

Letter by Popa and Netea Regarding Article, “Angiotensin-Converting Enzyme Inhibition Improves Vascular Function in Rheumatoid Arthritis”

To the Editor:

We read with great interest the article by Flammer et al,¹ in which the authors investigated the effects of ramipril on endothelial function during rheumatoid arthritis. They concluded that ramipril is able to significantly improve endothelial function as early as 8 weeks after daily therapy has been initiated. Therefore, their findings may have a significant impact on our attempts to diminish the increased cardiovascular risk of these patients and to improve their lifespan.

However, several important aspects should be considered in the interpretation of these results. First, the concentrations of tumor necrosis factor (TNF) detected by the authors are very low but are in the range of the minimum detectable dose of TNF stated by the manufacturer.² This may cause an important bias and therefore call into question the relation described by the authors between flow-mediated dilation and circulating levels of this cytokine. Second, 3 of the 11 patients included received anti-TNF agents. We have previously indicated that ELISA is unable to give a reliable TNF plasma concentration in this particular situation because it cannot distinguish between free and anti-TNF-bound TNF.³ Third, therapeutic TNF neutralization on its own also is able to improve endothelial function,⁴ adding to the complexity of the authors' findings. We therefore wonder if the authors' conclusions would be the same if these patients were excluded from the study analysis.

We believe that the authors' findings are biased by several methodological issues that cast a shadow on the impact of their conclusions. However, we also believe that further exploration of angiotensin-converting enzyme inhibitory strategies in rheumatoid

arthritis is of extreme importance to lessen the increased burden of cardiovascular disease characterizing these patients.

Disclosures

None.

Calin Popa, MD

*Department of Rheumatology
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands*

Mihai G. Netea, MD, PhD

*Department of General Internal Medicine
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands*

References

1. Flammer AJ, Sudano I, Hermann F, Gay S, Forster A, Neidhart M, Künzler P, Enseleit F, Périat D, Hermann M, Nussberger J, Lucher TF, Corti R, Noll G, Ruschitzka F. Angiotensin-converting enzyme inhibition improves vascular function in rheumatoid arthritis. *Circulation*. 2008; 117:2262–2269.
2. Quantikine [package insert]. Minneapolis, Minn: R&D Systems, Inc; 2008.
3. Popa C, Netea MG, Barrera P, Radstake TR, van Riel PL, Kullberg BJ, van der Meer JW. Cytokine production of stimulated whole blood cultures in rheumatoid arthritis patients receiving short-term infliximab therapy. *Cytokine*. 2005;30:72–77.
4. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, Garcia-Porrúa C, Llorca J, Gonzalez-Gay MA. Active but transient improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti-tumor necrosis factor alpha antibody. *Arthritis Rheum*. 2004;51:447–450.