

CORRESPONDENCE

Comment on letter to allergy: different types of tolerance

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We thank Jones and Jeal for raising some issues for discussion regarding our study. The role of IgG4 antibodies on tolerance is still an issue of debate. First of all, it is necessary to distinguish two different types of tolerance: clinical and immunological tolerance. Clinical tolerance can be defined as the absence of symptoms, even in the presence of specific IgE antibodies. This is the type of tolerance seen after immunotherapy, where IgE antibodies are still present but symptoms are reduced. We have found indications of clinical tolerance by IgG4 antibodies in occupational settings as well (1, 2). Clinical tolerance is probably the type of tolerance investigated earlier by Jones and Jeal (3). From their study, they conclude that specific IgG4 antibodies in the presence of IgE reduce the risk of symptoms.

The other type of tolerance is a form of isotype-specific immunological tolerance, in which specific IgE production is prevented and/or ongoing IgE production is abrogated. This is the type of tolerance we mainly investigated in the discussed paper (4). Isotype-specific immunological tolerance acts primarily at the level of the isotype switch of B cells. Aalberse and Platts-Mills (5) discussed that this isotype switch can go via a direct switch to IgE production or that IgG-switched B cells (including IgG4-switched B cells) can undergo a secondary switch to IgE production. As most of the participants in our study already had an IgG4 response, we were indeed too late to study the direct switch in the absence of IgG4-switched B cells. However, none of our participants had an allergen-specific IgE response at the start of the study. We therefore studied the influence of allergen-specific IgG4 antibodies on the (direct or indirect) switch to IgE.

Earlier studies have shown that the risk to become sensitized to laboratory animals within the first 2 years of exposure is high (6), so we assumed that a follow-up period of 2 years would be sufficient to include a large enough sample. After 2 years, 20% of the workers became sensitized, which is relatively high compared with other studies (2, 3, 6). We therefore believe our follow-up was long enough and our sensitization rate was high enough to study the immunological tolerance. For studying clinical tolerance, a longer follow-up and a higher number of participants would be better.

Jones and Jeal also argue that the range of exposure in our study was too low to demonstrate differences in the IgG4 response over time. The lowest and highest exposed groups in our population showed a difference of a factor 60 (mouse) to 300 (rat) in measured exposure levels, which is consistent with other studies on laboratory animal allergen exposure (3, 6). In addition, exposure was high enough to develop a high specific IgG4 response of more than 1 µg/ml in over 30% of

the individuals. Moreover, the range of IgG4 levels in our study (approximately factor 500) was comparable with the IgG4 range in the cat study of Platts-Mills (7). We believe these ranges enabled us to study the effect of IgG4 on the induction of IgE antibodies and on immunological tolerance.

Immunological tolerance may be a result of a direct influence of specific IgG4 antibodies on the B-cell switch towards IgE. In our study, (4) we showed that high levels of specific IgG4 in serum do not prevent B cells to switch to IgE and that IgG4 levels even tend to be higher in workers developing IgE, indicating a secondary switch may have occurred. Even though a cross-sectional study is not the best design to study consecutive processes, also Jeal et al. (3) found higher levels of specific IgG and IgG4 in IgE-positive workers, supporting our conclusion that high levels of IgG4 do not prevent the development of IgE.

Concerning the identification of a group of (clinical or immunological) tolerant workers, to our knowledge no study has ever shown a highly exposed group with IgG4 development in the complete absence of IgE development. Such a group would be a truly tolerant group. However, previous cross-sectional studies in laboratory animal workers showed that the highest exposed group is not the group with the highest rate of sensitization (3, 6). In cross-sectional studies, this group could be influenced by the healthy worker effect or by prejob selection. Although it was not the aim of our study and the number of sensitized individuals per exposure group is relatively low, we also see a lower incidence in seroconversion to IgE in the highest quintile of contact hours compared with the 4th quintile. This suggests that high exposure might induce protection against sensitization. However, high-risk workers (e.g. atopic workers) can be under-represented in the highest exposed category (3), which may bias inferences. Longitudinal studies with a large sample size and prolonged follow-up are needed to firmly establish whether high exposure lowers the risk of allergic sensitization and to identify the mechanism behind this.

Conflict of interest

There are no known conflicts of interest for the authors.

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