Efficacy of a short pretreatment with omalizumab in children with anaphylaxis to hymenoptera venom immunotherapy A report of three cases

Catherine Droitcourt, Claude Ponvert, Alain Dupuy, Pierre Scheinmann, Rola Abou-Taam, Jacques de Blic, Guillaume Lezmi

Allergology International 68 (2019) 268–269

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Letter to the Editor

Efficacy of a short pretreatment with omalizumab in children with anaphylaxis to hymenoptera venom immunotherapy: A report of three cases

Dear Editor,

Hymenoptera venom allergy is the second cause of anaphylaxis in European children.[1] Systemic reactions occur in up to 0.8% of schoolchildren.[2] Venom immunotherapy (VIT) is recommended in sensitized children having systemic skin reactions exceeding generalized skin symptoms.[3] VIT carries an 8–20% risk of systemic adverse events.[3] Short protocols achieve the maintenance dose faster than conventional protocols but are more frequently associated with anaphylactic reactions.[3]

We report the cases of teenagers who experienced severe anaphylactic reactions (SAR) during the rush phase of VIT (Table 1). After an informed consent, a second rush VIT was performed after a pretreatment with omalizumab and was tolerated. No injection of omalizumab was required during the maintenance phase.

Case 1. A 15-year-old boy, son of a beekeeper, experienced SAR to bee stings (urticaria, respiratory distress, hoarse voice, malaise). Intradermal (ID) test was positive (5 mm at 0.001 μg/ml), specific bee venom IgE level was 2.11 KU/L. The basal serum tryptase (BST) level was not determined. A first four-day rush VIT (Alyostal®, Stallergenes, Antony, France) was conducted in 2007. The child had a respiratory distress with generalized urticaria after an injection of 40 μg at day 2. At day 3, an injection of 10 μg was well tolerated, but he relapsed after an injection of 20 μg, despite a pretreatment with intravenous dexchlorpheniramine. Four hours later, he tolerated an injection of 10 μg, but relapsed after the injection of 20 μg. A second rush VIT was proposed in 2008 after a pretreatment with omalizumab (weight = 56 kg, total serum IgE level = 95 KU/l, dose = 150 mg, 4 and 2 weeks before the onset of VIT). No systemic reactions occurred during the second VIT, the patient tolerated the target dose of 100 μg. The maintenance protocol was performed and tolerated for five years (Table 1). At that time, ID were negative, the specific IgE level was 0.81 KU/L. In 2009, a field resting by a bee was tolerated.

Case 2. A 12-year-old boy experienced a SAR (facial angioedema, respiratory distress) to a wasp sting. ID test was positive for wasp venom (12 mm at 0.001 μg/ml) and the specific IgE level was 26.10 KU/L. The BST level was not determined. A first four-day rush VIT (Alyostal®) was conducted in 2008. The patient had more and more intense and early large local reactions during the updosing phase, and an anaphylactic shock occurred at day 4, immediately after the injection of 100 μg, despite pretreatment with dexchlorpheniramine. A second rush was performed after a pretreatment with omalizumab (weight = 43 kg, total serum IgE level = 790 KU/l, dose = 300 mg, 4 and 2 weeks earlier). No systemic reaction occurred during the rush, the target dose of 100 μg was achieved. VIT was continued without adverse events for 5 years. The patient was field restung by a wasp without any reaction in 2009. In 2011, the ID was positive (10 mm at 0.1 μg/ml), the specific IgE levels were 3.05 KU/l.

Case 3. A 14-year-old boy, son of a beekeeper, had a SAR to a bee sting (urticaria, facial angioedema, respiratory distress, dysphagia, abdominal pain, vomiting). ID test to bee venom was positive (8 mm at 0.001 μg/ml), specific IgE levels against bee venom and Api m 1 were both > 100 KU/L. The BST level was normal (2.7 μg/l). A first rush VIT (Alyostal®) was conducted in 2014, and stopped at day 2, due to a generalized urticarial with respiratory distress and stridor occurring after the injection of 40 μg, despite pretreatment with dexchlorpheniramine. A second rush VIT was performed successfully after a pretreatment with omalizumab (weight = 61 kg, total serum IgE level = 305 KU/l, dose = 450 mg, 4 and 2 weeks earlier). The child is currently under maintenance protocol for 4 years, without any adverse events. In 2016, specific IgE levels against bee venom and Api m 1 were 89.2 KU/L and 42.9 KU/L.

In our department, (located in a low risk area of hymenoptera stings), 90 children were treated with VIT between 1999 and 2016. Five (5.6%) experienced SAR during the rush phase. Two children (2/5) (both sons of beekeeper) stopped definitively the VIT at a time when omalizumab was not marketed. Case reports suggested that pretreatment ± cotreatment with omalizumab may prevent the recurrence of SAR during VIT in adults and children.[3–6] Our observations confirm that a short pretreatment with omalizumab may be effective in children in this indication.

Risk factors for SAR during VIT include mast cell disease (MCD), bee venom allergy, rapid dose increase during the updosing phase.[3] Neither the specific IgE levels nor the skin reactivity are good predictors. The BST was determined in only one child, and despite the other two did not develop any symptoms of MCD, the diagnosis of indolent MCD cannot be excluded. Large local reactions during rush VIT, as in case 2, are not predictive of further systemic reactions during VIT. The frequency of local and mild systemic reactions is generally reduced with H1 antihistamines pretreatment; in our cases, this pretreatment did not prevent the occurrence of SAR.[3] Api m 4 sensitization was associated with a higher risk of systemic reactions during the rush phase of bee VIT.[7] This suggests a potential interest for compound-resolved diagnosis in the evaluation of patients requiring bee VIT.

Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2018.09.003

Table 1
Protocol for administration of venom immunotherapy.

Day (D)	Vial n°	Concentration (μg/ml)	Dose (ml)	Dose (μg)	Interval between injections (mn)
D 1	n° 1	0.01 μg/ml	0.1 ml	0.001	90
			0.5 ml	0.005	
	n° 2	0.1 μg/ml	0.1 ml	0.01	
			0.5 ml	0.05	
	n° 3	1 μg/ml	0.1 ml	0.1	
			0.5 ml	0.5	
D 2	n° 4	10 μg/ml	0.1 ml	1	90
			0.5 ml	5	
	n° 5	100 μg/ml	0.1 ml	10	
			0.2 ml	20	
			0.4 ml	40	
D 3	n° 5	100 μg/ml	0.5 ml	50	120
			0.5 ml	50	
D 4[†]	n° 5	100 μg/ml	1 ml	100	

[†] Then maintenance dose of 100 μg at D11, D25 and D46. Then every 4 weeks during 1 year and a half, every 5 weeks from year 1.5–3, and every 6 weeks from year 3–5.

Although omalizumab may improve tolerability of VIT, the optimal dosing and duration of injections are unknown and vary among the reported cases.[4] Omalizumab is generally administered during both the rush and the maintenance phases. Recurrences of SAR under VIT have been reported despite the use of omalizumab.[8,9] These observations suggest that omalizumab itself may not induce long-term tolerance of VIT, but that it may rather decrease the time to reach the maintenance dose and improve safety, as reported for oral immunotherapy in patients with food allergy.[10] This is supported by studies showing that omalizumab may rapidly decrease basophil reactivity, before the onset of an immunotherapy.[11]

The reasons why most adults require more injections than our patients remain unclear. Rapid updosing phases seem safer in children than in adults, potentially because adults have more frequent cardiovascular diseases and medication use.[12] The absence of a reaction in the children who were field restung provides evidence that VIT was effective, even after discontinuation of omalizumab. However, our procedure may not be effective in all children, especially those with MCD.

In summary, a short pretreatment with omalizumab may improve the tolerance of a rush VIT in some children with SAR during a previous rush. A better recognition of the patients who will benefit the most of this strategy and the optimal treatment duration need to be evaluated.

Conflict of interest

The authors declare that there is no conflict of interest.

Catherine Droitcourt [a,b,c], Claude Ponvert [d], Alain Dupuy [a,c], Pierre Scheinmann [d], Rola Abou-Taam [d], Jacques de Blic [d,e], Guillaume Lezmi [d,e,*]

[a] *Department of Dermatology, University Rennes Hospital, Rennes, France*
[b] *Clinical Investigation Center 1414 Inserm, University of Rennes, Rennes, France*
[c] *Pharmacoepidemiology and Access to Health Care REPERES EA7449, University of Rennes and French School of Public Health, Rennes, France*
[d] *AP-HP, Hôpital Necker-Enfants Malades, Service de Pneumologie et d'Allergologie Pédiatriques, Paris, France*
[e] *Université Paris Descartes, Paris, France*

* Corresponding author. Department of Pediatric Pulmonology and Allergy, Necker-Enfants Malades Hospital, 149 rue de Sèvres, 75015 Paris, France.
E-mail address: guillaume.lezmi@aphp.fr (G. Lezmi).

References

1. Grabenhenrich LB, Dölle S, Moneret-Vautrin A, Köhli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: the European anaphylaxis registry. *J Allergy Clin Immunol* 2016;**137**:1128–37.
2. Jennings A, Duggan E, Perry IJ, Hourihane JO. Epidemiology of allergic reactions to hymenoptera stings in Irish school children. *Pediatr Allergy Immunol* 2010;**21**:1166–70.
3. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilò MB, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: hymenoptera venom allergy. *Allergy* 2018;**73**:744–64.
4. Galera C, Soohun N, Zankar N, Caimmi S, Gallen C, Demoly P. Severe anaphylaxis to bee venom immunotherapy: efficacy of pretreatment and concurrent treatment with omalizumab. *J Investig Allergol Clin Immunol* 2009;**19**:225–9.
5. Stretz E, Oppel EM, Räwer HC, Chatelain R, Mastnik S, Przybilla B, et al. Overcoming severe adverse reactions to venom immunotherapy using anti-IgE antibodies in combination with a high maintenance dose. *Clin Exp Allergy* 2017;**47**:1631–9.
6. Ricciardi L. Omalizumab: a useful tool for inducing tolerance to bee venom immunotherapy. *Int J Immunopathol Pharmacol* 2016;**29**:726–8.
7. Ruiz B, Serrano P, Moreno C. IgE-Api m 4 is useful for identifying a particular phenotype of bee venom allergy. *J Investig Allergol Clin Immunol* 2016;**26**:355–61.
8. Soriano Gomis V, Gonzalez Delgado P, Niveiro Hernandez E. Failure of omalizumab treatment after recurrent systemic reactions to bee-venom immunotherapy. *J Investig Allergol Clin Immunol* 2008;**18**:225–6.
9. Yılmaz I, Bahçecioglu SN, Türk Murat. Combination of omalizumab and bee venom immunotherapy: does it work? *Asia Pac Allergy* 2018;**8**:e2.
10. Lin C, Lee IT, Sampath V, Dinakar C, DeKruyff RH, Schneider LC, et al. Combining anti-IgE with oral immunotherapy. *Pediatr Allergy Immunol* 2017;**28**:619–27.
11. Frischmeyer-Guerrerio PA, Masilamani M, Gu W, Brittain E, Wood R, Kim J, et al. Mechanistic correlates of clinical responses to omalizumab in the setting of oral immunotherapy for milk allergy. *J Allergy Clin Immunol* 2017;**140**:1043–53.
12. Nittner-Marszalska M, Cichocka-Jarosz E, Małaczyńska T, Kraluk B, Rosiek-Biegus M, Kosinska M, et al. Safety of ultrarush venom immunotherapy: comparison between children and adults. *J Investig Allergol Clin Immunol* 2016;**26**:40–7.

Received 31 July 2018
Received in revised form 3 September 2018
Accepted 13 September 2018
Available online 17 October 2018