Original Article

Safety of specific immunotherapy using a four-hour ultra-rush induction scheme in bee and wasp allergy

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Summary. *Background:* Ultra-rush induction of immunotherapy with Hymenoptera venom is a reliable and efficacious alternative to the rush induction protocol, though not widely used in European countries yet. Its safety, however, has been intensively discussed over the last few years.
The aim of this retrospective case study was to examine the rate of allergic side-effects during our four-hour ultra-rush hymenoptera venom induction regimen. We evaluated risk factors for observed side-effects such as age, gender, severity of previous insect sting reactions according to the H.L. Mueller classification, concentration of venom inducing positive skin tests, level of specific IgE, serum tryptase concentration, and hymenoptera venom used for treatment.
Methods: 67 outpatients with Hymenoptera venom allergy received 80 courses of ultra-rush immunotherapy. Diagnosis and selection of patients for venom immunotherapy were carried out according to the European Academy of Allergology and Clinical Immunology. We applied a four-hour regimen, and local or systemic reactions were documented.
Results: In 78 courses (97.5%) the maintenance dose of 111.1 μg was reached within 4 hours and it was tolerated in 82.5% without any hypersensitivity reaction. Allergic side-effects were observed in only 17.5% (n=14): four severe local reactions (5%), eight grade I (10%) and two grade II (2.5%) systemic reactions. There was no significant difference in the number of systemic reactions comparing patients receiving wasp or honeybee venom extract. The number of systemic reactions was neither higher in patients with a severe prior insect sting reaction (grade III or IV) nor dependent on age, gender, skin test reaction, level of specific IgE or tryptase. Epinephrine as rescue medication was never needed. Interestingly, patients with a severe prior wasp sting reaction showed a significantly lower incidence of allergic side-effects during ultra-rush immunotheraphy with wasp venom extract as compared to grade III or IV honeybee venom allergic patients.
Conclusion: Our ultra-rush immunotherapy induction regimen shows a low incidence of systemic reactions. It proved to be safe and convenient for the patient, as it could be applied in a four-hour outpatient regimen.

Key words: Ultra-rush immunotheraphy, Hymenoptera venom allergy, wasp, honeybee, side-effects, safety.

Resumen. La inducción ultrarrápida de inmunoterapia con veneno de himenóptero es una alternativa eficaz y fiable para el protocolo de inducción rápida, aunque aún no se utiliza demasiado en los países europeos. Sin embargo, en los últimos años se ha debatido mucho sobre su seguridad.
El objetivo de este estudio de casos retrospectivo fue examinar la tasa de efectos secundarios alérgicos durante una pauta de inducción de veneno de himenóptero ultrarrápida de cuatro horas. Se evaluaron los factores de riesgo de los efectos secundarios observados, como la edad, el sexo, la gravedad de la reacción a picadura de insecto previa según la clasificación de H. L. Mueller, la concentración de veneno que genera pruebas cutáneas positivas, el nivel de IgE específica, la concentración sérica de triptasa y el veneno de himenópteros utilizado para el tratamiento.
Métodos: Sesenta y siete pacientes ambulatorios con alergia al veneno de himenópteros recibieron 80 tandas de inmunoterapia ultrarrápida. El diagnóstico y la selección de pacientes para la inmunoterapia con veneno se realizaron

de acuerdo con la Academia Europea de Alergología e Inmunología Clínica. Se utilizó una pauta de cuatro horas, y se documentaron reacciones locales o sistémicas.
Resultados: En setenta y ocho tandas (97,5%) se alcanzó la dosis de mantenimiento de 111,1 µg a las 4 horas y en un 82,5% se toleró sin ninguna reacción de hipersensibilidad. Sólo se observaron efectos secundarios alérgicos en un 17,5% (n = 14): cuatro reacciones locales graves (5%), ocho reacciones sistémicas de grado I (10%) y dos de grado II (2,5%). No se observó ninguna diferencia significativa en el número de reacciones sistémicas al comparar los pacientes que recibieron extracto de veneno de abeja o avispa. El número de reacciones sistémicas no fue superior en pacientes con una reacción a picadura de insecto previa grave (grado III o IV) independiente de la edad, el sexo, la reacción a la prueba cutánea, el nivel de triptasa o IgE específica. No se precisó de epinefrina como medicamento de rescate. Curiosamente, los pacientes con una reacción a picadura de avispa previa grave mostraron una incidencia significativamente menor de efectos secundarios alérgicos durante la inmunoterapia ultrarrápida con extracto de veneno de avispa, en comparación con los pacientes alérgicos al veneno de abeja de grado III o IV.
Conclusión: La pauta de inducción de inmunoterapia ultrarrápida muestra una baja incidencia de reacciones sistémicas. Ha demostrado ser segura y cómoda para el paciente, ya que pudo aplicarse en régimen ambulatorio de cuatro horas.

Palabras clave: inmunoterapia ultrarrápida, alergia al veneno de himenópteros, avispa, abeja, efectos secundarios, seguridad.

Background

Immediate type allergies to Hymenoptera venom occur with a prevalence of nearly 5% [1] and present with a variety of local and systemic symptoms such as local sting reaction, flush, generalized urticaria, angioedema, dyspnea or even anaphylactic shock. In some cases also neurological symptoms like pareses, dizziness, cephalea and headache have been described [2-3]. To date, specific immunotherapy is the only available causal treatment and has been recognized as safe and effective in patients with Hymenoptera venom allergy. Protection from future severe reactions can be achieved in up to 90% [1].

Systemic reactions during the initial phase of treatment are common, occuring in up to one third of all patients (10.7-38%) [4-7]. They pose a serious problem, since it is not possible to predict these reactions that may occur with any immunotherapy regimen.

In an effort to improve tolerability and to minimize the occurrence of serious side-effects, different dosing schedules (conventional, rush, cluster and ultra-rush regimen), which operate on a variety of either continuous or intermittent schedules, have been proposed and are presently in use [4-11].

However, current experience with the most rapid protocol, the ultra-rush immunotherapy, is still insufficient.

We studied safety in patients allergic to Hymenoptera venoms, having been treated following a four-hour ultra-rush protocol, and determined the incidence of hypersensitivity reactions, since objective comparisons of incidence rates are still difficult to achieve. Furthermore, we compared patients with allergic side-effects during ultra-rush immunotherapy with those who tolerated therapy very well, to identify potential risk factors for side-effects.

Material and Methods

Patients

We analyzed the data of 67 Hymenoptera venom allergic patients (23 f, 44 m) who were treated with ultra-rush immunotherapy in the Department of Dermatology and Allergy of the University of Zurich from January 2003 to September 2004. Patients were selected based on the criteria established by the European Academy of Allergy and Immunology [12]. Therefore, immunotherapy was recommended if there was a history of an immediate systemic reaction after a Hymenoptera sting and/or the demonstration of IgE-mediated serum antibodies to the respective venom. Immediate allergic reactions were classified according to the system proposed by H.L. Mueller [13]. Patients (40.4 ± 14.7 years) were split into four different age groups which were defined as I (0-20 years; 9 patients), II (21-40 years; 30 patients), III (41-60 years; 35 patients) and IV (> 61 years; 6 patients). Patients who received both venoms were considered twice in the evaluation.

Skin tests

In all patients skin tests were performed with 10-fold dilutions of wasp and honeybee venom (ALK-SQ™, ALK-Scherax GmbH, Hamburg, Germany). Skin test reactivity was tested by performing intradermal tests on the forearm with increasing concentrations from 0.00001 µg/mL to 1.0 µg/mL. Skin tests were considered positive if a weal of at least 5 mm in diameter with erythema occurred after 15 min at a concentration of 1 µg/mL or less [13]. The lowest concentration resulting in such a reaction was defined as the endpoint concentration. Control tests were performed with histamine as positive and NaCl 0.9% as negative control.

Laboratory

Allergen-specific IgE against wasp and honeybee venom were measured in the patients' sera using the Pharmacia-ImmunoCAP-System™ (Pharmacia Diagnostics, Uppsala, Sweden). Results > 0.35 kU/L were considered positive. Tryptase < 11.4 ng/ml was considered normal.

Ultra-rush immunotherapy regimen

Ultra-rush induction of immunotherapy was performed within four hours under resuscitation facilities with aqueous purified venom extract (Pharmalgen, Horshølm, Denmark). Thirteen patients were treated with both wasp and honeybee venom on two separate days, thirty-four patients with wasp and twenty patients with honeybee venom. All patients had in intravenous access using Saline during the ultra-rush-procedure. ECG was monitored continuously, and heart rate and blood pressure every 15 minutes or more often in case of interfering side effects.

Therapy was initiated with a venom dose of 0.1 μg, administered subcutaneously, followed by 1, 10, and 20 μg at 30-min intervals and then 30 and 50 μg at a 60-min interval (cumulative total dose of 111.1 μg). Patients who completed this protocol received booster injections of 100 μg on day 7 and 100 μg on day 14 (Alutard SQ, ALK, Horshølm, Denmark). Subsequently, 100 μg boosters were given every 4-6 weeks in our department or at the GP's office. Patients received pre-treatment with antihistamines (cetirizine or fexofenadine) for three days before and on the morning of ultra-rush itself. Subsequently, they also took antihistamines before booster-injections to reduce local side-effects.

Adverse reactions

Anaphylactic reactions during ultra-rush immunotherapy were measured, documented and classified according to the criteria of H.L. Mueller [13]. Objective reactions were followed by symptomatic treatment with oral or intravenous antihistamines or intravenous corticosteroids.

Results

Between January 2003 and September 2004, 67 outpatients (23 females, 44 males) ranging in age from 15-66 years (mean: 40.4 years) underwent four-hour ultra-rush immunotherapy. Since thirteen patients received both wasp and honeybee venom (32.5%), thirty-four wasp venom only (42.5%) and twenty patients honeybee venom only (25%), 80 immunotherapy courses were administered all together. Of these, 75 were performed in patients with grade II-III, III and IV to prior insect sting reactions. In the other 5 patients reacting only with grade I or II, specific immunotherapy was peformed due to very high exposure risk (3 pts) and extreme fear of new allergic reactions (2 pts). All patient details are summarised in Table 1.

Adverse reactions

In seventy-eight ultra-rush courses (97.5%) the maintenance dose of 111.1 μg was reached, and in sixty-six courses (82.5%) tolerated without any hypersensitivity reaction.

During the course of ultra-rush induction, 14 patients (17.5%; 6 f, 8 m) experienced allergic reactions which were mainly mild in character: a severe local reaction, defined as a swelling > 10 cm diameter and erythema, occurred in four patients (5%; 1 f, 3 m), grade I reactions in 8 patients (10%; 4 f, 4 m) and grade II reactions in two patients (2.5%; 1 f, 1 m). In these two patients induction of immunotherapy by ultra-rush regimen had to be stopped prematurely due to persistent side-effects despite treatment with intravenous antihistamines and corticosteroids. In those patients induction was completed by the conventional outpatient regimen.

There was no difference in the development of side-effects between men and women (p=.497).

Age, according to the four age groups, had no influence on the development of side-effects during ultra-rush immunotherapy (p=.454).

Most serious adverse events occurred after the injection of 30 μg venom extract (n=5, 6.3%). However, side-effects showed no significant dose-dependency (p> .05). 2.5% of allergic reactions (n=2) occurred after the injection of 0.1, 1 and 10 μg, respectively, 1.3% (n=1) after 20 μg and 2.5% (n=2) after 50 μg of venom extract. The time interval between injection and side-effect was below 30 min. No late reactions have been observed. 91.25% of all patients experienced no side-effects before receiving 30 μg venom extract, whereas only 85% were free of allergic reactions after the injection of 30 μg or accumulative venom dose of 61.1 μg, respectively (Figure 1, Kaplan-Meier analysis). The mean threshold dose for adverse events was 44.9 μg of venom extract.

The level of specific IgE, tryptase and skin test results did not show any correlation with the risk of developing side-effects, independently of the Hymenoptera species used (p>.05). Side-effects did not increase with higher

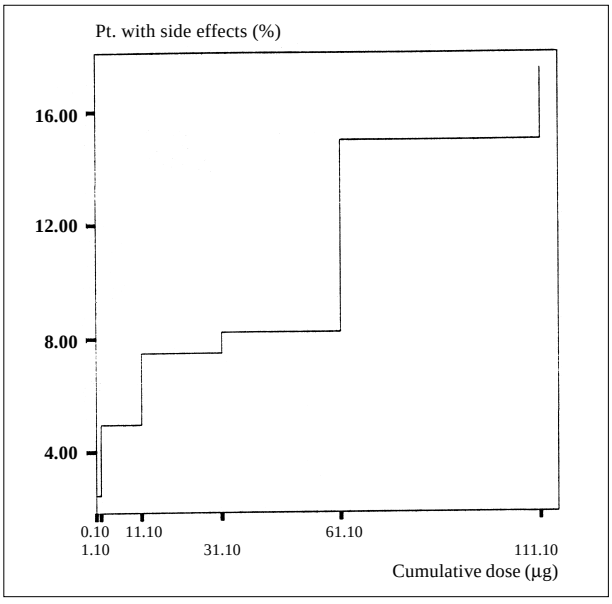

Figure 1. Cumulative incidence of adverse reactions depending on total dose applied.

Table 1. Clinical data of patients receiving ultra-rush venom immunotherapy.

No. of patients	Total 67	Honeybee	Wasp (yellow jacket)
Allergy			
Honeybee venom (HBV)	20 (25%)		
Wasp venom (WV)	34 (42.5%)		
Both	13 (32.5%)		
Age (y)			
Range	15-66		
Mean	40.4(±14.7 years)		
Gender			
Male	44 (65.7%)		
Female	23 (34.3%)		
Grade of prior insect sting reaction			
I	1 (1.3%)	0 (0%)	1 (1.3%)
II	4 (5%)	2 (2.5%)	2 (2.5%)
II-III	9 (11.3%)	5 (6.3%)	4 (5%)
III	37 (46.3%)	14 (17.6%)	23 (28.8%)
III-IV	5 (6.3%)	1 (1.3%)	4 (5%)
IV	24 (30%)	10 (12.5%)	14 (17.5%)
Specific IgE against bee venom (kU/l)	Mean value	58.60	–
	Standard deviation	36.14	–
Specific IgE against wasp venom (kU/I)	Mean value	–	15.37
	Standard deviation	–	10.15
Tryptase (ng/ml)	Mean value	6.24 (range:1.04-31.3)	
	Standard deviation	4.16	
Skin test results			
0.00001 µg/mL	9 (11.3%)	4 (5%)	5 (6.3%)
0.001 µg/mL	5 (6.3%)	2 (2.5%)	3 (3.8%)
0.01 µg/mL	30 (37.5%)	6 (7.5%)	24 (30%)
0.1 µg/mL	26 (32.5%)	15 (18.8%)	11 (13.8%)
1 µg/mL	9 (11.3%)	6 (7.5%)	3 (3.8%)
normal	1 (1.3%)	0 (0%)	1 (1.3%)
Adverse reactions under ultra-rush			
Severe local reaction	4 (5%)	1 (1.3%)	3 (3.8%)
Grade I	8 (10%)	4 (5%)	4 (5%)
Grade II	2 (2.5%)	0 (0%)	2 (2.5%)
Dose dependency of side-effects			
0.1 µg	2 (2.5%)	1 (1.3%)	1 (1.3%)
1 µg	2 (2.5%)	1 (1.3%)	1 (1.3%)
10 µg	2 (2.5%)	2 (2.5%)	0 (0%)
20 µg	1 (1.3%)	0 (0%)	1 (1.3%)
30 µg	5 (6.3%)	1 (1.3%)	4 (5%)
50 µg	2 (2.5%)	0 (0%)	2 (2.5%)

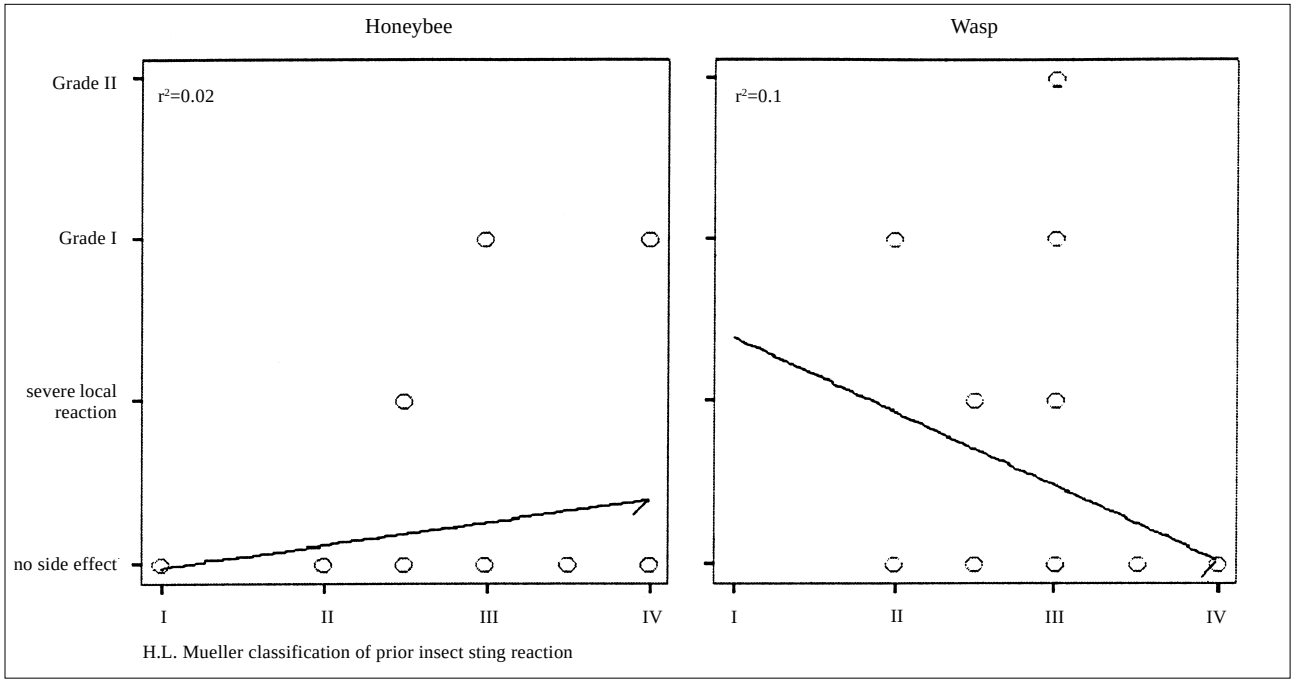

Figure 2. Correlations between reactions to prior insect sting according to H.L. Mueller and incidence of side-effects under ultra-rush immunotherapy in honeybee and wasp venom allergic patients. Regression lines are shown.

specific IgE against honeybee venom (p=.377), wasp venom (p=.197), or tryptase (p=.193). In patients who underwent ultra-rush immunotherapy, specific IgE against honeybee correlated very well with test results, independently of whether the patients were sensitized to honeybee or wasp venom (p=.019 and p=.000, respectively). However, wasp venom allergic patients tended to give rise to higher values of specific IgE against honeybee (p=.005) due to cross-reactivity. There was no significant difference (p=.643) in the number of systemic reactions between patients receiving wasp venom extract (n=9; 19.1%) and those receiving honeybee venom extract (n=5; 15.2%).

Moreover, significant correlations between grade of side-effects during ultra-rush and prior insect sting reaction could not be found. However, looking at prior insect sting reactions in detail, we could find a significant correlation between more severe allergic reaction to wasp stings (grade III/IV) and the absence of side-effects during ultra-rush immunotherapy (p=.022, Mann-Whitney-test). The expected value for side-effects would decrease by each reciprocally to the grade classified by grade with r square = 0.1 (Figure 2).

Discussion

Ultra-rush immunotherapy is a safe and very effective treatment to prevent potentially life-threatening reactions in Hymenoptera venom allergic patients. However, safety and efficacy have been intensely discussed, since the fast build-up phase of the treatment has been argued to cause more side-effects. It is hard to draw conclusions from so far published studies dealing with safety aspects of ultra-rush induction of immunotherapy, due to the application of highly different study designs.

Our aim was to define risk factors for side-effects to ultra-rush induction of immunotherapy in order to adapt the future immunotherapy regimens to the individual patient's risk profile. The most striking finding in our study was the comparable safety of ultra-rush immunotherapy with conventional rush-regimens at a short inpatient's stay.

Secondly, severe allergic reactions (grade III and IV according to the H.L. Mueller classification) to wasp stings have been accompanied by less side-effects during ultra-rush immunotherapy than severe prior honeybee sting reactions.

Our ultra-rush immunotherapy regimen was well tolerated. Only 17.5% of our patients developed hypersensitivity reactions during the build-up phase, and these were mostly mild in character and none of them life-threatening. Sturm et al. compared different publications in regard to regimens and side-effects and found a rate of systemic reactions under ultra-rush protocols of 11.3%. However, this figure represented an average of the results of only three studies. Contrarily, in other studies, the occurrence of adverse events during ultra-rush immunotherapy ranged between 10.7 and 30% [14].

One reason for the relatively low number of adverse events in our cohort treated with a four-hour induction scheme compared to other studies may be the reduced number of venom injections, though with a comparable cumulative total venom dose. Schiavino et al. studied a

total of 57 patients who underwent specific 1-day ultra-rush densensitization, reaching a cumulative dose of only 101.1 μg by application of six subcutaneous injections within 2.5 hours [15]. All patients but 1 completed the ultra-rush desensitization. However, 10 (18%) had a slight local reaction immediately after desensitization, 6 (11%) manifested a more severe local reaction and 4 patients (7%) presented mild systemic reactions that required emergency treatment. Birnbaum et al. used an identical protocol in 258 Hymenoptera venom-allergic patients with a cumulative dose of 101.1 μg, though over a period of 3.5 hours. In 325 ultra-rush immunotherapies performed, 33 (12.79%) patients experienced a systemic reaction during the increase in dose, comprising localized urticaria and/or angioedema and/or erythema in 24 patients and hypotension in 9 patients [16]. Bernstein et al. reports mild systemic reactions in only 5.2% of 77 patients, but in this study all patients received a cumulative total dose of only 58.55 μg on one day followed by an accelerated build-up over three weeks [11]. Another reason for the low incidence of allergic side-effects in our patients may be the pretreatment with antihistamines three days before the induction phase. Past research has shown that antihistaminic pretreatment reduces local allergic reactions and generalized symptoms, i.e., urticaria and angioedema, under immunotherapy.

Furthermore, it had a beneficial effect on long-term outcome of immunotherapy [17,18]. However, in those studies, the global incidence of systemic allergic symptoms under immunotherapy were not reduced by antihistamines.

There was a trend towards a higher incidence of adverse reactions in patients receiving wasp venom extract compared with those receiving honeybee venom extract. This is not in agreement with previous findings in which a higher incidence of side-effects in patients treated with honey bee venom during rush immunotherapy has been described [1, 5, 8, 14, 19-22]. However, with regard to the severity of side-effects, our results are in line with earlier reports demonstrating more severe side-effects in honeybee venom treated patients [1, 8, 19, 21, 23].

Our data suggest that there is no correlation between the incidence of side-effects and the severity of the prior insect sting reaction which has been controversially discussed in previous investigations [8, 14]. Moreover, we observed a significant trend towards a lower incidence of allergic side-effects in wasp venom allergic patients with severe prior insect sting reactions. These findings are in contradiction to the results published by Birnbaum et al., who reported that patients who experienced a grade 3 or 4 reaction after the sting, more frequently developed a grade 3 or 4 reaction to the venom immunotherapy. These discrepancies might have several reasons: sting reactions are graded according to the patients' case histories (recall bias) or by lay witnesses who lack the knowledge to correctly grade the allergic reaction. Second, and more likely, patients might experience an immunologic booster 'injection' when being stung by an insect with a large amount of venom. This could serve as a trigger for a strong immediate type immune response.

According to our results, neither the degree of positive reactions in skin tests, serum IgE concentration or tryptase, nor gender or age serve as a reliable predictor of side-effects during treatment independently of the responsible Hymenoptera species. The lack of correlation between the level of specific IgE and the risk of developing side-effects is independent of the Hymenoptera species. These findings have been described in previous studies [8, 14].

In other studies, however, the female sex has been reported to influence the risk of side-effects negatively [1, 5, 8, 19, 22].

The degree of positive venom skin tests was not significantly different between patients who experienced an adverse event and those who did not, when looking within the highly sensitized group-according to the skin test (0.00001 μg/mL) versus those with higher skin test results.

Regarding the dose-dependency of side-effects, most events occurred after injection of 30 μg or a cumulative dose of 61.1 μg, respectively. Usually, side-effects are observed between 10 and 40 μg [14]. Therefore we suggest administering the 30 μg dose with an interval of more than an hour after the 20 μg dose in risk patients in future.

Taking all our findings into account, safety is assured with this ultra-rush immunotherapy regimen. The number of side-effects compares favorably with or even exceeds conventional rush protocols, the majority of side-effects are mild, the duration of patient hospitalization reduced to a minimum, protection achieved most rapidly, and patient compliance is secured. Therefore, ultra-rush immunotherapy with short induction schemes can serve as first line treatment in Hymenoptera venom allergic patients in the future.

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