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Benefits of venom immunotherapy: how soon can they be expected

Корист од имунотерапије отровом инсеката:
Када се може очекивати

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SUMMARY

Introduction/Objective Allergic reactions to insect stings are medical emergencies that could be prevented by venom immunotherapy (VIT). The main purpose of VIT is to prevent fatal or life-threatening reactions.
We aimed to show the rapidity with which patients experience the benefits of VIT and estimate the number of emergency treatments that are prevented .
Methods We reviewed the medical files of patients who started VIT between 2010 and 2014. We calculated the costs of treatment of the sting reactions, the costs of immunotherapy and estimated the costs of the prevented allergic reactions.
Results In a cohort of 514 patients (40.9% female, age 47.2±14.4 years) the cost of treatment of the index sting reaction was 180.4±166.8 €. During VIT 195 patients experienced 446 field stings. In 86.3% of patients stings were well tolerated, and only patient experienced severe reaction (grade III, according to Mueller). 20.4% of VIT treated patients were stung during the first year of VIT and 57.0% during 5 years VIT. The expenditure for 5 years of VIT was 2886 € per patient, which corresponded to an average of 16.0 emergency treatments for systemic reactions.
Conclusion Emergency situations are prevented in a substantial number of venom allergic patients and a beneficial effect was observed already during the first year of VIT.
Keywords: Hymenoptera venom allergy; anaphylaxis; immunotherapy; emergency treatment; costs.

САЖЕТАК

Увод/Циљ Алергијске реакције на убод инсеката спадају у хитна медицинска стања која могу бити спречена применом специфичне имунотерапије отровом инсекта (ИОИ).
Основна сврха ИОИ -а је да спречи фатални исход и стања која непосредно угрожавају живот.
Циљ рада је био да укажемо на период примене ИОИ са којим оболели имају добит и утврдимо број хитних стања који су њиме спречени.
Методе Анализиране су историје болести лечених ИОИ од 2010. до 2014. године. Обрачунали смо трошкове лечења од реакција на убод, трошкове имунотерапије и спречених алергијских реакција.
Резултати У групи од 514 пацијената (40,9% жена, старости 47,2±14,4 година), трошак лечења индексне реакције је био 180,4±166,8 €. Укупно 195 пацијената је доживело 446 убода током ВИТ-а, 86,3% су га добро толерисали, а само код једног се је развио тежи облик реакције (III степен по Милеру). Укупно 20,4% су били убодени током прве године примања ИОИ, а 57,0% током пет година. Расход за пет година узимања ИОИ је био 2886 € по пацијенту, што је одговарало просеку од 16 хитних лечења за системске реакције.
Закључак Хитна стања се спречена код значајног броја пацијента алергичних на отров већ током прве године ИОИ -а.
Кључне речи: алергија на отров опнокрилаца; анафилакса; имунотерапија; хитно лечење; трошкови.

INTRODUCTION

Up to 7.5% of the population report systemic allergic reactions (SAR) to honeybee, wasp, or hornet stings [1]. In frequently stung subjects, such as beekeepers, the prevalence of SAR could exceed 30%.[1] In total, 39.1% of reactions are mild (grade I], and 43.5% are moderate (grade II), according to the Ring and Messmer classification [2]. Patients of advanced age and those with concomitant cardiovascular diseases and elevated basal serum tryptase are prone to severe reactions [3]. After a person becomes allergic, allergic reactions are expected after further stings, and there is a tendency for repeated sting reactions to be as severe as the index reaction with 10-15% being more severe [4, 5].

Allergic reactions to insect stings are medical emergencies. Patients require activation of emergency teams or are transported to emergency centres. In accordance with EAACI anaphylaxis guidelines, patients who fulfil the criteria for anaphylaxis should be hospitalized overnight [6]. Some patients require treatment in an intensive care unit.

Up to 0.5 per 1 million people die per year from allergic reactions to Hymenoptera venom [1,7]. Venom allergic patients have a decreased quality of life. Venom immunotherapy (VIT) is the therapy of choice for patients who have experienced a severe IgE mediated sting reaction of Mueller grade III (dyspnea) or IV (hypotension), particularly if there is a substantial risk of further stings because VIT prevents serious allergic reactions to Hymenoptera stings [7]. Increasing amounts of venom to which the patient is allergic are given subcutaneously, starting with less than 1 microgram and then approximately doubling doses in interval from 20 minutes to a week until reaching the maintenance dose of 100 micrograms (equivalent to 2–10 insect stings). Maintenance doses are applied every 4 to 12 weeks for 3–5 years. In addition to preventing life-threatening reactions, VIT significantly improves health related quality of life (HRQL) scores [7].

There are very few studies on the cost effectiveness of VIT, and those studies focus exclusively on preventing fatal reactions [8-10].

We aimed to show the advantages of venom immunotherapy, specifically, the rate at which patients experience benefit and the number of emergency treatments that are prevented. In addition, we aimed to estimate the costs of various therapeutic decisions.

METHODS

The study was performed at a tertiary institution as a part of research program P3-0360 financed by Slovenian Research Agency and approved by State ethic committee (number of approval 86/05/05).

We reviewed the medical files of consecutive patients who started VIT from 2010 to the end of 2014. The diagnosis of venom allergy was made according to medical history and sensitisation to venom was assessed by skin tests, measurement of specific IgE (Immulite system, Siemens, Munich, Germany) or basophil activation test. The severity of the index reaction was assessed according to Mueller grades (grade I – generalised urticaria; grade II - angioedema; grade III - dyspnoea; grade IV – cardiovascular collapse).

Table 1. The costs of treatment according to the Slovenian health care insurance price list.

Activity / drug	Price (€)
Emergency management at patient's home	208
Emergency management, primary care	65
Emergency management, secondary care	76
Hospitalization, 1 day	195
Hospitalization in intensive care unit, 1 day	503
Immunotherapy, outpatient visit	74
Maintenance dose of venom (100 µg)	25.5
Epinephrine 0.5 mg	1
Clemastine 2 mg	6
Methylprednisolone, i.v. 125 mg	10
Methylprednisolone tablet 64 mg	1
Antihistamine tablet	0.3
EpiPen epinephrine auto injector	33.2

We calculated the expense of treatment for index sting reactions, which was an indication for VIT and the costs of immunotherapy. The costs were assessed according to the Slovenian health care insurance price list (Table 1). The costs of treatment for the index sting reaction were calculated for a subgroup of patients for whom the index reaction treatment data were available.

In the immunotherapy files, we searched for data on insect stings during VIT, the consequences of the stings and their management. We calculated the number of prevented systemic allergic reactions: We assumed that if patients had not been treated with VIT, an allergic reaction similar to the index reaction would have occurred after each sting which was suffered during VIT and that the treatment would have been similar to the treatment of the index reaction, although it is known from epidemiologic studies, that up to 50% of patients don't experience any reaction after a subsequent sting and in up to 15% of patients a reaction is more severe than the index reaction. We assumed that patients not treated with VIT would be equipped life-long with an epinephrine auto injector, which should be refilled yearly.

The initial phase of immunotherapy was performed as 1-day ultrarush immunotherapy with Venomenhal (HAL, Leiden, The Netherlands) or Alyostal (Stallergen, Antony Cedex, France) venom. A maintenance dose of 100 micrograms was reached in 3 hours, using 10 mg of desloratadin as a premedication. Maintenance doses of 100 micrograms were given on days 3, 10, 24, and 45 and then monthly for first year. Each year, the maintenance interval was prolonged for 2 weeks. The duration of immunotherapy was planned to be 5 years.

Statistics

The data are presented as the mean±standard deviation. The differences between the groups were calculated using the Student's t-test and chi-square test.

The life expectancy data were found on the web page of the Statistical Office of the Republic of Slovenia [11].

RESULTS

Patients

We included 514 patients (210 female, 40.9%). Their age at the beginning of VIT was 47.2±14.4 years. The severity of the index reaction according to Mueller was as follows: grade I 0.4%; grade II 2.8%; grade III 26.8%; grade IV 70.0%. In all patients sensitisation to venom was confirmed.

Treatment of index reaction

The data on the treatment of the index reaction were available for 462 (89.9%) subjects. In total, 442 (95.7%) patients sought medical treatment. In 125 patients (36.0%), the treatment began at the site of the sting. Of the patients, 331 were treated at primary emergency care centres, and 161 at secondary emergency care centres; 105 were hospitalized in hospital wards, and 6 were hospitalized in intensive care units. In total, 20 patients did not receive medical intervention for an index sting. The cost of treatment for an index reaction was estimated at 180.4±166.8 € (for honeybee allergy, 190.8±150.3 €; for wasp allergy, 174.2±176.6 €, p>0,05).

Detailed information on the drugs used for treatment were available for 301 patients, as follows: the use of epinephrine was documented in 135 (44.9%) patients; parenteral antihistamines and steroids were used in 116 patients; 50 patients received peroral treatment only; and in 88 patients, we found no details on the drugs used for emergency treatment.

Efficacy of VIT

At the time of the analysis, 159 patients had been treated with VIT for up to 1 year, 75 for up to 2 years, 111 for up to 3 years, 83 for up to 4 years and 86 had been treated for up to 5 years (Table 2). The venom used was from honeybees in 186 (36.2%) cases and wasps in 328 cases.

Table 2. Cohorts of patients according to duration of VIT and sting frequency.

Duration of treatment	Number of patients	Patients being stung
Up to 1 year	159	35 (22.0%)
Up to 2 years	75	22 (29.3%)
Up to 3 years	111	49 (44.1%)
Up to 4 years	83	42 (50.6%)
Up to 5 years	86	49 (57.0%)

In total, 195 patients experienced field stings during VIT; 68 (36.6% of the patients treated for honeybee stings) received honeybee stings, and 127 (38.7% of the patients treated for wasp stings) received wasp stings ($p>0,05$). The total number of field stings was 446. The patients stung by honeybees were stung 2.9±1.4 times, and the patients stung by wasps were stung 1.9±1.7 times ($p>0.05$). The proportion of patients who received a field sting during VIT is shown in the table 2. In total, 105 (20.4%) patients were stung already during the first year of immunotherapy.

In total, 27 (13.7%) patients reported systemic symptoms after receiving a field-sting during VIT;18 reported only subjective symptoms, and 6 (3%) sought medical intervention. Only 1 reaction was severe (grade III, according to Mueller).

Cost of treatments

For the comparison of the costs of immunotherapy and the costs of prevented systemic reactions, the expenditures for VIT were calculated for an average duration of VIT (26 months), which consisted of 1-day hospital immunotherapy plus 25 outpatient maintenance injections, for a total of 1925 €. The cost of the allergen was 662.0 € per patient. In a group of 514 patients treated for an average of 26 months, the total costs were estimated to be 989.450 €. During the same time, the patients experienced 446 field stings, of which only 6 were treated by medical professionals. The estimated cost of 440 prevented sting reactions was 79.388 €.

To compare the costs of VIT with a lifelong supply of emergency epinephrine auto injectors, the price for a complete 5-year course of immunotherapy was calculated at 2886 € per patient, corresponding to 16.0 average emergency treatments of systemic reactions following unprotected Hymenoptera insect stings. The cost of the allergen used for VIT is 992 €. The price of epinephrine auto injectors in patients not treated with VIT were calculated as one auto injector per year per patient. The average patient was born in 1968, and the life expectancy was assumed to be 27 years for males and 33 years for females. An average patient would be prescribed 29.5 auto injectors, costing 980.4 €

per patient. The additional cost of VIT over epinephrine auto injectors was estimated at 1905.6 € per patient.

DISCUSSION

We showed that more than one-half of the patients treated with venom immunotherapy for up to 5 years received an in-field insect sting while on maintenance immunotherapy and 20.4% received a sting during the first year of immunotherapy.

Venom allergy is the most common cause of anaphylaxis [12]. Although the clinical presentation is dramatic and is frequently treated by emergency doctors, less than one-half of patients are treated with epinephrine, as documented also in our analysis.

After an acute episode, a decision should be made to prevent further sting reactions. Avoidance measures are the cornerstone of prevention; however, those measures are sufficient in less than one-half of patients, specifically, in those with a low exposure to Hymenoptera stings. Von Moos et al. retrospectively analysed the re-sting data of 96 bee-venom-allergic and 95 vespid-venom-allergic patients [13]. They showed that the benefits of VIT are greater in subjects with higher exposure to further stings. In bee-venom-allergic patients who lived in the vicinity of beehives, the median sting-free interval was 5.25 years compared to 10.75 years in subjects with less exposure. One-half of vespid-venom-allergic outdoor workers were re-stung within 3.75 years compared to 7.5 years for indoor workers. Von Moos concluded that in highly exposed subjects, it is worth to offer VIT, even to patients with less severe allergic reactions because of the high probability of a re-sting. In our study, the risk of a re-sting was higher and it was equal in the bee- and wasp-allergic subjects.

Patients with severe reactions are equipped with epinephrine auto injectors or/and are offered immunotherapy [14]. In addition to being life-threatening, an allergy to insect venom negatively affects the quality of life. Carrying an EpiPen as the sole treatment does not prevent deterioration of the quality of life [15]. It was shown that HRQL is improved by VIT [7]. Moreover, in most patients, compliance in carrying an EpiPen is low, and the ability to correctly self-administer an EpiPen is poor; relying on self-treatment of severe allergic reactions is not a safe strategy [16]. Oude Elberink found that only 48% of patients with a severe venom allergy and who received an EpiPen were positive regarding their treatment. Of these patients, 68% would have preferred to be treated with VIT. On the other side, 91.5% of the VIT-treated patients were positive regarding their treatment, and 85% would select VIT again [17]. We showed that the additional cost of VIT over having an emergency EpiPen is, at most, 1905.6 E, not taking into account the costs of yearly medical visits and patient education for refilling a prescription for an EpiPen and possible emergency medical visits after insect stings in patients using only an EpiPen.

Focusing only on preventing fatal reactions, Hockenhull et al. calculated that VIT combined with an adrenaline auto injector and antihistamine compared with sting avoidance alone yields an ICER of £7,627,835 per QALY gained. In the subgroup of patients at high risk of future stings (five

stings per year), the VIT ICER is £23, 868 per QALY gained. In the subgroup of patients whose QoL improves because of anxiety reduction, VIT ICER is in the range of £25.767–27.504 per QALY gained [8].

In our study the calculated costs avoided by the VIT are the minimal estimate, since it is conceivable that at least some of the patients, if they were not on VIT, would progress to more severe and hence more costly reactions.

Beside prevention of fatal outcomes, quality of life is also an important outcome measure when considering this type of treatment. In the majority of patients, VIT is effective after the maintenance dose is reached, as shown by Hunt and Goldberg [18,19]. However, Koschel et al. observed that some VIT treated patients remained frightened of re-stings to the extent that the anxiety had a significant effect on the quality of life (e.g., avoidance of outdoor activities) [20]. Oude Elberink et al performed a sting challenge, which was negative in 100 of 103 VIT treated patients predominantly allergic to wasp venom. After a well-tolerated sting, 40 patients reported increased quality of life, as measured by the Vespid Allergy Quality of Life Questionnaire [15].

Not all patients who tolerate VIT injections are fully protected against insect stings [21]. A total of 16% of bee-allergic patients and 7.5% of wasp-allergic patients developed systemic reactions after stopping immunotherapy; however, most reactions were mild [22]. Some reactions are most probably psychogenic, resulting from fear, as patients frequently describe only subjective symptoms. Objective reactions might occur in VIT non-responders and in patients sensitized to minor venom epitopes, which are missing in commercial allergens used for VIT [23]. More severe systemic reactions could occur, particularly in patients with mastocytosis, thus mastocytosis has to be considered in insect allergic individuals and when confirmed patients should be offered epinephrine autoinjectors beside VIT [24].

CONSCLUSIONS

We confirmed that emergency situations are prevented in a substantial number (over 20%) of venom allergic patients already during the first year of VIT and that more than one-half of treated patients benefit from VIT during a maintenance period of 5 years, for an additional cost of at most 1905.6 E per patient.

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