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Role of T Regulatory Cells in the Pathogenesis of Asthma

To the Editor:

Smyth and colleagues¹ recently reported in *CHEST* (October 2010) that CD4⁺FoxP3⁺ T regulatory cells (Tregs) were increased in BAL of patients with moderate to severe asthma compared with patients with mild asthma and healthy subjects. Their findings are intriguing in that they shed new light on the role of Tregs in the pathogenesis of asthma, but we have some concerns about the interpretation of the results.

Tregs have been revealed to suppress the activity of effector T lymphocytes. However, the hypothesis in their research that the numbers of Tregs would be increased in patients with more severe asthma lacks theoretical support. Although further studies are still needed, data from a series of studies have suggested that

there may be an inverse correlation between Treg activity and clinical manifestations of allergic diseases.² CD4⁺CD25⁺ T cells from individuals allergic to grass pollen were less able to suppress proliferation and IL-5 production by CD4⁺CD25⁻ T cells.³ To identify whether clinical disease manifestations of asthma are the cause or the consequence of decreased Treg activity, multiple lines of evidence point to a contributory role of decreased Treg activity in the pathogenesis of asthma. Limited data have supported decreased levels of FoxP3⁺ Tregs in asthmatic lungs compared with healthy lungs.⁴ In addition, adoptive transfer of antigen-specific CD4⁺CD25⁺ Tregs was found to suppress allergic inflammation and hypersensitivity. Moreover, strategies to boost endogenous Tregs have been proposed as a new focus of research for clinical application of Tregs in allergic diseases such as asthma.

As mentioned by the authors, corticosteroids are known to induce FoxP3 expression and to increase CD4⁺CD25^{bright} cells.⁵ In their study, no significant difference was seen in the number of Tregs between mild asthma and healthy control subjects. Taken together, we strongly believe that the increased levels of Tregs in this study primarily arise from the use of corticosteroids.

Another pitfall of the study is that the authors did not use CD4⁺CD25⁺FoxP3⁺ to characterize Tregs, which is a well-established and acknowledged way to differentiate Tregs. Although other subgroups of T cells, including IL-10-secreting T cells, IL-10-secreting natural killer cells, CD8⁺ Tregs, and IL-17-producing $\gamma\delta$ T and natural killer cells, also have been shown to have regulatory activities, either CD4⁺FoxP3⁺, CD4⁺CD25⁺CD127⁻, or CD4⁺CD25^{bright} could not replace CD4⁺CD25⁺FoxP3⁺ in identifying natural Tregs.

In summary, it is promising to figure out the role of Tregs in the pathogenesis of asthma. Although more studies are needed, Tregs may provide new possibilities for monitoring disease process and developing novel therapeutic strategies for asthma.

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Response

To the Editor:

We thank Yang and colleagues for their interest in our recent article in *CHEST* (October 2010).¹ We found that the number of T regulatory cells (Tregs) was increased in the BAL of patients with moderate to severe asthma. We found evidence of an association, albeit weak ($R^2 = 0.16$, $P = .01$), between Treg numbers and FEV₁, but no association between corticosteroid dose and FEV₁. These associations favor the possibility that disease severity has influenced Treg numbers, although our analysis by associations cannot provide a definitive answer as to whether disease severity and/or corticosteroid use are driving the increase in Treg numbers. The concern of Yang et al that our results could be due to corticosteroid use are already discussed extensively in our article.

Yang states that "...there may be an inverse correlation between Treg activity and clinical manifestations of allergic disease." We could not agree more! Our discussion clearly states that we have studied the numbers of Tregs, but this may not be indicative of functional suppressive ability. It is probable that the Tregs in the lungs of patients with moderate to severe asthma contain a subpopulation of inducible Tregs. These may have a different functional capacity compared with naturally occurring Tregs, and this is clearly an area for further study. The effects of cytokines within the local microenvironment can influence both the induction of Tregs and their functional capacity.²⁻⁴ Functional studies using Tregs from the lungs of patients with asthma are technically difficult to perform but will provide clarification of this issue.

Yang et al raise concerns about our method of quantifying Treg numbers. We used three well-cited methods: CD4⁺FoxP3⁺, CD4⁺CD25^{bright} and CD4⁺CD25⁺CD127⁻. There is no consensus regarding the best method of measuring Treg numbers, so we took a comprehensive approach. Although Yang et al favor CD4⁺CD25⁺FOXP3 for quantifying Tregs, it should be noted that many scientists agree that CD4⁺FoxP3⁺ expression is of key importance, as we described previously. We have plotted the

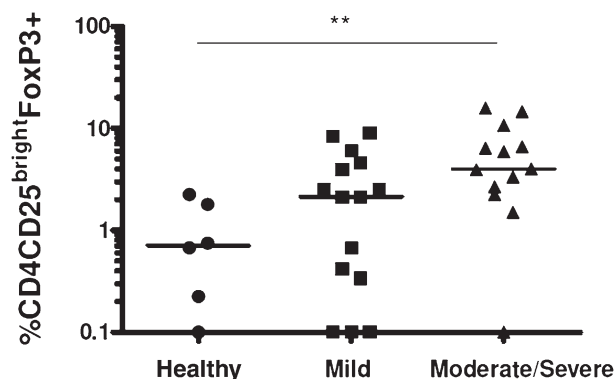


FIGURE 1. %CD4⁺CD25^{bright}FoxP3⁺ cells present in healthy patients (n = 6), patients with mild asthma (n = 15), and patients with moderate to severe asthma (n = 13) BAL. ** $P < .01$; horizontal line represents group median.

data using CD4⁺CD25⁺FOXP3 (Fig 1), which gives a similar pattern to the analysis using CD4⁺FOXP3 (healthy vs moderate/severe, $P = .003$). Either approach appears valid for identifying Tregs in the airways.

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Noninvasive Ventilation as a Weaning Tool

To the Editor:

We read with great interest the article recently published in *CHEST* by Ortiz et al (June 2010)¹ about the use of synchronized intermittent mandatory ventilation with pressure support (SIMV-PS) compared with assist-control (A/C) ventilation as the primary mode of ventilatory support using the data of an international prospective cohort study of mechanical ventilation. The authors have analyzed the SIMV-PS and A/C modes as weaning modes. Although this is a statistical study, not a clinical study, the absence of any commentary about noninvasive ventilation

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