Original Article

Rush Hymenoptera Venom Immunotherapy Is Efficacious and Safe

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Abstract. *Background*: Although rapid venom immunotherapy (VIT) protocols have been shown to be safe and effective, this issue has not yet been clarified in Turkey.
Objective: The aim of this study was to evaluate the side effects of rush VIT as well as early clinical and immunological responses in patients with a venom allergy.
Methods: Eighteen patients who had a history of severe systemic reactions after Hymenoptera sting were included in the study. The diagnosis was made on the basis of positive skin test reactivity and the presence of specific IgE in serum to either bee or vespid venoms. Fourteen patients underwent an average 7-day rush VIT regimen under careful monitoring in our clinic. Among them 7 patients were treated with *Vespula* species and 7 with *Apis mellifera* venom extracts. Four patients were followed up as a control group. Skin test response, specific IgE and IgG4 levels were determined before and after a year of VIT. Local and systemic reactions due to injections were monitored during the induction and maintenance phases of VIT.
Results: Specific IgG4 levels significantly increased after 1 year compared with levels before VIT (mean concentration before and after; 13.04 vs 21.85 mg/L, respectively; $P <$ .05) whereas specific IgE levels did not change (11.54 vs 13.32 kU/L). No significant differences were observed before and after one year of VIT in skin prick (2.34 vs 3.66 mm) and intradermal (0.12-0.11 μg/mL) test reactivities ($P >$ .05). A single patient treated with bee venom developed 4 mild systemic reactions (4/469 injections, 0.85%) during the course of VIT. More local reactions occurred in patients receiving bee venom extract (3.33%) than in those receiving yellow jacket venom (1.33%). Two patients tolerated field stings without reactions.
Conclusion: Our experience confirms that rush VIT is safe and has a low systemic reaction. It can be considered for patients requiring rapid protection.

Key words: Venom immunotherapy. Efficacy. Safety.

Resumen. *Antecedentes:* Aunque se ha demostrado que los protocolos de inmunoterapia con veneno (ITV) mediante una pauta de iniciación rápida son seguros y efectivos, este punto aún no se ha aclarado en Turquía.
Objetivo: El propósito del estudio fue evaluar los efectos secundarios de la ITV de iniciación rápida y las respuestas clínicas e inmunológicas inmediatas de los pacientes con alergia al veneno.
Métodos: Participaron en el estudio 18 pacientes con un historial de graves reacciones sistémicas a picaduras de himenópteros. El diagnóstico se estableció a partir de la reactividad positiva en pruebas cutáneas y por la presencia de IgE sérica específica a venenos de abeja o de véspidos. Catorce pacientes se sometieron a un régimen de ITV de inicio rápido durante siete días de promedio bajo estricta vigilancia en nuestra clínica. El tratamiento de siete de ellos fue con especies del género *Vespula* y los siete restantes con extracto de veneno de *Apis mellifera*. Se realizó el seguimiento de cuatro pacientes como grupo de control. Antes de la ITV y un año después de la misma, se realizaron pruebas cutáneas y se determinaron los niveles de IgE específica e IgG4. Se monitorizaron las reacciones sistémicas y locales debidas a las inyecciones durante las fases de inducción y mantenimiento de la ITV.
Resultados: Los niveles de IgG4 específica aumentaron notablemente al cabo de un año comparado con los niveles anteriores a la ITV (concentración media antes y después, 13,04 frente a 21,85 mg/L, respectivamente; $P <$ 0,05), mientras que los niveles séricos de IgE específica no cambiaron (11,54 frente a 13,32 kU/L). No se observaron diferencias significativas antes y un año después de la ITV en las pruebas cutáneas (2,34 frente a 3,66 mm) y en las pruebas intradérmicas (0,12-0,11 μg/mL) ($P >$ 0,05). Un solo paciente tratado con veneno de abeja

presentó cuatro reacciones sistémicas leves (inyecciones 4/469, 0,85%) durante el transcurso de la ITV. Tuvieron más reacciones locales los pacientes tratados con extracto de veneno de abeja (3,33%) que aquéllos que lo fueron con veneno de avispa (1,33%). Dos pacientes toleraron el ser expuestos de nuevo a picaduras sin reacciones.
Conclusión: Nuestra experiencia confirma que la ITV con pauta de iniciación rápida es segura y presenta una baja incidencia de reacciones sistémicas. Puede tenerse en cuenta para los pacientes que necesiten una protección rápida.

Palabras clave: Inmunoterapia con veneno. Eficacia. Seguridad.

Introduction

Approximately 0.8% to 5.0% of the general population suffer from generalized skin or systemic allergic reactions following a Hymenoptera sting [1]. An estimated 20 to 50 people die every year in the United States of America as a result of severe anaphylaxis after bee, wasp, and ant stings [1]. Honeybee (*Apis mellifera*) and yellow jackets (*Vespula germanica* and *Vespula vulgaris*) are primarily responsible for sting-induced systemic reactions in Europe [2]. Patients with Hymenoptera venom allergy can be effectively treated with venom immunotherapy (VIT) to prevent further sting-induced anaphylactic reactions [2]. Various immunotherapy schedules have been designed to treat Hymenoptera-induced anaphylaxis ever since VIT first began to be utilized [3]. Hunt et al [4] demonstrated that almost complete protection could be obtained via treatment with insect venom. The time required to reach the maintenance dose of 100 μg varies depending on the protocol. Several months to weeks are needed for the conventional protocol, days for the rush protocol, and hours for the ultra-rush protocol [5, 6]. VIT is used to create tolerance to Hymenoptera venom, but such treatment can also induce systemic reactions. Such treatment schedules have been utilized to protect the patient, minimize side effects and costs, and optimize convenience for the patient, and various regimens have been utilized to build up and maintain VIT [7, 8]. Rush protocols seem to be as safe as slower protocols, but systemic reactions can be an important problem, particularly with honeybee venom [9], although in some studies it is well tolerated [10]. The purpose of this study was to determine the efficacy and safety of rush VIT in a population of Hymenoptera venom allergic individuals in Turkey.

Methods

Patients

The study included 18 patients (4 females, 14 males; aged 18-53 years). They all had a personal history of systemic allergic reactions to a Hymenoptera sting. The patients' history of symptoms after an insect sting was evaluated in a standardized questionnaire. Eleven of the patients had had grade II and 7, grade IV reactions. Hypersensitivity to honeybee or yellow jacket venom was confirmed by skin testing and elevated serum titers of venom-specific IgE (sIgE) antibodies. Fourteen patients were treated with a rush VIT regimen at our clinic. Inclusion criteria were based on the European Academy of Allergology and Clinical Immunology position paper [11]. Seven of 14 patients were allergic to bee venom and 7 to yellow jacket venom. Four patients who did not accept VIT because of cost or inconvenience were followed as a control group. Skin tests, sIgE and sIgG4 measurements in serum were performed before and at the end of the first year of rush VIT. Local and systemic reactions due to injections were recorded. Immediate systemic reactions were classified from grade I to grade IV according to the method of Ring and Messmer [12].

Skin Tests

Skin prick tests were performed with standardized pure venom extracts of the honeybee and yellow jacket (ALK-Abelló, Hørsholm, Denmark). Histamine dihydrochloride (10 mg/mL) and glycerol diluent were used as positive and negative controls, respectively. Prick test results were read after 15 minutes; a wheal diameter of 3 mm or greater produced by the control solution was considered a positive reaction.

The prick test was followed by an intradermal test on the forearm with increasing concentrations from 0.001 μg/mL to 1 μg/mL. Intradermal tests were considered positive if reactions (wheal of at least 5 mm in diameter with erythema) occurred after 15 minutes at a concentration of 1 μg/mL or less. The lowest concentration resulting in such a reaction was defined as the endpoint concentration [13]. Histamine and physiological saline with 0.4% phenol were used as positive and negative controls, respectively.

In all patients, venom-sIgE and sIgG4 antibodies to honey bee and yellow jacket were determined by using a florescence-immunoassay (CAP, Pharmacia, Uppsala, Sweden). Results were calculated in mg/L for sIgG4 antibodies, and in kU/L for sIgE antibodies. All sIgE antibody values of 0.35 kU/L or more were considered positive.

Rush VIT

The rush VIT regimen was completed within 7 days while the patients were hospitalized at our clinic. The protocol began without premedication with an initial dose of 100 standardized quality units (SQ-U)/mL of aqueous

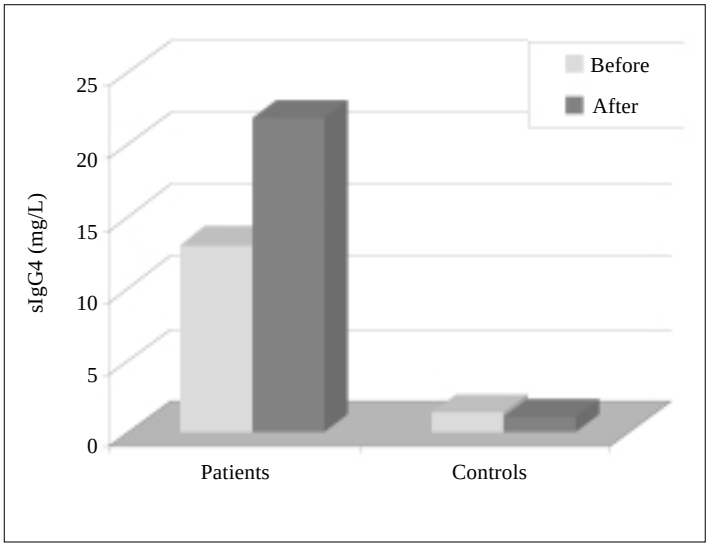

Figure 1. Specific IgG4 levels of treated and control patients at baseline and after 1 year of venom immunotherapy. The difference was significant at $P < .05$.

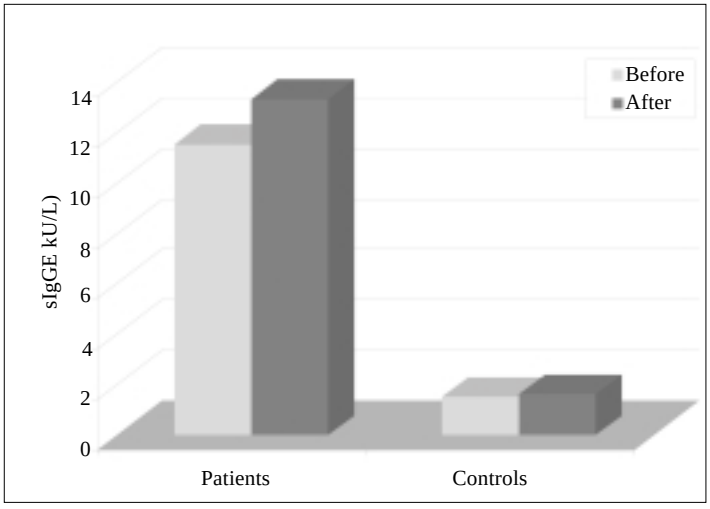

Figure 2. Specific IgE levels of treated and control patients at baseline and after 1 year of venom immunotherapy. The differences were not significant.

extract. Rush VIT was initiated on inpatients with a very low concentration (10 SQ-U/mL) for high risk patients and then increased gradually at intervals of 30 minutes up to 100 000 SQ-U/mL. A total of 14 injections of the respective venom preparations (ALK-Lyophilisate Aqueous SQ 801 and 802, Abelló) were administered subcutaneously until the maintenance dose of 100 µg (1 mL of 100 000 SQ-U/mL) was reached. Booster injections of 100 µg were given at 7, 14, and 21 days after the completion of the rush schedule. Thereafter, patients received monthly injections of 100 µg of bee or yellow jacket venom (ALK depot SQ 801-802, aluminum-hydroxide—adsorbed venom, ALK- Abelló) over a period of at least 1 year. The maintenance dose of allergens was the maximal tolerated dose of the highest antigen concentration. All injections were applied subcutaneously to the outside of the upper arm. Vital signs of all patients were checked at the beginning of the protocol, then before and between each injection. Full emergency resuscitation equipment was readily available at all times. Allergen extract dosage, local and systemic reactions, and treatment of side effects were recorded.

We determined the incidence and nature of side effects during the initial and maintenance phases of the treatment for at least a year. If a patient developed a systemic allergic reaction during a dose increase, treatment was interrupted until complete recovery was obtained, and then restarted with a dose reduced by 2 steps. The patients received injections of adrenaline, antihistamines, and corticosteroids according to the severity of the systemic reaction. In case of large local reaction with pronounced erythema and/or swelling (>8 cm in diameter) of both upper arms, the protocol continued without dose reduction. Field sting reactions were recorded during the VIT.

Statistical Analysis

Statistical analysis was carried out using SPSS 10.0. Data were expressed as means ± SD. Analysis of differences between the patients who were receiving rush VIT and the control subjects was based on the Mann Whitney U test and comparison of the data within groups was performed with the Wilcoxon rank sum test. A 2-tailed *P* value equal to or less than .05 was considered statistically significant.

Results

Patients

Between July 2001 and April 2003, 14 patients with an insect venom allergy (4 females, 10 males) ranging in age from 18 to 46 years (mean, 34.50 ± 8.29 years) were administered rush VIT. Seven patients were vaccinated with bee venom and 7 with yellow jacket venom. The control group comprised 4 patients (all male) ranging in age from 29 to 53 years old (mean, 42.50 ± 11.47 years) who were not treated with rush VIT. Three control subjects were allergic to bee venom and 1 to yellow jacket venom.

We found significant increases in sIgG4 levels after a year of VIT when compared with baseline levels (mean concentration at 1 year, 21.85 mg/L in comparison with 13. 04 mg/L at baseline) ($P < .05$) (Figure 1). However, sIgE levels did not change at the end of the first year of VIT in comparison to baseline (mean concentration at 1 year, 13.32 versus 11.54 kU/L) ($P > .05$) (Figure 2).

The mean wheal diameter of the skin prick test reaction at baseline and at the end of the first year of VIT did not change in either the treated or control groups. The mean diameter in the treated group was 3.66 mm at baseline and 2.34 mm after 1 year ($P > .05$). There was also no significant difference in intradermal skin test reactivity before and after one year of VIT (mean concentration of antigen, 0.12 μg/mL at baseline vs 0.11 μg/mL after 1 year) ($P > .05$).

There were no significant correlations between species of venom extracts and skin test results and the levels of specific IgE and IgG4 ($P > .05$).

Adverse Effects

Throughout the entire immunotherapy period, 14 patients received a total of 469 injections within 1 year; 240 of the injections (51.2%) were bee venom extracts and the remaining 229 (48.8%) were yellow jacket extracts. A total of 4 systemic reactions (0.85% of all injections) and 11 late local reactions (2.34% of the total) were observed. All 4 systemic reactions were to bee venom (4/240, 1.66%, grade II) and were observed in a single female patient after the last dose of highest concentration (1 mL of 100 000 SQ-U/mL) during the build-up period. The dose was reduced to 0.5 mL of 100 000 SQ-U/mL, and then was gradually increased to obtain a maintenance venom dose of 100 μg/mL over several weeks. All the systemic reactions responded well to treatment with adrenaline, antihistamines, bronchodilators, and corticosteroids. None was life-threatening or fatal. In case of systemic reactions, immunotherapy was continued by restarting with a lower dose. All of the local reactions developed during the maintenance period. There were no systemic reactions with yellow jacket venom. Eight local reactions occurred with bee venom (3.33% of the 240 bee venom injections) and 3 occurred with yellow jacket venom (1.33% of the 229). No dose adjustments were required for large local reactions, and local reactions did not require therapy. There were no significant correlations between species of venom, allergic reactions, age, or sex ($P > .05$).

Field Stings

Two patients experienced field stings while receiving immunotherapy. One of the patients was a beekeeper and he was re-stung several times during the immunotherapy. None of the stings resulted in any systemic symptoms.

Discussion

VIT is established as a highly effective, specific form of treatment to prevent life-threatening reactions in Hymenoptera allergies. The goals of VIT are to reach an allergen dose inducing tolerance to Hymenoptera venom with the lowest rate of systemic reactions [3]. A maintenance dose of 100 μg is usually recommended. However, many VIT schedules for build-up and maintenance have been proposed. They range from very slow protocols to 1-day rush protocols. With a rush protocol, the time required to reach the maintenance dose ranges from 1 to several days instead of weeks or months [14]. These methods are quite variable, and no standard rapid VIT protocol has been widely adopted. In addition, their safety is controversial because of a potentially higher frequency of severe systemic reactions. In this study, we evaluated the early clinical and immunological efficacy and safety of rush VIT through focusing on skin test reactivity and serum levels of sIgE and sIgG4. Fourteen patients with a history of severe systemic reactions after an insect sting were treated with VIT using a 7-day rush protocol. They were all able to tolerate a subcutaneous injection of 100 μg of venom as early as treatment day 7.

In the literature, 17.9% to 45% of VIT applications have been reported to cause side effects [10, 15-19]. Various classification systems for the severity of side effects utilized by investigators make it quite difficult to compare these incidence reports for different VIT protocols. Up to 20% to 40% of patients may develop systemic allergic reactions particularly against honeybee VIT [7, 11]. Rush regimens have caused systemic reactions in 13% to 46% of those with a honeybee venom

allergy and in 0% to 21% of those with yellow jacket venom allergies [6, 15, 20]. In contrast, frequencies of 40% to 46% with honeybee venom and of 12% to 25% with yellow jacket venom have been noted with the conventional weekly build-up regimens [21, 22]. In our study, we recorded a mild systemic reaction in only one patient, giving a risk of 0.85% per total number of injections. None of the reactions were life-threatening, and adrenaline was never used. Sturm et al [23] also reported a 0.47% risk per injection in their 4-day rush regimen. Hence, the risk for systemic reaction to VIT was shown to be much more related to the nature of the venom than to the regimen used. VIT with vespid venoms is evidently better tolerated than treatment with bee venom, but it has not been elucidated why VIT with honeybee venom causes more systemic reactions. An explanation for this could be the lack of nonallergenic proteins in more purified bee venom extract [24, 25]. Supporting these data, we observed a rate of systemic reaction of 1.66% per bee venom injection during a 7-day rush regimen, whereas the yellow jacket venom injections resulted in none.

In a multicenter study, 1.9% of 26 661 injections caused systemic reactions during the dose increase phase; the rate was only 0.5% during the maintenance phase of VIT. Female gender, bee venom extract and the rapid dose increase proved to be the risk factors for systemic reaction [17]. In our study, the fact that the only systemic reaction occurred in a female patient receiving bee VIT during the highest dose of build-up is consistent with the literature.

In studies comparing VIT performed with depot or with aqueous preparations, the depot preparation caused fewer side effects following the injections [26]. This may be due to slower allergen release from depot preparations than from aqueous ones. Also, conventional schedules which deliver the maintenance dose after several weeks appear to result in fewer systemic reactions than rush protocols performed over a few days. The effectiveness of the two extracts has been found similar in rush and slow up-dosing regimens [26, 27]. However, rapid protection is needed for many patients, and a rapid dose increase can only be done with aqueous venoms. Moreover, the compliance of patients who were initially treated as inpatients with rush protocols is better than that of those who were outpatients throughout the whole treatment [28]. Thus, the initial use of the aqueous preparation for rush VIT, followed by maintenance treatment with the depot preparation, seems to be an appropriate regimen [28].

The clinical efficacy of VIT has been proven by several trials, but the underlying immunoregulatory mechanisms of protection remain poorly understood. The immunological parameters such as sIgE and sIgG antibody levels are most frequently used to assess the therapeutic efficacy of VIT. Skin test reactivity results also allow us to evaluate the clinical response in patients undergoing VIT. It has been demonstrated that an initial rise in sIgE antibodies over the first few months of VIT is followed by a gradual decrease over a period of years [27, 29-32]. During the course of treatment, an increase in the concentration of sIgG4 was observed in all groups. In earlier studies, the induction of blocking IgG antibodies, especially IgG4, was held responsible for this protective effect. However, the protective function of an increase in the venom-specific IgG4 or a decrease in IgE with respect to the efficacy of VIT has been debated by various authors [33, 34]. Indeed, a decline of sIgE and an increase of sIgG production can be detected after immunotherapy in the long run [35, 36].

Although there is poor correlation between the amount of sIgG and clinical protection, sIgG correlates with the dose of allergen that has been given**,** yet in most studies, the changes in serum levels show no relationship with clinical response [37]. In any case, serum sIgE has a shorter life span than cell-bound sIgE and can not reliably predict the sensitivity of a patient [38, 39]. It is true that in patients treated for venom anaphylaxis, the development of sIgG antibodies correlates with clinical efficacy, but for other allergens, the magnitude of the sIgG response is unrelated to the degree of efficacy [40]. Furthermore, there is accumulating evidence that regulatory T-cells may suppress sIgE production and increase sIgG4 and sIgA synthesis via interleukin (IL) 10, which is induced and progressively secreted during successful rush VIT [41, 42]. In our study, skin test reactivity and sIgE levels did not change but protective sIgG4 antibodies significantly increased after the first year of VIT. Schiavino et al [43] demonstrated a rapid increase in sIgG4 levels whereas sIgE remained higher than normal after 1 year of ultrarush VIT consistent with our results. This increase of sIgG4 may account for the important role of IL-10.

In recent years, sting challenge tests have been recommended in order to evaluate the effectiveness of immunotherapy. However, performing intentional sting challenges remains controversial for ethical reasons and because of practical difficulties. Therefore, routine application has not been established yet [3]. Sharing the same concerns, we did not use a sting challenge test in this study. Field re-stings occurred in 2 patients while they were receiving sufficient immunotherapy and none of the stings resulted in any systemic symptoms. The rest of our patients were not stung during the period of 1 year.

In conclusion; various protocols are currently used to induce tolerance to hymenoptera venom in order to eliminate the risk of anaphylaxis during a subsequent sting. The adverse effect rate is an important factor to consider when selecting a protocol and maintenance dose. Taken together, this study indicates that the use of aqueous extract initially for rush VIT, then later continuing with the depot extract, is a safe method even without premedication and is also clinically efficacious for venom allergy treatment. We suggest that if a fast line of protection is required, the utilization of rapid VIT protocols can reduce the cost and time commitment for clinics as well as patients. Our patients are still under

observation and treatment. We are also aiming to study the long-term effectiveness of rush VIT.

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