

## Blockade of Interleukin 6 Signaling Induces Marked Neutropenia in Patients with Rheumatoid Arthritis

To the Editor:

Therapies aimed at inhibiting interleukin 6 (IL-6), a pleiotropic cytokine implicated in the immune response, inflammation, hematopoiesis, and bone metabolism, are effective for rheumatoid arthritis (RA)<sup>1,2</sup>. We have found that a humanized anti-IL-6 receptor antibody (tocilizumab; Chugai, Japan) induced prompt and potent suppression of neutrophil recruitment into peripheral blood in patients with RA.

One day after tocilizumab (8 mg/kg) was first administered to patients with active RA, the number of neutrophils in peripheral blood decreased significantly (Figure 1). This suppression partially and completely recovered 1 week and 4 weeks, respectively after the treatment. However, the number of lymphocytes, monocytes, basophils, and eosinophils did not decrease significantly with tocilizumab treatment in these patients (data not shown). Interestingly, infliximab (Centocor, Malvern, PA, USA), a monoclonal antibody against tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), did not induce neutropenia (Figure 1), suggesting that this phenomenon was not due to the immunoglobulin itself but to the biological effects of IL-6. There were no differences in the clinical backgrounds [age, C-reactive protein (CRP) values] of the patients treated with tocilizumab and infliximab. Patients' ages were 59.9 years (tocilizumab group) and 58.3 years (infliximab group) on average (no significant difference). CRP values before treatment (Day 0)

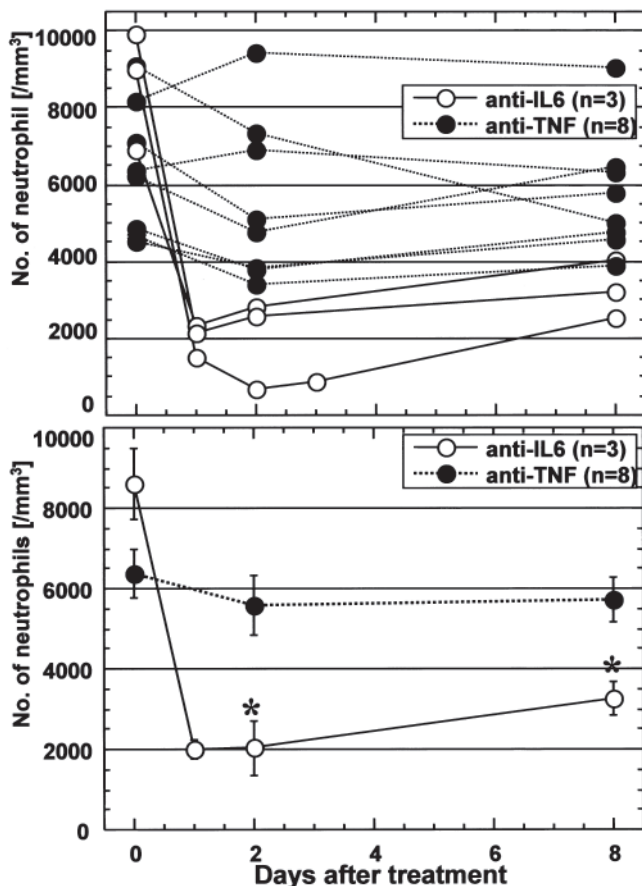


Figure 1. Time course of the number of neutrophils in peripheral blood in patients with RA treated with tocilizumab. Tocilizumab (n = 3) but not infliximab (n = 8) induced marked neutropenia, 1 day after treatment. Data in the lower panel are means  $\pm$  SE. \* $p < 0.05$  compared with infliximab-treated patients (t test). There was no significant difference in the neutrophil number at Day 0 between the tocilizumab and infliximab groups.

were  $5.23 \pm 1.38$  mg/dl (average  $\pm$  standard error) in the tocilizumab group and  $6.08 \pm 0.75$  mg/dl in the infliximab group (also nonsignificant).

In mice, several lines of evidence have shown the involvement of IL-6 in neutrophil recruitment in acute inflammatory diseases such as pneumonia<sup>3,4</sup>. Another possibility is that IL-6 is involved in neutrophil apoptosis, although further studies are needed to clarify the mechanism of IL-6-induced severe neutropenia<sup>5</sup>.

We have observed, for the first time in humans, the potent biological effect of IL-6 on the recruitment of neutrophils into peripheral blood, even in chronic inflammatory diseases such as RA. To date, the patients treated with tocilizumab have shown no side effects related to severe neutropenia. However, we call attention to the immunosuppressed condition of patients during therapy with an anti-IL-6 agent.

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