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Efficacy and Safety of Rush Immunotherapy in Patients with *Hymenoptera* Allergy in Japan

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SUMMARY **In Japan, approximately 40 persons die annually from anaphylaxis caused by *Hymenoptera* stings. Venom immunotherapy is considered safe and effective for the treatment of allergic systemic reactions caused by *Hymenoptera* stings in patients with *Hymenoptera* allergy. We studied the efficacy and safety of rush immunotherapy in patients who had a history of systemic reactions to *Hymenoptera* stings in Japan. Between 1988 and 2002, 95 patients with a history of systemic reactions to *Hymenoptera* stings were investigated. The stings originated from honeybees in 5 patients, yellow jackets in 28, wasps in 48, both yellow jackets and wasps in 9, and both yellow jackets and honeybees in 5. All patients had venom-specific IgE antibodies in sera (RAST score ≥ 2) and received rush immunotherapy with venom extracts at our hospital. Forty-three patients had 63 field re-stings during immunotherapy. Of these patients, 41 (95.3%) with 59 field re-stings (93.7%) had no systemic reactions. Two patients (4.7%) with four field re-stings (6.3%) had anaphylactic shock. Although anaphylactic reactions developed in two patients (2.1%) during rush immunotherapy with honeybee venom and one patient (1.1%) during maintenance therapy wasp venom, systemic adverse reactions were mitigated by treatment with antihistamines before venom injection. Our results show that immunotherapy is safe and effective for the prevention of systemic reactions to *Hymenoptera* re-stings in patients with *Hymenoptera* allergy. We therefore recommend that patients who are allergic to *Hymenoptera* venom prophylactically receive immunotherapy.**

In Japan, approximately 40 persons die annually of anaphylaxis caused by *Hymenoptera* stings. Venom immunotherapy is considered a safe and effective for the treatment of allergic systemic reactions caused by *Hymenoptera* stings in patients with *Hymenoptera* allergy.[1-3] However, treatment success rates vary considerably between different centers. Medical indications for venom immunotherapy are strongest for adults who have had a life-threatening reaction to stings; without treatment, this group faces a 50% to 60% risk of systemic reactions if stung again.[1] Full protection, defined as the absence of systemic allergic symptoms after a sting challenge during venom immunotherapy, is reported to be nearly 100% by some authors,[4-7] but only 70% to 80% by others.[8-11] The incidence of systemic reactions during venom immunotherapy also varies greatly. Some researchers report that systemic reactions occur in less than 5% of patients who receive venom immunotherapy,[3,6,12] whereas others estimate the rate of systemic reactions to be 50% or higher.[9,10,13,15]

Analysis of these widely diverging results suggests that the outcome of venom immunotherapy is influenced by a variety of factors, including the treatment protocol, the use of conventional and clustered

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immunotherapy, which take a few month to reach the maintenance dose, [4,11] and the clinical characteristics of the population treated, such as age and the severity of previous reactions.[16-18] The species of venom used for venom immunotherapy may be an important determinant of outcome. To gain further insights into the responses to venom immunotherapy, we studied the efficacy and safety of rush immunotherapy, which is possible to reach the maintenance dose in a few week, in patients who had a history of systemic reactions to *Hymenoptera* stings in Japan.

MATERIAL AND METHODS

Patients

Between 1988 and 2002, we studied patients with a history of systemic reactions to *Hymenoptera* stings who received venom immunotherapy. All subjects gave informed consent to participate in the study and met the following criteria: (1) venom-specific IgE antibody in their sera as detected by CAP RAST (RAST score ≥ class 2), and (2) a positive skin test response to venom. Patients who discontinued immunotherapy because of noncompliance and those who continued immunotherapy at another hospital or clinic before starting maintenance therapy were excluded. None of the noncompliant patients discontinued the immunotherapy because of adverse reactions.

Immunotherapy protocol

All patients were hospitalized during rush immunotherapy, and four injections were administered daily. Subjects received subcutaneous injections of increasing doses of venom extracts (honeybee, yellow jacket, wasp; Hollister-Stier, Spokane, WA, USA) at 2-hour intervals. The dose of the first injection was determined on the basis of skin test reactions to venom extracts. After a maximal dose of 100 μg had been reached over 1 to 2 weeks, the patients were given a maintenance dose of 100 μg per venom at 4- to 6-week intervals. An example of the immunotherapy schedule is shown Table 1, where the dose of venom extract, that caused a positive skin reaction was 10^{-3} μg/ml.

Table 1 An example schedule of rush immunotherapy

Day	Concentration (μg/ml)	Quantity (ml)	Quantity of antigen (μg)
1	0.0001	0.1	0.00001
		0.2	0.00002
		0.4	0.00004
		0.8	0.00008
2	0.001	0.1	0.0001
		0.2	0.0002
		0.4	0.0004
		0.8	0.0008
3	0.01	0.1	0.001
		0.2	0.002
		0.4	0.004
		0.8	0.008
4	0.1	0.1	0.01
		0.2	0.02
		0.4	0.04
		0.8	0.08
5	1.0	0.1	0.1
		0.2	0.2
		0.4	0.4
		0.8	0.8
6	10.0	0.1	1
		0.2	2
		0.4	4
		0.8	8
7	100	0.1	10
		0.2	20
		0.3	30
		0.4	40
8	100	0.5	50
		0.6	60
		0.7	70
		0.8	80
9	100	0.9	90
		1.0	100

RESULTS

Patients

The clinical characteristics of the patients are presented in Ta-

ble 2. A total of 95 patients (70 men and 25 women) were studied. Their mean age was 50.1 years (range 18-77 years). Honeybee venom was administered to 5 patients, yellow jacket venom to 28, wasp venom to 48, both honeybee venom and yellow jacket venom to 5, and both wasp venom and yellow jacket venom to 9 who were stung by unidentified species of *Hymenoptera*. The severity of the initial systemic reaction according to the grading of Mueller[19] was as follows: grade I, 9 patients; grade II, 5 patients; grade III, 19 patients; and grade IV, 52 patients.

Adverse reactions

After reaching the maximal dose, patients received maintenance therapy for a mean interval of 47.5 months (range 9-162 months). Although anaphylactic reactions developed in two patients (2.1%) during rush immunotherapy with honeybee venom and one (1.1%) during maintenance immunotherapy with wasp venom, systemic adverse reactions could be completely prevented by oral treatment with antihistamines before venom injection (Table 3).

Field stings

Forty-three patients had a total of 63 field re-stings while receiving immunotherapy. Forty-one patients (95.3%) with 59 field re-stings (93.7%) had no systemic reac-

Table 2 Clinical data of patients

Parameter	Total patients	HB	YJ	WA	YJ/HB	YJ/WA
No. of patients (n)	95	5	28	48	5	9
Mean age (yrs) (range)	50.1 (18-77)	45.2 (33-58)	48.1 (30-77)	51.8 (18-77)	54.8 (43-74)	47.3 (34-63)
Sex M/F	70/25	3/2	21/7	35/13	3/2	8/1
***Severity of anaphylactoid reaction in history** (n)						
Grade I	9	0	4	5	0	0
Grade II	5	0	4	1	0	0
Grade III	19	1	6	18	2	2
Grade IV	52	4	14	24	3	7
Specific IgE (mean CAP RAST class)		3.8	2.3	2.9	2.7/3.9	2.1/2.6
Duration of maintenance immunotherapy (months) (range)	47.5 (9-162)	40.0 (10-49)	38.0 (10-112)	47.0 (9-162)	36.8 (32-37)	90.1 (54-120)

*According to the method of Muller and Helbling[20]
M, males; F, females; HB, honeybee; YJ, yellow jacket; WA, wasp.

Table 3 Adverse reactions during rush immunotherapy (RIT) or maintenance therapy

Patient No.	Age (yrs)	Sex (M/F)	Treatment	*Grade before RIT	Specific IgE before RIT (class)	Adverse reaction during immunotherapy
1	50	M	HB	IV	3	Systemic urticaria during RIT
2	33	M	HB	IV	4	Systemic urticaria during RIT
3	43	F	WA	IV	2	Systemic urticaria and hypotension during maintenance therapy

*According to the method of Muller and Helbling[20]
M, males; F, female; HB, honey bee; YJ, yellow jacket; WA, wasp; RIT, rush immunotherapy

tions. Anaphylactic shock developed in two patients (4.7%) after a total of four field re-stings (6.3%) (Table 4). In one patient, grade IV systemic reactions occurred on each of three field re-stings. In the other, systemic urticaria and anaphylactic shock occurred on one of three field re-stings (Table 5).

DISCUSSION

Venom immunotherapy has been established to be highly effective: during treatment with *Hymenoptera* venom 95% to 100% of patients no longer react to *Hymenoptera* stings, and during treatment with honeybee venom about 80% of patients are completely protected.[20,21] Trials of various regimens of injectable immunotherapy have led to the development of treatment schedules combining rapid attainment of protection with minimal risk of adverse reactions.[8,11] However, many open questions remain about venom immunotherapy, such as differences in response among genetically distinct populations and different types of venom. This study addressed several of these issues.

At the usual maintenance dose of 100 μg, the rate of clinical protection afforded by rapid venom immunotherapy is approximately 98% in children as well as adults.[1,4-7,22] Reducing the venom maintenance dose to 50 μg protects only 79% of adults from reactions to stings.[5] Furthermore, when monthly maintenance doses of venom have been tolerated for 6 months, the interval between injections can be lengthened to 6 to 8 weeks[23] or 8 to 12 weeks.[22,25] We found that the rate of clinical protection provided by rush immunotherapy in patients who received maintenance doses of 100 μg at 4- to 6-week intervals was 96%, consistent with the results of previous studies.[4-7] Among the 43 patients who had 63 field re-stings in our study, however, anaphylactic shock developed after 4 field re-stings (6.3%) in 2 patients (4.7%), one of whom was allergic to yellow jackets and the other to both wasps and yellow jackets. This finding suggests that immunotherapy with a routine dose of 100 μg does not modify the response in some patients; these patients may thus require higher doses. Up to about 20% of patients with venom allergy treated with the conventional 100-μg dose are not protected from sting challenge.[5,10,21,22,26] Muller *et al.*[21] treated 119 patients allergic to bee venom with a maintenance dose of 100 μg and another 29 with an increased dose of 200 μg. They reported treatment failure rates of

Table 4 Field re-stings after rush immunotherapy

Parameter	Total patients	HB	YJ	WA	YJ/HB	YJ/WA
No. of patients in re-sting (n)	43	3	10	22	2	6
Total re-stings	63	3	12	30	4	14
Severity of anaphylactoid reaction in re-stings (n)						
Local reaction	41	3	9	20	2	5
***Grade IV**	2	0	1	0	0	1

*According to the method of Muller and Helbling[20]
HB, honey bee; YJ, yellow jacket; WA, wasp

Table 5 Clinical data of patients who experienced systemic reaction in field re-stings during maintenance therapy

Patient No.	Age (yrs)	Sex (M/F)	Treatment	*Grade before RIT	Specific IgE before RIT (class)	Total	Grade IV in total re-sting(s)
1	46	M	YJ,WA	I	3	3	3
2	66	M	YJ	IV	2	3	1

*According to the method of Muller and Helbling[20]
M, males; F, females; HB, honey bee; YJ, yellow jacket; WA, wasp; RIT, rush immunotherapy

26.1% and 10.3% for the lower and higher doses, respectively, on sting challenges. The use of higher doses for maintenance therapy may thus be warranted in selected patients with very severe anaphylactic reactions who are at increased risk of further stings.

Venom immunotherapy is generally well tolerated. Approximately 12% of persons have allergic reactions during treatment, some during the build-up phase at doses ranging from 1 to 50 μg and others during maintenance therapy with 100 μg; systemic reactions are more apt to occur with honeybee or wasp immunotherapy.[27] We also found that allergic reactions developed in patients with honeybee venom allergy during the build-up phase at doses of 10 to 20 μg and in patients with wasp venom allergy at the 100-μg maintenance dose. Adverse reactions were successfully managed by pretreatment with antihistamines, similar to findings reported by Knut *et al.*[28] If systemic reactions occur during the build-up phase, the dose should be reduced and then gradually increased again thereafter. We also recommend that patients receive pretreatment with antihistamines to prevent systemic adverse reactions caused by immunotherapy with *Hymenoptera* venom.

Golden *et al.*[29] followed up 74 patients who had discontinued venom immunotherapy after receiving maintenance treatment for 5 or more years. Patients returned for deliberate insect-sting challenges every 1 to 2 years after the discontinuation of immunotherapy. Systemic reactions occurred after challenge in 7 of the 74 patients (10%) and after 8 of 270 stings (3%); only 2 reactions were clinically significant (generalized urticaria). More recently, Golden *et al.*[30] reported that the risk of systemic sting reactions 5 to 10 years after the termination of at least 5 years of venom immunotherapy remains in the range of 5% to 15%. These results suggest that venom immunotherapy can be safely discontinued after 5 years.

In conclusion, we have demonstrated that venom immunotherapy is safe and effective for the prevention of systemic reactions to *Hymenoptera* re-stings in patients with *Hymenoptera* allergy in Japan. Future studies should analyze the effects of longer injection intervals and of discontinuation of immunotherapy.

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