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CORRESPONDENCE

The role of omalizumab or rhuMAb-E25 in the treatment of allergic rhinitis

To the Editor:

I read with interest the recent article by HANF *et al.* [1], demonstrating the significant inhibition of both allergen challenge-induced nasal symptoms and the increase of human serum albumin in nasal lavage fluid after allergen challenge, in addition to the significant reduction in tumour necrosis factor-α levels in basal nasal lavage fluid, following administration of omalizumab.

However, it is difficult to gauge from the study, the exact degree of disease severity in the study population, as no data were given with regards to the patients′ usual therapy for allergic rhinitis, be it topical or oral, and hence no assessment of correlation between treatment and symptoms can be made. In addition, the characterisation of the study population was inadequate, as to whether patients suffered from seasonal or perennial allergic rhinitis, as no detailed data with regards to each individual′s aeroallergen sensitisation were presented. Moreover, one has to be wary of the potential confounding effects of conducting the study during the pollen season, especially in patients who were sensitised to birch and grass pollen.

Although the study did shed some light on the potential for the use of omalizumab in allergic rhinitis, the exact indications for its use remain unclear. It is a pity that patients were not better categorised or characterised, as one could have perhaps argued a case for the role of omalizumab as a second- or third-line agent following failure with conventional therapy, such as corticosteroids, histamine H_1-receptor antagonists and leukotriene $CysLT_1$-receptor antagonists. Furthermore, the fact that the mode of delivery of omalizumab is through subcutaneous administration must not be ignored, as this will disadvantage it against other established first-line topical or oral therapy for allergic rhinitis.

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From the authors:

In our recent article, we demonstrated the inhibitory effect of subcutaneously administered monoclonal anti-immunoglobulin-E antibody, omalizumab, on nasal responses to allergen challenge in patients with allergic rhinitis [1]. Omalizumab-treated patients showed reduced nasal symptoms, an inhibition of the increase of human serum albumin in the nasal lavage fluid after allergen challenge and a decrease in tumour necrosis factor-α in basal nasal lavage fluids.

D.K.C. Lee mentioned in his Letter to the Editor, that no exact degree of disease severity and no data with regards to the usual therapy for allergic rhinitis were given in the article. Moreover, D.K.C. Lee missed an exact indication for the use of omalizumab and an estimation of the role of omalizumab in the therapy of allergic rhinitis compared to the conventional therapy. Furthermore, D.K.C. Lee missed detailed data with regards to each individual′s aeroallergen and mentioned a possible influence of the pollen season on the results of our study. Finally, D.K.C. Lee stresses the subcutaneous way of application of omalizumab, as this will be a disadvantage against the established therapies for allergic rhinitis.

The target of our study was the effect of omalizumab on the nasal symptoms and the inflammatory markers in nasal lavage fluid before and after allergen challenge of patients with allergic rhinitis. The degree of disease severity and the usual therapy were not a target of our study, moreover the patients had no symptoms at the time-points of allergen challenge. However, we think the influence of severity and usual therapy would be very interesting for further studies.

As our study was a model of allergen provocation, of course it was not possible to get exact results for the indication for omalizumab in the therapy of allergic rhinitis. There are other studies which have investigated the effect of omalizumab on allergic rhinitis during the allergy season [2]. Further studies like these may have the possibility to analyse the rank of omalizumab in the therapy of allergic rhinitis. At this time, omlizumab is approved for the additional treatment of severe asthma. From our point of view, omalizumab has its advantage in the treatment of multiple allergic diseases, such as allergic asthma and allergic rhinitis simultaneously.

As mentioned above, all patients who participated in the study were symptom-free at the time-points of allergen-challenge. This includes the seasonal und perenial allergens. Consequently, we had no influence of seasonal effects on the results of our study.

The subcutaneous application of omalizumab was no problem for our patients. Yet we agree with D.K.C. Lee, that we would prefer a different way of administration or a longer period between the injections. However, the route of administration is defined by the pharmacokinetics and pharmacodynamics of the compound.

Over all, the interest of our studies of the effect of omalizumab was mainly the influence on inflammatory processes. As in the recently published article concerning allergic asthma [3], we focused on the description of the effect of omalizumab on allergic inflammation to get a more detailed insight into the reasons of the clinical effect of omalizumab.

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Alveolization: does "A" stand for appropriate morphometry?

To the Editor:

In a recent issue of the *European Respiratory Journal*, HIND AND MADEN [1] reported a series of well-designed experiments conducted to further enlighten the role of retinoic acid in alveolar regeneration. The ability of retinoic acid to rescue emphysematous lungs, which was initially reported by MASSARO and MASSARO [2], has attracted great attention. However, the potential of retinoic acid is still controversially discussed [3]. Unquestionably, the study of HIND and MADEN [1] added important new data to our knowledge of the role of retinoic acid in alveolization, as was emphasised in an accompanying editorial [4]. In their editorial, TORDAY and REHAN [4] ask "Does "A" stand for alveolization?". Can this question be answered on the basis of the data presented?

In the context of lung development, alveolization is recognised as the process of subdivision of lung saccules by outgrowing secondary septa, which results in an increased number of smaller subunits, now termed alveoli [5]. As a consequence, total alveolar surface area is considerably enlarged. Hence, alveolization is defined by changes in at least three morphologic characters: alveolar size (volume), total alveolar surface area and number of alveoli. Unfortunately, HIND and MADEN [1], in pursuing to demonstrate that retinoic acid induces alveolar regeneration in the adult mouse, used but one single parameter to assess alveolization: the mean chord length (Lm), also called mean linear intercept length.

The Lm is a measure of the average distance between two intercepts of a test-line, arbitrarily superimposed on parenchymal tissue, with the alveolar walls. No distinction is made between test lines running within alveoli and those crossing alveolar ducts. Hence, changes in Lm may reflect changes in alveoli or in alveolar ducts. In turn, if alterations are present in both alveoli and alveolar ducts, but are of opposite sign, this may not result in any differences in Lm at all. Therefore, determining Lm provides us with an indicator of changes in airspace (alveoli plus alveolar duct) size, but it cannot be used to assess changes in alveoli with sufficient certainty, as has been emphasised by others [6].

The enthusiastic reader might argue that the authors also presented data on the total alveolar surface area (Sa). However, as was stated in the Material and methods section, this parameter was derived by calculation from Lm and lung volume according to WEIBEL [7]. Hence, this calculation is based on the inverse relationship between the surface-to-volume ratio (S/V) of an object and Lm according to the formula $S/V=4/Lm$. Thus, the total alveolar surface area of the lung is calculated as $Sa=4\times Vlung/Lm$. As the surface-to-volume ratio strongly depends on the shape of the object measured, the alveolar surface area calculated from Lm may be affected by changes in shape; as was convincingly demonstrated (fig. 4c and d of [1]), there were considerable alterations in alveoli from control as compared with dexamethasone-treated animals. Even if we accept the assumption to be true that alveoli are of equivalent shape irrespective of treatment with disulphiram, dexamethasone or/and retinol, one problem still needs to be addressed. Measurements of Lm were done on sections of lungs embedded into paraffin, whereas organ volume was determined prior to embedding. Paraffin embedment introduces considerable tissue shrinkage, which affects Lm measurements [8], and no details are given how measurements were corrected for tissue shrinkage.

E.R. Weibel and his co-workers and colleagues have greatly advanced the field of quantitative morphology during the last decades. Today, a whole range of stereological tools is available that can readily be applied to the quantification of morphologic characters related to volume and size, surface area and numbers [9–11], and new promising tools are still emerging [12]. Quantitative morphology does no longer need to make assumptions about the shape or other features of structures to be analysed. MASSARO and MASSARO [2], for example, have already demonstrated how the tools of design-based stereology can be implemented into the investigation of alveolization (including the effects of retinoic acid) as well as alveolar regeneration, and how these tools enormously increase the impact of such studies. It is a pity that HIND and MADEN [1], as well as others [3], wasted so much of the inherent power of their beautifully designed experiments by relying on a single (biologically ill-defined) morphometric measurement, the mean linear intercept length. A variety of versatile design-based stereological tools are available today. Researchers in respiratory medicine should no longer hesitate to make their choice to get better answers to questions like "does "A" stand for alveolization?".

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