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Successful use of a subcutaneous injection port for modified cluster venom immunotherapy

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Long title: Successful use of a subcutaneous injection port for modified cluster venom immunotherapy

Short title: Desensitization of venom immunotherapy

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All authors were involved in the acquisition, analysis, and interpretation of empirical data.

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33 **Clinical Implications:** We report successful venom immunotherapy (VIT) using a
34 subcutaneous injection port for desensitization in modified cluster VIT in an adolescent with
35 recurrent anaphylactic reactions during conventional VIT despite receipt of antihistamine and
36 omalizumab therapy as premedication for one year.

Hymenoptera venom allergy is a life-threatening allergic reaction that develops after a honeybee, vespids (wasps), or ant sting. Severe reactions can be life-threatening or fatal. Beekeeping families are at a higher risk of honeybee stings, the risk of systemic reaction in this group being 14-38% (1).

The only known effective treatment in venom allergy is venom immunotherapy (VIT) (2). However, VIT may exhibit rare side-effects, such as mild or severe systemic reaction ranging from urticaria to anaphylaxis (2). Systemic reactions may lead to the discontinuation of VIT. The results of case reports involving the administration of omalizumab before and/or during VIT have been controversial. A number of issues regarding the use of omalizumab during VIT, such as the duration of administration, dosage, and time interval, are still unresolved (3).

Desensitization is used to elicit a state of unresponsiveness to an allergen, such as a drug or food, responsible for a hypersensitivity reaction. Desensitization starts with low doses, which are increased over a short time (from a few hours to a few days) up to the total cumulative therapeutic dose or tolerated dose of the relevant allergen.

We present a case of a 16-year-old girl who had been diagnosed with anaphylaxis after a severe systemic allergic reaction to honeybee stings on her neck at eight years of age, on her hands at 10 years, and on her feet at 12 years. She had no allergic rhinitis, conjunctivitis, or asthma. Her family was engaged in beekeeping, a cousin had died at the age of 21 following a bee sting, and her brother also had a history of bee-related anaphylaxis and was receiving VIT (*Apis* and *Vespula*) in our clinic. The patient subsequently presented to us for further examination and treatment. Venom-specific IgE (ImmunoCAP, Phadia, Uppsala, Sweden) concentrations were 11.4 kU/L for *Apis* and 0.77 kU/L for *Vespula*. Component-based diagnostic tests (CRD) revealed Api m1 phospholipase A2: 8.72 kU/L, Ves v5 common wasp: 0.28 kU/L, and Ves v1 phospholipase A1: 0.14 kU/L. Basal tryptase was 10.2 ug/L.

ALK conventional VIT was started in the present case involving *Apis mellifera* sensitivity. Anaphylaxis was noted in the third month (initial phase) of VIT, and two doses of 0.5 mg intramuscular adrenaline were administered. VIT was discontinued, and once-monthly omalizumab therapy was initiated (weight: 50 kg, total serum Ig E level: 3002 IU/mL, dose: 300 mg). Following omalizumab therapy for six months without VIT, VIT was restarted uneventfully in combination with omalizumab. Omalizumab was discontinued after one year. The patient subsequently developed anaphylaxis during VIT two months after omalizumab therapy was stopped (Fig. 1). Her parents refused to consent to further VIT combined with omalizumab due to their concerns about the potential long-term side effects of omalizumab.

As an alternative, a 10-step dosing protocol without premedication at each weekly visit of a cluster regimen was facilitated by using the subcutaneous injection port (i-Port Advance®, Medtronic MiniMed, Northridge, CA, USA) in this patient with repeated reactions to conventional VIT even with omalizumab. The i-port was placed on the patient's arms (Fig. E1 available in this article's Online Repository at www.jaci-inpractice.org). This 10-step "desensitization"-style regimen was better tolerated than the typical 3-4 step dosing in other cluster regimens.

In the build-up phase, VIT was performed using venom extract (Alutard SQ, ALK Laboratories, Denmark) at a concentration of 100 mcg/mL which equals 100,000 SQ-U/mL (vial 4). A total dose of 40 mcg was given on the first day and increased to 100 mcg per day for maintenance, once a week for six weeks as a modified cluster VIT regimen. During the maintenance phase, VIT was applied once every two weeks for the first month, and subsequently once every month (Table 1). She received a total of 15 doses of VIT with no reaction.

The patient was stung by a honeybee on her foot 10 months after the initiation of VIT with a subcutaneous injection port and exhibited no local or systemic reaction. The monthly maintenance VIT was planned to continue for a total of five years.

A recent systematic review reported that the risk of side-effects was 14.2% for honeybee venom and 2.8% for *Vespula* in patients treated with VIT (2). Consistent with the literature, systemic allergic reactions developed twice in the dose-escalation phase of VIT and a systemic reaction developed despite premedication with antihistamines from the commencement of VIT. Despite a total of one-year omalizumab therapy, a subsequent systemic reaction developed during VIT two months after the discontinuation of omalizumab. It therefore appeared that omalizumab lost its efficacy within two months after discontinuation. A report in the literature describes relapse of anaphylaxis during VIT after omalizumab was discontinued in an adult patient who exhibited no systemic reaction during omalizumab therapy. The authors reported that omalizumab could not be used as a long-term preventive treatment method (4). In addition, omalizumab had to be discontinued due to adverse reactions such as crippling fatigue and feebleness in an adult patient with systemic mastocytosis who received omalizumab as add-on therapy to improve VIT tolerability (5). There are no available data concerning the use of omalizumab therapy in children with VIT.

In the present case, the total treatment was given as a modified clustered VIT regimen while the total daily dose was desensitized. The successful administration of 10 divided doses of VIT with a subcutaneous injection port eliminated the need for premedication drugs such as antihistamines, corticosteroids, and omalizumab. We therefore suggest that the desensitization method can represent an alternative and successful approach in VIT. Consistent with our finding, ultra-rush VIT was successfully administered by desensitizing a high-risk adult patient with a history of severe systemic reaction during

conventional VIT in another report (6). Similarly, a previous study provided evidence for the safety and efficacy of one-day ultra-rush VIT by desensitization, with adjuvant omalizumab in adults refractory to traditional VIT or at highest risk of life-threatening Hymenoptera reactions (7).

Although the normal range for serum total tryptase was known to be between 1 and 11.4 ng/mL, serum total tryptase level ≥ 8 ng/mL can be found in hereditary α -tryptasemia (8). The potential mast cell diseases which may be responsible for systemic anaphylaxis with Hymenoptera venom and VIT could not be completely excluded in this case.

The i-Port Advance® is a new and advanced subcutaneous injection tool that is generally used for subcutaneous insulin therapy in diabetic children and eliminates the puncture for multiple injections (9). It also reduces the psychological effects in children, such as anxiety and fear. From that perspective, we suggest the use of a subcutaneous injection port to ensure pain control and increase compliance with desensitization of VIT. Single subcutaneous injection port costs approximately \$4 in Turkey. The i-port device was applied once on each visit, and 10 injections were administered with that device in a single day. A single device can remain in place on the patient for three days, but since we applied our treatment weekly, we used a new device on each visit (9).

This is the first case report that describes our experience of desensitizing VIT using a subcutaneous injection port as an alternative treatment in a high-risk adolescent with recurrent anaphylactic reactions during VIT despite receipt of antihistamine and omalizumab therapy for one year. We report the management of anaphylactic reactions during bee venom desensitization by changing from a conventional dosing regimen to a modified cluster regimen using 10-step desensitization dosing at each weekly visit. The subcutaneous injection port is introduced for the first time for greater patient comfort during administration of 10 doses per

131 visit. This has eliminated the need for premedication drugs such as antihistamines,
132 corticosteroids, and omalizumab. We anticipate that desensitizing VIT with a subcutaneous
133 injection port without premedication may represent a useful alternative to VIT and omalizumab
134 combination therapy in high-risk, recalcitrant cases. However, our results now need to be
135 confirmed, since our success was limited to a single case.

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164 **Figure Legends:**

165 Fig. 1. Time course of immunotherapy, omalizumab, and adverse reactions in an adolescent
166 patient with venom allergy.

167

Table 1. Desensitization protocol performed at each dose of cluster venom immunotherapy by 10-step at 30-minute intervals performed using allergen extract at a concentration of 100 mcg/mL

Cluster venom immunotherapy protocol				Desensitization protocol for each cumulative venom immunotherapy dose per day via the subcutaneous injection port
Visit	Interval	Cumulative Dosage (mcg)	Volume (mL)	Dosage (mcg) (10-step at 30-minute intervals)
1	weekly	40	0.4	1, 1, 2, 2, 4, 4, 5, 6, 7, 8
2		60	0.6	3, 3, 4, 5, 6, 6, 7, 8, 9, 9
3		70	0.7	4, 4, 5, 5, 7, 8, 8, 9, 10, 10
4		80	0.8	4, 4, 6, 6, 8, 8, 10, 10, 12, 12
5		90	0.9	5, 5, 7, 7, 9, 9, 11, 11, 13, 13
6		100	1.0	5, 5, 7, 8, 10, 10, 12, 13, 15, 15
7	biweekly	100	1.0	5, 5, 7, 8, 10, 10, 12, 13, 15, 15
8		100	1.0	5, 5, 7, 8, 10, 10, 12, 13, 15, 15
9		100	1.0	5, 5, 7, 8, 10, 10, 12, 13, 15, 15
10	monthly	100	1.0	5, 5, 7, 8, 10, 10, 12, 13, 15, 15
11		100	1.0	5, 5, 7, 8, 10, 10, 12, 13, 15, 15
12		100	1.0	5, 5, 7, 8, 10, 10, 12, 13, 15, 15
13		100	1.0	5, 5, 7, 8, 10, 10, 12, 13, 15, 15
14		100	1.0	5, 5, 7, 8, 10, 10, 12, 13, 15, 15
15		100	1.0	5, 5, 7, 8, 10, 10, 12, 13, 15, 15

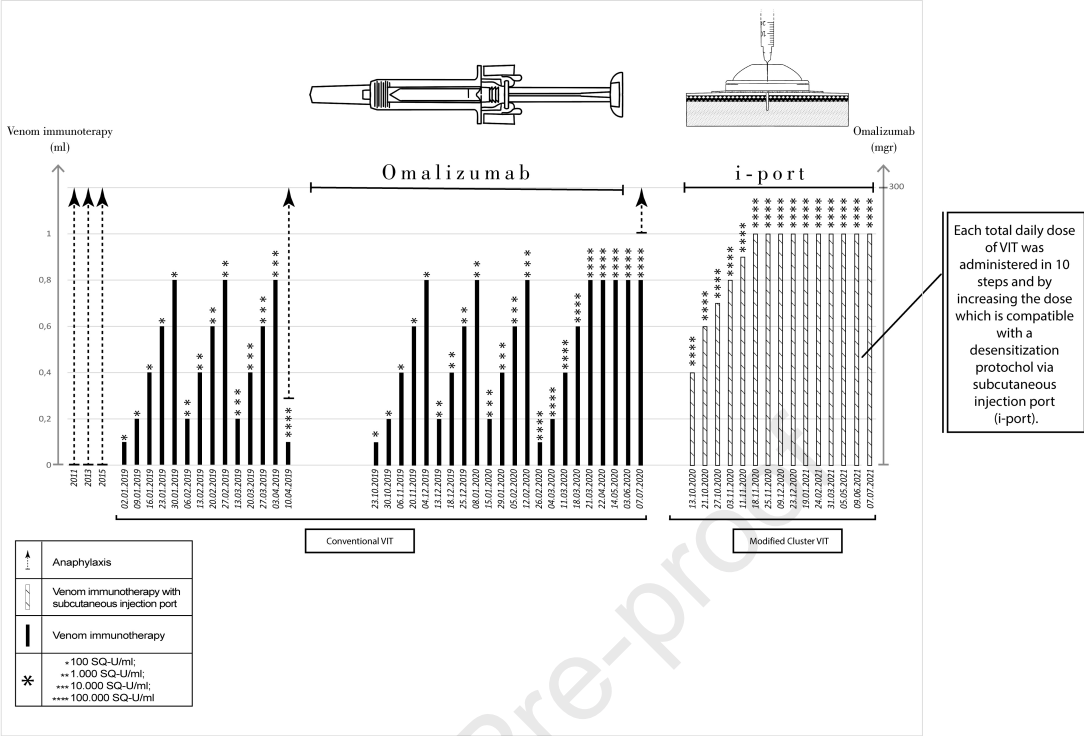


Figure Legends:

Fig. E1. The subcutaneous injection port on the patient's arm. It is a silicone cannula which is placed under the skin in injection areas such as the abdomen, upper thighs, back of the arms, and hips. It protects against the adverse effects of repeated injections, such as pain, bleeding, and bruising.

