

Correspondence

Reply

To the Editor:

We are writing in reply to the comments of Baumgrass et al¹ regarding our publication in the October 2009 issue of the *Journal* in which we describe decreasing percentages of regulatory T cells during cyclosporin A (CsA) treatment.² In a recent report they have shown that low-dose (2 mg/kg/d) CsA treatment increased the percentage of regulatory T cells.³ However, in contrast to a publication by Ou et al,⁴ our article,² and a recent article by Ito et al,⁵ Baumgrass et al found similar percentages of regulatory T cells in patients with atopic dermatitis (AD) and healthy control subjects. Interestingly, in subsequent experiments they now show that in 2 patients with AD treated with a higher dose of CsA (3-5 mg/kg/d), T cells have decreased IL-2-producing capacities. Although they did not include forkhead box protein 3 (FOXP3) analysis in their additional dataset, this might suggest that there is a differential effect of high versus low CsA dosage on the regulatory T cell population.

However, in our patients, when we decreased the dose of CsA (from 5 to 3 mg/kg/d after 6 weeks of treatment) we found no changes in the percentages of FOXP3⁺ regulatory T cells (manuscript in preparation). In addition, we also found decreasing percentages of FOXP3⁺ regulatory T cells during treatment with enteric coated mycophenolate sodium. The latter immunosuppressive drug has effects on a different pathway from CsA but also results in significant clinical improvement.

Furthermore, Ito et al⁵ have recently shown that the percentage of FOXP3⁺ regulatory T cells in the blood of patients with AD also correlates to disease severity in patients not using systemic immunosuppressive drugs. In addition, Mantel et al⁶ have shown that CsA directly inhibits FOXP3 expression *in vitro*.

In conclusion, the question remains unanswered by which mechanism CsA treatment decreases the percentage of FOXP3⁺ regulatory T cells, and further investigation is needed to unravel the mechanism causing the apparently differential effects of low- versus high-dose CsA treatment.

DirkJan Hijnen, MD, PhD
Carla Bruijnzeel-Koomen, MD, PhD
Edward Knol, PhD

From the Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands. E-mail: dirkjanhijnen@gmail.com.

Disclosure of potential conflict of interest: The authors have declared that they have no conflict of interest.

REFERENCES

1. Baumgrass R, Brandt C, Wegner F, Abdollahnia M, Worm M. Low-dose, but not high-dose, cyclosporine A promotes regulatory T-cell induction, expansion, or both. *J Allergy Clin Immunol* 2010;■■■■■■■■.
2. Hijnen D, Haeck I, van Kraats AA, Nijhuis E, de Bruin-Weller MS, Bruijnzeel-Koomen CAFM, et al. Cyclosporin A reduces CD4⁺CD25⁺ regulatory T-cell numbers in patients with atopic dermatitis. *J Allergy Clin Immunol* 2009;124:856-8.
3. Brandt C, Pavlovic V, Radbruch A, Worm M, Baumgrass R. Low-dose cyclosporine A therapy increases the regulatory T cell population in patients with atopic dermatitis. *Allergy* 2009;64:1588-96.
4. Ou LS, Goleva E, Hall C, Leung DY. T regulatory cells in atopic dermatitis and subversion of their activity by superantigens. *J Allergy Clin Immunol* 2004;113:756-63.
5. Ito Y, Adachi Y, Makino T, Higashiyama H, Fuchizawa T, Shimizu T, et al. Expansion of FOXP3-positive CD4⁺CD25⁺ T cells associated with disease activity in atopic dermatitis. *Ann Allergy Asthma Immunol* 2009;103:160-5.
6. Mantel PY, Ouaked N, Ruckert B, Karagiannidis C, Welz R, Blaser K, et al. Molecular mechanisms underlying FOXP3 induction in human T cells. *J Immunol* 2006;176:3593-602.

doi:10.1016/j.jaci.2010.04.034