

Correspondence

Reply

To the Editor:

We thank Ghoreschi et al¹ for their commentary and response to our study on the association between allergen-specific immunotherapy (AIT) and risk of autoimmune disease (AD). In a nation-wide registry-based pharmacoepidemiologic study we found that patients receiving AIT compared with patients receiving conventional allergy treatment (local steroids or systemic antihistamines) apparently had a lower incidence of AD.² As noted by Ghoreschi et al,¹ we looked at the overall risk of AD from the start of AIT (or conventional allergy treatment) and throughout the follow-up period independently of whether the patient discontinued treatment during this period. This decision was made to ensure that any side effects that might have led to cessation of AIT would also be accounted for as a possible side effect of AIT. Thus any case of AD development after cessation of AIT would be defined as a side effect of AIT. However, we also examined whether the lower risk of AD after AIT differed between the first 6 months of treatment and after the first 6 months. It showed that the negative association was significantly stronger (more negative) during the first 6 months after the start of treatment compared with that after the first 6 months. Therefore it seems likely that the effect is mainly seen during treatment and, to a lesser extent, after cessation of treatment. Nevertheless, we emphasized that the apparent negative association between AIT and AD should be interpreted with caution, and we are reluctant to conclude that AIT prevents AD. It is likely that at least some of the negative effect is explained by confounding factors, such as the possibility that patients receiving AIT are healthier than patients receiving conventional allergy treatment, as discussed in more detail in our article.² Because little is known about the risk factors for AD, it is difficult to control for these unknown risk factors. Our key message was that our study, being the first attempt to perform a controlled investigation of this issue, does not support that AIT increases the overall risk of AD.

Ghoreschi et al¹ present a case of rheumatoid arthritis (RA) development during the course of venom AIT. The temporal relationship between AIT and development of RA seems convincing, although it cannot be completely ruled out that the development of RA could have occurred by chance. Interestingly, immunologic evaluation was possible in blood that had been stored before the

start of AIT, and anti-cyclic citrullinated peptide results turned out to be positive before the start of AIT, indicating that this patient was at increased risk of RA. It is thus possible that AIT acted as a trigger of RA in this immunologically predisposed patient. Very few cases of AD have been reported in the literature. We have recently reviewed the literature for cases of AD with possible relationship to AIT.³ We retrieved 15 articles representing 22 cases of AD. Vasculitic reactions in the skin accounted for the majority of cases (13/22 cases). A type III immune complex immune response is a plausible underlying mechanism for vasculitic reactions and should probably not be viewed as an autoimmune reaction when triggered by injection of large doses of allergens.³ Only 2 cases were RA reactions like the case reported by Ghoreschi et al.¹ Nevertheless, some cases are likely not published. It is important that such cases are published, and we encourage physicians to do so.

In our review we concluded that development of AD in allergic patients treated with AIT is rare, but as a principle of caution, it seems reasonable to carefully evaluate the indication for AIT (ie, risk vs benefits) in patients with established AD or a strong family history of AD.³ We believe that the case reported by Ghoreschi et al¹ lends support to this cautious position on this delicate topic.

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REFERENCES

1. Ghoreschi K, Fischer J, Biedermann T. Manifestation of rheumatoid arthritis during subcutaneous allergen-specific immunotherapy. 2012;■■■■■■■■■■.
2. 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.
3. Linneberg A, Madsen F, Skaaby T. Allergen-specific immunotherapy and risk of autoimmune disease. *Curr Opin Allergy Clin Immunol* 2012 [Epub ahead of print].

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