

Anti-inflammatory effects of seven years treatment with Omalizumab in severe uncontrolled asthmatics

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Keywords: exacerbations; inflammation; severe asthma; therapy.

Severe persistent asthma causes a substantial morbidity and mortality burden and is frequently inadequately controlled despite intensive guideline-based therapy (1). Omalizumab represents in these patients an alternative anti-inflammatory therapy.

Omalizumab controls severe uncontrolled asthmatics modulating CREB activation and FoxP3 and IL-8 expression.

As the control of inflammation represents the main target of the therapy in severe persistent asthma, it is important to determine the effects of omalizumab on markers of inflammation. This study was aimed to assess whether long-term treatment with omalizumab was able to reduce inflammation other than to improve clinical control in severe asthmatics. Severe uncontrolled asthmatics showed an increased activation of cyclic adenosine mono-phosphate response element-binding protein (CREB) (p-CREB) in the epithelium and in the submucosa as well as in peripheral blood mononuclear cells (PBMC) (2). CREB activation promotes transcription of inflammatory cytokines crucially important in the pathogenesis of asthma, including IL-8 (3), and is involved in the FoxP3 expression in T regulatory cells (Tregs) (4). FoxP3 functions as activator of Tregs activities and as a potent repressor of CREB-dependent transcriptional activation (5). Omalizumab was administered to seven severe corticosteroid-dependent asthmatics (2) from 1999 to 2006 (7 years) as part of a prospective clinical trial CIGE0250011 (Novartis), followed by three extensions. In the recruited

patients, symptom score, spirometry, and also p-CREB/CREB ratio (western blot analysis) (2), FoxP3 (western blot analysis) and IL-8 expression (immunocytochemistry) in PBMC were assessed at the end of omalizumab trial and after 6 months from omalizumab discontinuation. No additional inflammatory markers were tested. All patients had a positive skin prick test and a positive radioallergosorbent test for *Dermaphagoides pteronyssinus* and *Dermaphagoides farinae*. Eligible patients had a baseline IgE > 76 IU/ml, a predicted forced expiratory volume in 1 s (FEV1) < 80%, regularly occurring day or nighttime asthma symptoms and at least two documented asthma exacerbations, requiring systemic corticosteroids or emergency services/hospitalization, during the year before the initiation of omalizumab. Nighttime and daytime asthma symptoms were rated on a 4-point scale: 0 = none; 1 = mild (awareness of symptoms that were easily tolerated); 2 = moderate (symptoms with some discomfort, causing some interference to sleep or daily activities); 3 = severe (inability to sleep or in daily activities).

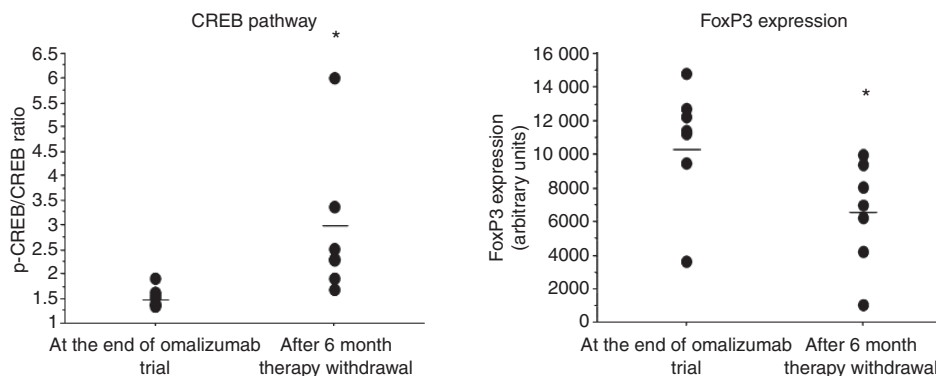


Figure 1 p-CREB/CREB ratio or Foxp3 expression was assessed by western blot analysis. Corresponding signals were semi-quantified by densitometric scanning and normalized for b-actin (arbitrary units). * $P < 0.05$.

This study provides compelling evidences that omalizumab is effective in severe uncontrolled asthma by modulating mechanisms crucially involved in the inflammatory processes of the disease. An increased p-CREB/CREB ratio is shown after 6 months from omalizumab discontinuation in comparison with the p-CREB/CREB ratio at the end of omalizumab trial, confirming the anti-inflammatory activities exerted by omalizumab (Fig. 1).

Patients at the end of omalizumab trial showed increased FoxP3 expression in comparison with the expression observed in the same patients 6 months after therapy discontinuation (Fig. 1).

According to previous findings (6), omalizumab is able to significantly ($P < 0.05$) decrease IL-8 expression, as patients at the end of omalizumab trial showed reduced percentages of IL-8 positive cells (0.6 ± 0.2) in comparison with the percentages observed in the same patients 6 months after therapy discontinuation (4 ± 2).

The p-CREB/CREB ratio, the FoxP3 expression, and the IL-8 expression correlate with the FEV1 values ($\rho = 0.55$, $P < 0.05$; $\rho = 0.7$, $P < 0.01$; $\rho = 0.78$, $P < 0.01$) and the symptom score ($\rho = 0.7$, $P < 0.02$; $\rho = 0.5$, $P < 0.05$; $\rho = 0.5$, $P < 0.03$) supporting the concept

that omalizumab improves the clinical control of asthma through a better control of inflammation.

In conclusion, this study demonstrates that after 7 years of treatment, omalizumab increased FEV1 and reduced asthma symptom score, all events correlated to a reduced p-CREB (activator of pro-inflammatory events) and IL-8 (mediator of inflammation associated to frequent exacerbations) and to an increased FoxP3 (regulation of inflammation) expressions. The effects of omalizumab in modulating CREB, FoxP3, and IL-8 expression do not persist long after omalizumab discontinuation and need to be further validated in larger patient cohorts.

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Accepted for publication 31 March 2010
Allergy 2010
© 2010 John Wiley & Sons A/S
DOI: 10.1111/j.1398-9995.2010.02403.x

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