□ LETTERS TO THE EDITOR □

Interleukin-18 in Adult-onset Still's Disease: Treatment Target or Disease Activity Indicator?

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The Authors Reply We appreciate the comments by Nagashima et al. In their case of adult-onset Still's disease (AOSD), the serum level of IL-18 decreased from 220,000 pg/mL to 7,000 pg/mL in 4 months as the result of treatment with tocilizumab (TCZ). They stopped the administration of TCZ after 18 treatments. The level of IL-18 had dropped to 384 pg/mL before the cessation of TCZ.

In our case, however, the level of serum IL-18 did not drop, even though all his symptoms had disappeared and the other laboratory data normalized soon after the beginning of TCZ. This is exactly the point which took us by surprise. It made us suspect that a state of macrophage activation might have persisted in the patient. We recently encountered a second patient having AOSD treated with TCZ. TNF blockers such as etanercept and adalimumab were not sufficiently effective in the second case, too. Her high spiking fever disappeared soon after treatment with TCZ, and the levels of both CRP and ferritin came down to the reference range within 2 weeks. In this case, however, the IL-18 level dropped significantly, i.e. from over 5,000 pg/mL to 348 pg/mL in 6 months. Thus, this case is similar to that of Nagashima et al. As the final levels of IL-18 were also similar (384 pg/mL vs. 348 pg/mL), we may be able to stop treating her with TCZ. The fact that their patient remained drug-free for more

than 2 years is really encouraging. As for the case of the first patient, the final level of IL-18 was 4,400 pg/mL, which is still high. We will monitor IL-18 level again in an effort to determine the proper timing of TCZ cessation.

It has become clear that TCZ is a very effective drug against AOSD and, in our opinion, it may ultimately prove to be more effective than TNF blockers. In order to clarify whether IL-18 is an indicator of AOSD activity or in fact it is a therapeutic target, we have to wait for the development of IL-18 blockers. On the other hand, IL-1 blockers have also been reported to be effective in AOSD treatment. IL-1 and IL-18 are both inflammatory cytokines released from macrophages. We are interested in the relationship among IL-1, IL-6 and IL-18. Regrettably, since IL-1 blockers are not available in Japan, we cannot observe the change in the levels of IL-6 and IL-18 in AOSD patients after treatment with the drugs. It is to be hoped that the hierarchical relationship among those cytokines will be made evident in the near future.

As for the matrix metalloproteinase (MMP)-3, we do know that glucocorticoids can increase the serum level of the enzyme. But in our second case, for example, her serum MMP-3 decreased from 517.7 ng/mL to 114.5 ng/mL in 5 months, and she continued to take 5 mg of prednisolone daily during this time. Thus, we do not know if the change in the MMP-3 level should be attributed solely to the dose of glucocorticoids. We do agree, however, that ferritin and C-reactive protein are more useful markers for the activity of AOSD than MMP-3.

The authors state that they have no Conflict of Interest (COI).

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