

Correspondence

Manifestation of rheumatoid arthritis during subcutaneous allergen-specific immunotherapy with bee venom

To the Editor:

Linneberg et al¹ performed a registry-based observational study in which they found a lower incidence of autoimmune disease (AD) in patients treated with subcutaneous immunotherapy (SCIT; 206/18,841) compared with that seen in patients treated with conventional allergy treatment (6,071/428,484) within a 10-year period. Data on the long-term side effects of SCIT are sparse. This important study offers “safety data” of SCIT,¹ which is especially important because, anticipating possible effects on the immune system, it was generally agreed that SCIT should not be used in patients with AD.² However, the observation by Linneberg et al¹ was focused on the overall incidence of AD and not on the actual coincidence of SCIT and AD during SCIT.

In our department a 56-year-old woman presented with a history of a systemic anaphylactic reaction to a bee sting. There was no medical history of AD symptoms or rheumatoid arthritis (RA). Skin prick testing revealed a strong reaction to bee venom at 10 µg/mL, and serum analysis showed bee-specific IgE (2.1 kU/L). The patient was advised to undergo bee venom SCIT according to an ultrarush protocol.³ After initial SCIT with no adverse reaction, therapy was continued with 100-µg booster injections. Subsequently, for the first time, the patient complained of symmetric joint pain and swelling of the knees and metatarsophalangeal joints of both feet. Treatment with betamethasone, dexamethasone, and ibuprofen cleared her symptoms, allowing SCIT to be continued. After injection on day 42, she reported increasing joint pain and swelling, demanding further investigation. Magnetic resonance imaging showed pronounced inflammation of the soft tissue affecting the metatarsophalangeal joints and several tendons. Fortunately, the patient's serum samples from before SCIT induction were still available, and magnetic resonance imaging findings could be correlated with increased C-reactive protein levels from baseline before SCIT to 1.34 mg/dL, and rheumatoid factor (RF), which was not detectable before SCIT, was 33 kU/L. Importantly, anti-cyclic citrullinated peptide (CCP) antibody levels increased dramatically from 80 U/mL before to greater than 1600 U/mL after 42 days of SCIT. Bee venom-specific IgE levels increased to 5.9 kU/L, and IgG₄ levels increased from 0.10 to 1.32 mg_A/L (Table I). Cellular delayed-type immune responses to bee venom were excluded. RA was diagnosed. Because primary manifestation of RA occurred in close association with SCIT applications and the increase in both allergen-specific (bee venom) and antigen-specific (RA) serum antibodies were detected in parallel with SCIT and RA symptoms, SCIT was terminated, and therapy with methotrexate and prednisolone was initiated, resulting in clinical improvement and normalization of C-reactive protein levels.

Here we report that bee venom SCIT induced first-time manifestation of RA in a previously RF-negative patient without a history of arthritis. Low anti-CCP titers before SCIT initiation in our patient indicate a previously unknown risk for RA in this patient. To our knowledge, only 2 patients with manifestations of classical AD during SCIT have been reported thus far.^{4,5}

TABLE I. Changes in titers of bee venom-specific antibodies and RA-related markers before and during SCIT

Parameter	Titer before starting specific immunotherapy	Titer during onset of RA
Bee venom-specific IgE (kU/L)	2.1	5.9
Bee venom-specific IgG ₄ (mgA/L)	0.1	1.32
C-reactive protein (mg/dL)	0.55	1.34
RF (kU/L)	Not detectable	33
Waalser-Rose assay	—	1:16
Anti-CCP antibodies (U/mL)	80	>1600

Stimulation of the immune system by SCIT can lead to activation of mast cells, releasing TNF and promoting arthritis⁶ and/or to polyclonal activation of B cells, resulting in autoantibody production.⁷ Importantly, our data indicate that SCIT-induced polyclonal B-cell activation could be responsible for RA manifestation in our patient because a log increase in her anti-bee venom IgG₄ antibody levels and the 2.8-fold increase in bee venom-specific IgE levels directly correlated with the more than 20-fold increase in anti-CCP antibody levels and subsequent detection of RF (Table I). RA symptoms in our patient appeared during initial bee venom injections, correlated with consecutive SCIT applications, and persisted until SCIT was terminated, allowing specific RA treatment to be successful. The clinical course of RA and SCIT initiation together with the biomonitoring data based on allergen/antigen-specific detection of serum antibodies in both cases, bee venom allergy and RA, strongly support our conclusion of RA manifestation caused by bee venom SCIT. Linneberg et al¹ concluded from their investigations that SCIT is associated with a generally lower risk of AD because fewer patients with SCIT had AD compared with those receiving conventional allergy treatment.¹ Our observation of 1 patient with SCIT and concomitant AD suggests that careful history and even autoantibody testing before SCIT might be helpful in selected patients to identify those at risk for AD during SCIT. In general, the benefit/risk ratio in patients with venom allergy favors induction of SCIT, and further investigations will be necessary to be able to evaluate the risk for AD during SCIT.

Kamran Ghoreschi, MD

Jörg Fischer, MD

Tilo Biedermann, MD

From the Department of Dermatology, University Medical Center, Eberhard Karls University Tübingen, Tübingen, Germany. E-mail: Tilo.Biedermann@med.uni-tuebingen.de.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Linneberg A, Jacobsen RK, Jespersen L, Abildstrøm SZ. Association of subcutaneous allergen-specific immunotherapy with incidence of autoimmune disease, ischemic heart disease, and mortality. *J Allergy Clin Immunol* 2012;129:413-9.
2. Zuberbier T, Bachert C, Bousquet PJ, Passalacqua G, Walter Canonica G, Merk H, et al. GA²LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy* 2010;65:1525-30.

3. Wenzel J, Meissner-Kraemer M, Bauer R, Bieber T, Gerdson R. Safety of rush insect venom immunotherapy. The results of a retrospective study in 178 patients. *Allergy* 2003;58:1176-9.
4. Turkcapar N, Kinikli G, Sak SD, Duman M. Specific immunotherapy-induced Sjögren's syndrome. *Rheumatol Int* 2005;26:182-4.
5. Nakajima H, Ohtsuka S, Nishina T, Sugino M, Kimura F, Hanafusa T, et al. Multiple sclerosis after allergen-specific immunotherapy and influenza vaccination. *Eur Neurol* 2003;50:248-9.
6. Kneilling M, Hültner L, Pichler BJ, Mailhammer R, Morawietz L, Solomon S, et al. Targeted mast cell silencing protects against joint destruction and angiogenesis in experimental arthritis in mice. *Arthritis Rheum* 2007;56:1806-16.
7. Leadbetter EA, Rifkin IR, Hohlbaum AM, Beaudette BC, Shlomchik MJ, Marshak-Rothstein A. Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature* 2002;416:603-7.

<http://dx.doi.org/10.1016/j.jaci.2012.08.052>