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# Correspondence

## Is Anti-Tumor Necrosis Factor Therapy Associated with Increased Mortality in Patients with Severe Sepsis Caused by Pneumonia?

**To the Editor**—We read with great interest the article by Rijneveld et al. [1] suggesting that anti-tumor necrosis factor (TNF) therapy may impair the therapeutic efficacy of betalactam antibiotics during pneumococcal pneumonia. Moreover, in the Discussion, Rijneveld et al. raised the question of whether patients with severe sepsis caused by bacterial pneumonia who are enrolled in clinical trials investigating anti-TNF agents experience increased mortality because of the anti-TNF treatment.

To test this hypothesis, we conducted a retrospective cohort study including 1342 patients with severe sepsis and early septic shock who were enrolled in a double-blind, placebo-controlled phase III trial to determine the safety and efficacy of p55 IgG TNF-receptor fusion protein (lenercept) [2]. Mortality was analyzed by multivariate Cox proportional-hazards regression. Results of standard tests showed no disagreement with the proportional-hazards assumption.

A total of 365 patients (27%) had bacterial pneumonia causing severe sepsis or septic shock. There were 57 deaths (32%) among the 179 patients receiving lenercept, compared with 63 deaths (34%) among the 186 patients receiving placebo (crude hazard ratio [HR], 0.9; 95% confidence interval [CI], 0.6–1.3). The risk of death remained unchanged after adjustments for differences in the appropriateness of the initial antibiotic treatment, in the number of baseline organ dysfunctions, and in the severity of illness.

We also observed 92 patients with pneumococcal pneumonia who received beta-

lactam antibiotics as their initial antimicrobial treatment. In agreement with the findings cited above, exposure to lenercept was not found to be associated with a significantly increased risk of death (adjusted HR, 0.7; 95% CI, 0.3–1.6), after patients were stratified by receipt of either lenercept ( $n = 42$ ) or placebo ( $n = 50$ ) and after adjustments for potential confounders. In a separate conditional regression analysis, which grouped patients either by center or country (to avoid confounding by possible cluster effects), we confirmed the absence of an association between anti-TNF treatment and increased risk of death in patients with sepsis caused by pneumonia.

These data suggest that the reported association between anti-TNF treatment and adverse outcomes in murine pneumococcal pneumonia may not be observed in patients with severe sepsis caused by bacterial pneumonia. Several reasons may explain the discrepancy between our findings and the results reported by Rijneveld et al. [1]. First, the size of our sample of patients with sepsis caused by pneumococcal pneumonia may have been too small to show a deleterious effect of anti-TNF treatment. However, the 95% CI of our estimate indicates that, if such an effect exists, its magnitude and clinical importance would be rather small. Second, the relatively low dosage and weak pharmacologic effect of the anti-TNF agent in our study may have prevented adverse effects. Higher doses of similar anti-TNF agents have been shown to induce adverse outcomes and to be associated with increased mortality [3]. Finally, the timing of the administration of anti-TNF and antibiotics in Rijneveld et al.'s animal experiment may have been different from the treatment schedule in our clinical trial. Although Rijneveld et al. addressed this lim-

itation, in a real-life clinical situation the administration of anti-TNF agents may occur much later in the course of the anti-inflammatory response, compared with the animal experiment.

Overall, we believe that the study conducted by Rijneveld et al. is valuable in that it shows the potential hazards of blocking local TNF production in mice with pneumococcal pneumonia. However, caution should be applied when these findings are generalized and compared with the results of previously published clinical trials performed in humans.

**Stephan Harbarth,<sup>1</sup> Jorge Garbino,<sup>1</sup> Didier Pittet,<sup>1</sup> and Jérôme Pugin<sup>2</sup>**

Divisions of <sup>1</sup>Infectious Diseases and <sup>2</sup>Medical Intensive Care, University of Geneva Hospitals, Geneva, Switzerland

## References

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Reprints or correspondence: Dr. Stephan Harbarth, Infection Control Program, University of Geneva Hospitals, 1211 Geneva 14, Switzerland ([harbarth@post.harvard.edu](mailto:harbarth@post.harvard.edu)).

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