Our group has demonstrated that Th17 cells are greatly increased in RA synovial fluid compared to RA and normal peripheral blood (4). Others have shown that the levels of IL-17 and the percentage of Th17 cells in peripheral blood correlate with the 28-joint Disease Activity Score (5) at the onset and during the progression of RA (6). Further, RA patients who receive disease-modifying antirheumatic drugs (DMARDs) plus neutralizing antibody against IL-17 achieve a response according to the American College of Rheumatology 20% improvement criteria (7) more rapidly than do those receiving DMARDs alone (8). As in RA, post-onset treatment with neutralizing antibody to IL-17 reduces the severity of CIA (9). This evidence suggests that IL-17 has important clinical implications in RA as well as in CIA.

It has been shown that IL-27 is present in RA synovial fluid and synovial tissue (1,4). However, for IL-27 to effectively suppress Th17 cell differentiation, high levels of this factor are required in the early phase of RA, prior to IL-17 secretion from mature Th17 cells. Consistently, in studies of CIA and AIA (1,2), post-onset treatment with IL-27 did not affect disease progression due to its inability to reduce differentiated Th17 cell numbers. Therefore, use of IL-27 as a therapeutic agent in RA may be limited to patients whose disease is in an early stage and may not be useful in patients with established disease.

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A possible role of leptin-associated increase in soluble interleukin-2 receptor diminishing a clinical response to infliximab in rheumatoid arthritis: comment on the article by Klaasen et al

To the Editor:

We read with great interest the article by Klaasen et al (1), who reported that rheumatoid arthritis (RA) patients who have a high body mass index (BMI) exhibited a diminished clinical response to infliximab treatment, and that adipose tissue could play a role in the pathophysiology of RA. However, they did not suggest possible mechanisms.

We speculate that soluble interleukin-2 receptor (sIL-2R), a marker of T lymphocyte activation, might influence the clinical response to infliximab in RA patients. Although it has not yet been extensively studied, Kuuliala et al recently demonstrated that low baseline sIL-2R levels may be predictive of a rapid clinical response in patients with conventional treatment–refractory RA being treated with infliximab (2). Also, it has been reported that human leptin enhanced the proliferation and activation of circulating T lymphocytes in a dose-dependent manner, by stimulating the synthesis of IL-2 (3). Because leptin concentrations are positively correlated with the BMI (4), it is possible that obese RA patients have increased leptin levels, which could activate circulating T lymphocytes (increased IL-2 and sIL-2R), thus resulting in a diminished clinical response to infliximab.

Furthermore, we wonder about the percentage of smokers in each BMI group in the study by Klaasen et al (1), because smoking can increase sIL-2R levels (5), which might affect the clinical response to infliximab (6) and act as a confounding factor. Recently, Abhishek et al demonstrated that anti–tumor necrosis factor α (anti-TNFα) agents were less effective in the treatment of RA in current smokers (6), and we speculate that this might also be due to levels of sIL-2R that were increased because of smoking (5).

It has been shown that anti-TNFα therapy does not modulate leptin in patients with severe RA (7). We thus speculate that the IL-2–sIL-2R system might not be influenced by infliximab itself, but instead by serum leptin levels associated with BMI.

Therefore, it would be of interest to measure serum leptin and sIL-2R levels and ascertain smoking status in addition to BMI when evaluating the clinical response to infliximab. Further studies are needed to investigate our speculations on the possible role of leptin as well as the potential effect of racial differences, as white patients have previously been shown to have significantly higher sIL-2R levels than black patients (mean 455 units/ml versus 365 units/ml; $P < 0.001$) (5).

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Reply

To the Editor:

We would like to thank Dr. Shin and colleagues for their interest in our work. Based on circumstantial evidence, they suggest that activation of T cells in response to leptin might result in diminished clinical improvement in obese patients treated with infliximab. It should be noted that leptin may also stimulate monocytes (1), and together, these may promote a proinflammatory state (2). We previously found that increased inflammation in RA synovial tissue is predictive of a better response to infliximab treatment (3–5). Based on these findings, we would not predict that a state of increased inflammation is related to a decreased clinical response, but we cannot exclude the possibility that results may be different in peripheral blood compared to the synovium. We can only resolve this interesting issue in future studies by directly examining the relationship of obesity, leptin, and sIL-2R with the clinical response to infliximab treatment.

Smoking can increase sIL-2R levels and has been associated with a diminished clinical response to anti-TNFα therapy, which led Dr. Shin and colleagues to question whether smoking was a possible confounder in our study. The percentages in each BMI group of patients who smoked were 26% in responders (Disease Activity Score in 28 joints [DAS28] $\geq$1.2) and 31% in nonresponders (DAS28 $<$1.2). When smoking status at baseline was included in the statistical analysis, no influence on our results was found.

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