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HYMENOPTERA VENOM IMMUNOTHERAPY: A LIFESAVING TREATMENT INDUCING IGE MODIFICATIONS IN REAL LIFE POLYSENSITIZED SUBJECTS

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ABSTRACT

Hymenoptera venom allergy is an IgE-mediated cause of anaphylaxis even life-threatening. Venom Immunotherapy (VIT) is described as a highly effective treatment if administered at least for 3 years and therefore considered as life-saving. We retrospectively evaluated Venom Immunotherapy influence on total and specific IgE (sIgE) in a population of 21 Hymenoptera allergic patients referring to the Allergy Unit of Messina University Hospital, who had been screened for Hymenoptera allergy and resulted polysensitized to different Hymenoptera venoms, Apis, Vespula and Polistes venoms. Both total and specific IgE were monitored before and after 3-years of VIT with a single venom extract chosen according to history and grade of sensitization. Hymenoptera venom sIgE resulted significantly reduced not only for the venom extract used for VIT (P = 0.01) but also for the other Hymenoptera venoms and precisely Vespula sIgE showed a statistically significant decrease (P = 0.01) non only in patients treated with Vepula venom extract but also in patients treated with Apis mellifera extract while Apis mellifera sIgE levels showed a statistically significant decrease (P = 0.01) non only in patients treated with Apis mellifera venom but also in patients treated with Vespula venom extract. Therefore, VIT in our patients resulted effective in reducing overall Hymenoptera venom sensitization also in polysensitized patients.

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INTRODUCTION

Hymenoptera venom allergy is a potentially life-threatening allergic reaction as a consequence of an Hymenoptera sting: the estimated prevalence is of 0.3-7.5% and even higher among outdoor workers (Ricciardi, 2018). The most frequent clinical signs of Hymenoptera venom allergy (HVA) are large local reactions (LLR), characterized by swelling exceeding a diameter of 10 cm, which can last for longer than 24 hours, and systemic severe reactions (SSR), characterized by flushing, urticaria/angioedema, dyspnoea, nausea, loss of consciousness, cardiac/respiratory arrest (Sturm, 2019). The diagnosis is the result of a positive clinical history of Hymenoptera sting reactions and the demonstration of an IgE-mediated mechanism, such as positive skin test and/or in vitro identification of specific IgE(sIgE) against the venom (Bilò, 2005). Patients are prescribed an emergency kit, including adrenaline autoinjector, corticosteroids and H1-antihistamines to be promptly administered, based on the gravity of sting reactions, nevertheless, the onlyeffective treatment to prevent further systemic sting reactions which has shown to be lifesaving is venom immunotherapy (VIT) (Bilò, 2016 and Sturm, 2018). In case of polysensitization, i.e. sensitization to venoms of more than one Hymenoptera species, treatment with only one venom is indicated as sufficient (Stoevesandt, 2013), currently available tests are in fact considered not able to distinguish between asymptomatic sensitization and clinically relevant HVA (Sturm, 2018).Selection of the correct venom preparation is still considered important to ensure optimal efficacy of VIT; the reduction of sIgE closely matches the VIT-induced protection (Albanesi, 201). We report the results of a retrospective real-life study on Hymenoptera allergic patients treated with Hymenoptera VIT in Messina's G.

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Martino University Hospital Allergy Unitfor 3 years in order to evaluate its efficacy in terms of tolerance to occasional stings and total and specific IgE (sIgE) modifications.

MATERIALS AND METHODS

The study was conducted retrospectively on 21 consecutive patients (18 males, 3 females; mean age 50.9 ± 14.39) who had referred to our Hymenoptera Allergy Unit becauseof a positive history of SSR to an Hymenoptera sting Grade 3 or 4 according to Mueller's classification (Mueller, 1966). Diagnosis of HVA was based on the classification of the type of reaction, confirmation of the IgE-mediated pathogenesis and identification of the stinging insect. Patients were shown an entomological notice board to facilitate the identification of the stinging insect.*In vivo* and *in vitro* tests were performed before starting Hymenoptera VIT and after 3 years' treatment. Intradermal tests were carried out with 0.1 to 1 mcg/mL concentrations,using standardized extracts of Apis mellifera, Vespula, Polistesand Vespa Crabro venoms(Anallergo, Florence, Italy).Serum sIgE were measured by RAST for Apis mellifera, Vespula, Polistes, Vespa Crabrovenoms at diagnosis, before starting Hymenoptera VIT, and after 5 years' treatment. Serum tryptase were measured in all patients in order to rule out Mastocytosis. VIT was performed in each patient with the venom extract of the Hymenoptera recognized to be the stinging culprit and in relation to tests results. The induction phase was carried out following a rush schedule;16 patients with Vepula extracts (9 were from Alk-Abellò VIT supplier, Milan Italy and 7 from Anallergo VIT supplier), 4 with Apis mellifera (2 from AlkAbellò and 2 from Anallergo) and 1 with Polistes extract (Anallergo). Both Alk-Abellò and Anallergo VIT extracts were purified, biologically standardized and adsorbed on hydroxide gel and L-Tyrosine respectively. The maintenance dose of 100 mcg was given every 5 weeks for 3 years. No severe systemic reaction occurred during VIT but only local reactions at the injection site. All patients were interviewed for occasional Hymenoptera re-stings during the VIT treatment.

Statistical analysis: A statistical analysis was performed, using SPSS for Windows (version 17.0). Data were presented as mean ± standard deviation (SD). Differences between two paired groups were analysed by Wilcoxon test. Statistical significance was set at $P < 0.05$.

RESULTS

After 3 years of treatment, skin intradermal tests were negative in all 21 patientsfor the venom extract used for VIT and was correlated with a lower skin test reactivity, than before VIT treatment, to the other tested venoms. An occasional Hymenoptera sting was tolerated without any reaction in all 21 patients during VIT; one male patient sensitized to Vespula venom resulted affected from Indolent Systemic Mastocytosis (ISM) with elevated serum tryptase levels and positivity to KIT mutation D816V. Levels of serum sIgE against the venom used for VIT decreased statistically significantly in l8 out of 21 patients ($P = 0.01$) (Fig. 1); Apis mellifera, Vespula and PolistessIgE levels decreased in a statistically significant way from T0 to T1 after 3 years' treatment with respectively Apis mellifera, Vespula and PolistesVIT extracts. Among patients with statistically significant decrease of venom sIgE there was also the male patient with ISM.

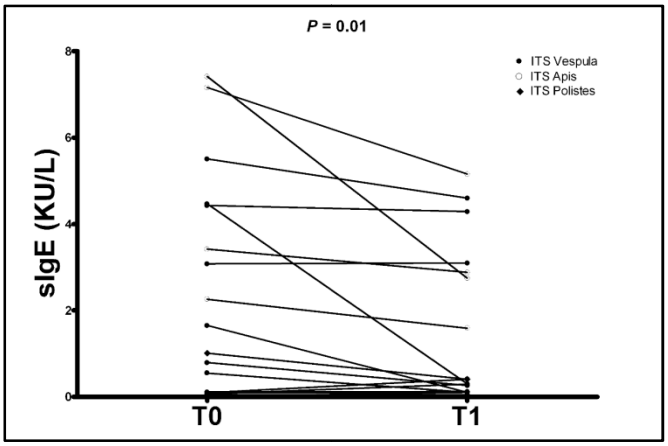

Figure 1. Apis mellifera, Vespula and PolistessIgE levels decreased in a statistically significant way from T0 to T1 after 3 years' treatment with respectively Apis mellifera, Vespula and PolistesVIT

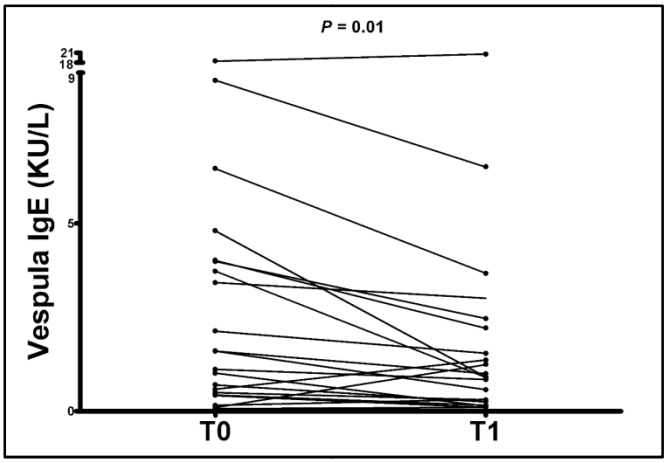

Figure 2. Apis mellifera sIgE levels decreased in a statistically significant way from T0 to T1, also in patients treated with Vespula venom extract

Furthermore, Vespula sIgEshowed a statistically significant decrease ($P = 0.01$) not only in patients treated with Vespula venom but also in patients treated with Apis mellifera extract(fig.2) while ApissIgE showed a statistically significant decrease ($P = 0.01$) not only in patients treated with Apis mellifera venom but also with Vepula venom extract (Fig. 3).Total serumIgE levels of all 21 patients, either treated with Apis mellifera, Vespula or Polistes venom extracts decreased, but not in a statistically significant way (respectively, T0: 242.15 ± 245.4 vs. T1: 186.64 ± 153.59 UI/L, $P = 0.07$).

DISCUSSION

Hymenoptera venom allergy, although is among the causes of severe allergic reactions, even life-threatening, can be prevented if treated with Hymenoptera VIT (Sturm, 2018). The efficacy of VIT is reported in 77-84% of patients treated with honeybee venom (HBV) and in 91-96% of patients treated with vespid venom (VV); it has been reported to improve patients' quality of life and life expectancy (Mueller, 1966). It is recommended in children and adults with known sensitization to Hymenoptera venom which causes systemic allergic reactions, possibly life-threatening anaphylaxis, or in patients with only skin symptoms (urticaria/angioedema), but at high risk of re-exposure and/or impairment of quality of life

[9].Our population with HVA was prevalently of males (18 out of 21) with reported allergic reaction and sensitization to vespids (16 out of 21); male sex and vespid venom allergy have already been reported as factors correlated to an increased risk of severe allergic reactions after Hymenoptera sting (Bilò, 2018).

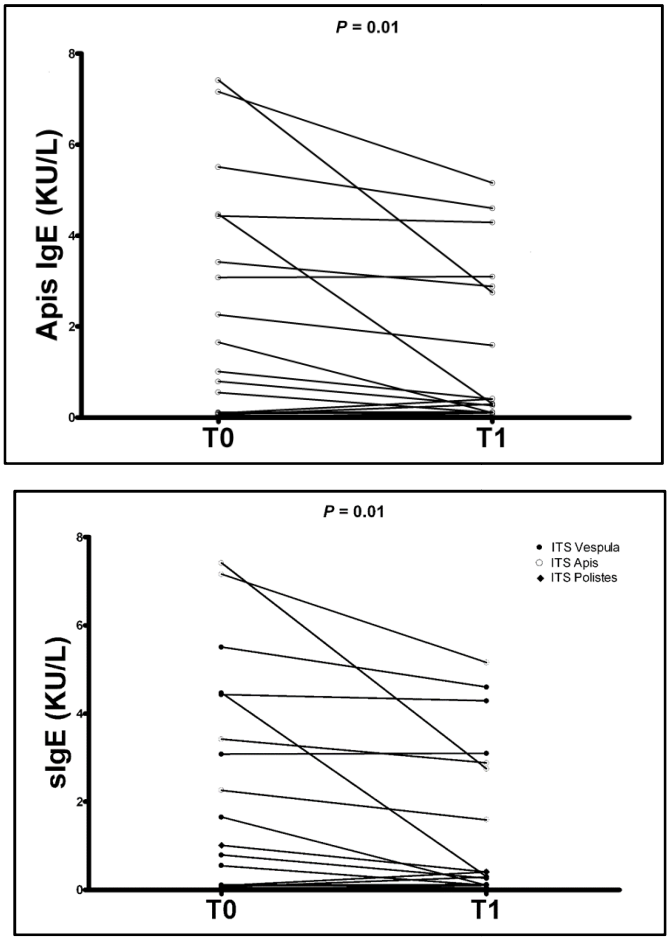

Figure 3. Vespula sIgE levels decreased in a statistically significant way from T0 to T1, also in patients treated with Apis mellifera venom extract

It has already been reported that sIgE levels to the respective venom decrease during VIT (Nittner Marszalska, 2015) and that total and sIgEvariations in patients that completed VIT correlate with no severe reactions upon field stings (Incorvaia, 2018). IgE modifications are described as a consequence of B cell compartment changes during VIT; a switch from IgE-producing pro-allergic B cells to IgG4-producing B cells with a regulatory phenotype, IL-10 and TGF-β dependent, is suggested to have a protective anti-inflammatory role (Brasch, 2009). Furthermore, Hymenoptera VIT has already been reported to be associated to a progressive expansion of circulating regulatory T cells, defined as CD25bright and/or Foxp3+ CD4+ T cells; this result was correlated to the venom-specific IgE decrease induced by VIT (van de Veen, 2016). Considering the complex sensitization profiles usually found in venom allergic patients (Schiener, 2017), also present in our population with poly-venom-sensitization, a relevant data from our study was the reduction not only of sIgE to the venom used for VIT but also to the other Hymenoptera venom to which they resulted sensitized. In our populationskin tests results after 3 years of VIT were negative for the venom used for immunotherapy and correlated to the decrease of sIgE. Low skin reactivity after >3 years of VIT has been reported to beinversely correlated to venom-specific IgG/IgE ratio (Pereira-Santos, 2008). Venom specific IgE decrease, after at least 3-year Hymenoptera VIT,has been reported as statistically significant, despite patients' age and high Mueller grade SR, either grade III or IV (Saulite, 2017 and Pravettoni, 2015). These characteristics were also found in our real life population as venom sIgE statistically significantly decreased after 3 year VIT. Desensitization is reported to be among the breakthrough novel treatments for patients with anaphylaxis; VIT, used for the treatment of life-threatening anaphylaxis when venom sensitization is confirmed, is among strategies which can be included in precision medicine interventions in order to prevent anaphylaxis (Labella, 2018). This can be valid also for polysensitized patients as highlighted from our data as VIT with a single venom extract showed to reduce venom sIgE to different venom extracts.

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