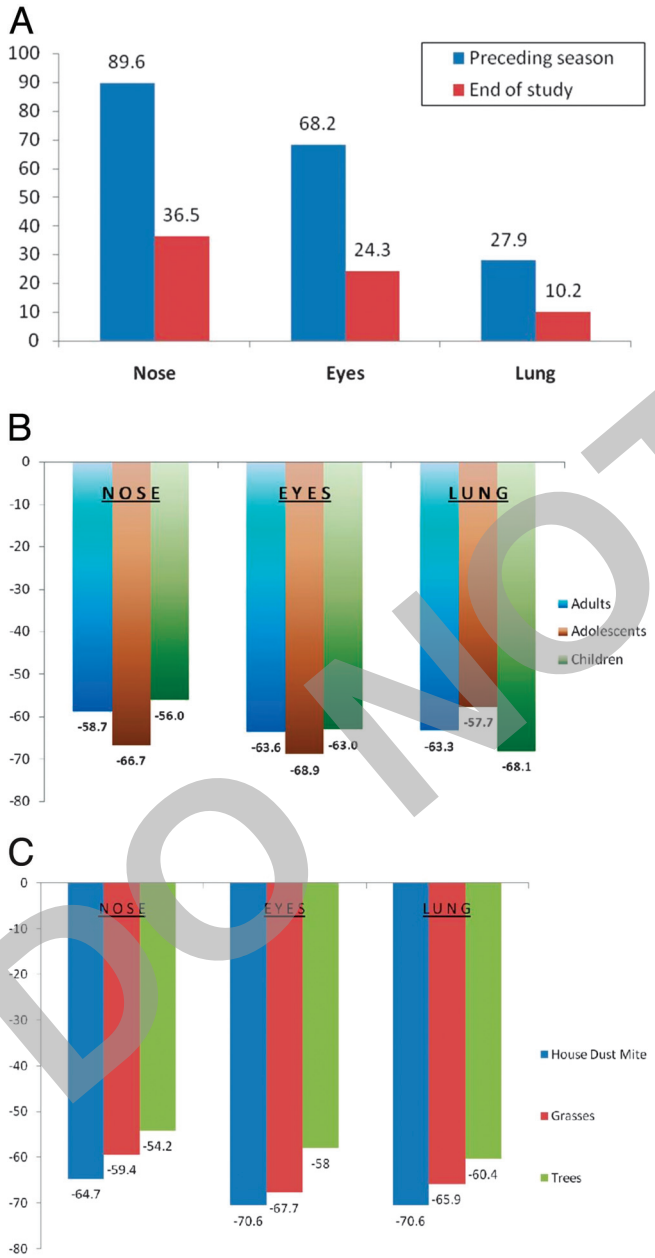

Figure 3. (A–C) Symptoms rated by the physicians as "moderate" or "severe" before the beginning of immunotherapy (i.e., baseline or preceding season) and at the end of the observation period. (A) Frequency (in percent) in all patients (n = 768). (B) Reduction of symptoms (in percent of patients) by age group during immunotherapy (n = 113 [children], 97 [adolescents], and 549 [adults]). No age data were available for nine patients. (C) Shows the reduction of symptoms (in percent of patients) by allergen group during immunotherapy.

DISCUSSION

In this study, treatment with a therapeutic vaccine containing depigmented and polymerized allergen extracts was evaluated in a large cohort of 768 patients. The inclusion of 238 centers helped in avoiding bias of a single or few physicians administering the treatment and made our results more representative of real-life conditions.

Less than 5% of subjects reported AEs. AEs possibly related to the study medication occurred even less frequently (1.95% of patients). Rates of local (2.4/1000 injections) and systemic reactions possibly related to the study medication (4.6/1000 injections) were low with no grade 3 or 4 systemic reactions, and none required medical treatment except for one female patient vaccinated against grass pollen who had to be hospitalized because of an exacerbation of her coexisting atopic dermatitis. The use of SIT for atopic dermatitis is growing but firm guidelines for treatment still are not established, and further safety data in this indication will be required.[26] The best safety results were seen for the 132 patients vaccinated against house-dust mites with only two local and four grade 1 systemic reactions.

The safety profile of this Depigoid SIT seen here is comparable with previous studies on Depigoid SIT.[20,23,24,27–31] In a prospective open study on 1068 patients with rhinoconjunctivitis and/or asthma sensitized to mites and/or pollen immunotherapy with an ultra-rush 1-day uptitration schedule was performed and the maximum dose was even reached during the 1st day of therapy. Only five grade 1 and three grade 2 reactions occurred, although all patients reached the maximum dose on the 1st day.[21] In a double-blind placebo-controlled study of Alvarez-Cuesta *et al.*, seven patients experienced local reactions and no systemic reactions occurred among patients from the active group.[23] In another double-blind placebo-controlled trial five patients (out of 29 patients in the active-group) had systemic reactions over 1 year of immunotherapy with glutaraldehyde-polymerized mite extracts.[20] These data compare with systemic reaction rates of 2.9

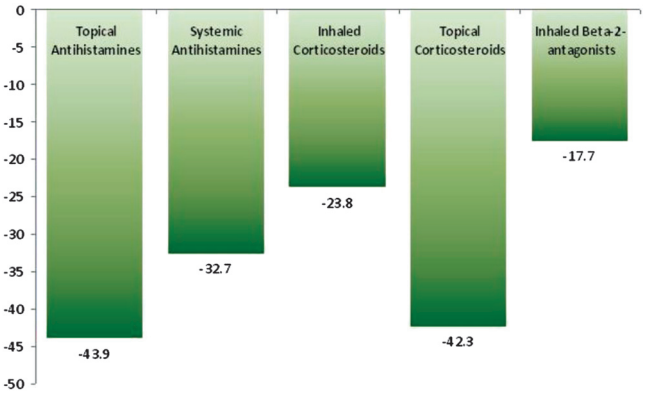

Figure 4. Reduction in concomitant medication at the end of observation period in comparison with baseline or to the preceding season (percent).

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and 2.1% that have been reported on two large U.S. series reporting safety of SIT.[32] Direct comparison between unmodified extracts and Depigoid in a small study indicated four systemic reactions (one grade 1 and three grade 2) in 12 patients treated with unmodified allergen extract compared with one grade 2 reaction in a parallel group of 11 patients treated with Depigoid at a dose 10 times higher than that of the unmodified extract.[33] Taken together, these data suggest that SIT with Depigoid has an improved safety profile compared with unmodified extract, which may thus allow higher and therefore more effective dosing. The current study confirms the safety profile of Depigoid in a large number of patients monitored prospectively in a clinic setting. The fact that our rates of systemic reactions are a bit higher than in the study of Casanovas *et al*.[21] is probably caused by the study setting. Our results reflect real-life conditions and thus also may be more relevant to safety considerations than those of formal clinical trials.

Overall, clinical effects of SIT appeared to be good with reductions in concomitant medication between 17.7 and 43.9%. Furthermore, improvements for nose and eye symptoms in more than two-thirds of patients and for lung symptoms in more than one-third were recorded at the end of the study after a short-time therapy interval of 180 days on average. Analysis of age groups revealed similar improvements. In every age group, including the group of children <12 years of age, patients experienced a positive effect of the treatment, with reductions for all symptoms amounting to >50%. Analyzing different allergen groups showed the greatest improvements for patients vaccinated against house-dust mites.

The positive outcome of Depigoid SIT is probably related to the high accumulated dose applied during the course of SIT. Because of effective depigmentation and polymerization of the allergenic extracts, the amount of native material processed into this specific type of immunotherapy leads to an ~10-fold higher dose of major allergens (measured before polymerization) compared with current literature.[3,4,25,27,28,34] During 24 weeks of study period patients received relatively high doses of allergens that had no negative influence on the safety profile.

Taken together, this study revealed a good safety profile of Depigoid under daily practice conditions. Reflecting real life is regarded as very important, because patients included in many clinical trials are not really representative of the general population.[35]

ACKNOWLEDGMENTS

The authors thank all participants for their engagement in this multicenter trial. Furthermore, the authors thank Dr. Frank Erdnüß, Wiesbaden, Germany, for editorial assistance.

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