Dr. Nagashima and Dr. Minota reply

To the Editor:

We thank Dr. Lewicki, *et al* for their report supporting our finding that blood adiponectin levels increase after administration of anti-tumor necrosis factor (TNF) agents to patients with rheumatoid arthritis (RA). As we discussed in our earlier article, there are conflicting reports about whether adiponectin increases or not after administration of anti-TNF agents to patients with RA. We previously considered that the differing results may have been due to racial factors, because other studies that supported our results were performed in Japanese patients with RA[1,2]. However, similar results have also been obtained in studies performed in Europe[3,4], so we are now confident that anti-TNF therapy increases serum adiponectin levels in all races. We agree with Lewicki, *et al* that the conflicting results are due to differences in the extent of TNF-α suppression at the time of blood collection, as we also speculated earlier.

In vitro studies have shown both pro- and antiinflammatory effects of adiponectin on synovial fibroblasts. However, in clinical practice, we have never experienced exacerbation of RA after anti-TNF therapy in spite of the increase of serum adiponectin levels. Although adiponectin is partly proinflammatory *in vitro*, its net effect may be antiinflammatory *in vivo*, i.e., the complex cytokine network in inflamed joints[5]. We consider that adiponectin has little role in the pathogenesis of RA and is just a "bystander" in the joints. As far as we know, there are no reports that either adiponectin knockout mice or adiponectin-overexpressing mice develop arthritis.

The remaining problem is why baseline levels of adiponectin are higher in patients with RA than in healthy controls. Most studies apart from ours have found high serum levels of adiponectin in patients with RA[4,6,7]. Serum levels of adiponectin would be expected to be lower in patients with RA than in the general population, because of their higher circulating levels of cytokines and C-reactive protein, as well as their higher rate of cardiovascular events. Thus, the high levels in patients with RA apparently contradict a large body of previous evidence. We cannot explain this by a simple interaction between TNF and adiponectin, as Lewicki, *et al* suggest. Elevation of adiponectin as a compensatory mechanism under catabolic/anabolic imbalance is a more plausible explanation[7], but we have no clear answer yet.

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