Tocilizumab Ameliorates Clinical Symptoms in Polymyalgia Rheumatica

To the Editor:

Polymyalgia rheumatica (PMR) is a chronic inflammatory disorder of unknown etiology that affects the elderly[1]. The disease is characterized by aching and morning stiffness in the shoulders, neck, and pelvic girdles. Although the pathogenesis of PMR remains unknown, overproduction of proinflammatory cytokines has been demonstrated to contribute to its development[1,2]. Corticosteroids constitute the preferred treatment for PMR and prednisolone 10–20 mg/day is usually adequate. But when prednisolone is tapered, the disease sometimes flares and continuous treatment with corticosteroids is needed. As alternative therapies, methotrexate and tumor necrosis factor (TNF)-blocking agents showed promise, but the use of these drugs remains controversial[1,3]. Since interleukin 6 (IL-6) has been shown to play a major role in sustaining disease activity in PMR[1,2,4-6], treatment of a patient with PMR refractory to corticosteroids was initiated with the humanized anti-IL-6 receptor antibody tocilizumab[7].

A 65-year-old woman presented in 2002 with morning stiffness, aching of the shoulders, myalgia in the upper limbs, and difficulty with elevating the upper limbs. Although C-reactive protein (CRP) was highly elevated, creatine phosphokinase was within normal range, and antinuclear, antineutrophil cytoplasmic, and anti-Jo1 antibodies and rheumatoid factor were all negative. She had been diagnosed with PMR at another hospital, where treatment with prednisolone 20 mg/day had resulted in prompt disappearance of clinical symptoms. But when prednisolone was tapered to 8–10 mg/day, the disease flared repeatedly (Figure 1) and was made worse by diabetes mellitus, hypertension, and osteoporosis. She was referred to our hospital in 2006. Informed consent by the patient and approval by the Ethics Committee of Osaka University Hospital were obtained for the injection of tocilizumab 8 mg/kg every 4 weeks starting in October 2008, in combination with oral prednisolone 10 mg/day. Prior to the treatment, she felt morning stiffness for 3 hours and pain in shoulders, pelvic girdle, and knee joints. Edema in the lower limbs was also observed. Serum levels of CRP and serum amyloid A (SAA) were elevated to 0.62 mg/dl (normal < 0.2 mg/dl) and 86 μg/ml (normal < 8 μg/ml), respectively. Serum IL-6 level was 4.7 pg/ml. Her PMR activity score (PMR-AS), which consists of CRP value, visual analog scale (0–10) of patient's pain and physician's assessment of disease activity, duration of morning stiffness, and ability to elevate the upper limbs[8], was 22.12, indicating high disease activity. After 1 injection of tocilizumab, serum CRP and SAA levels became normal and pain in the shoulders and pelvic girdle improved, but morning stiffness persisted. After 5 infusions of tocilizumab, morning stiffness disappeared and the PMR-AS decreased to 0.74, indicating remission according to the PMR-AS criteria[9]. Continued tocilizumab treatment ended clinical symptoms, so that prednisolone could be reduced to 6 mg/day (Figure 1).

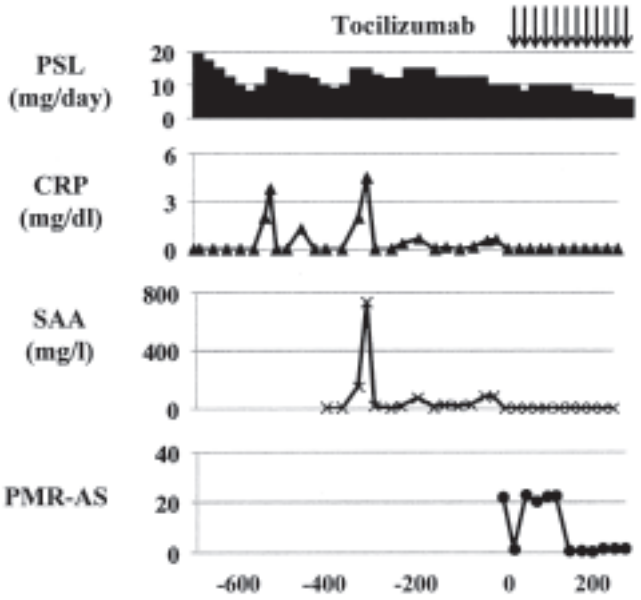

Figure 1. Clinical course of PMR. Administration of tocilizumab was started on Day 0. Changes in prednisolone (PSL) dose, serum levels of C-reactive protein (CRP), serum amyloid A (SAA), and the PMR activity score (PMR-AS) are indicated.

To our knowledge, this is the first study to demonstrate the ameliorative effect of tocilizumab on symptoms caused by PMR. Increased serum concentrations of proinflammatory cytokines, including IL-1ß, TNF-α, and IL-6, in patients with PMR have been reported, but no elevation of IL-1ß or TNF-α was found in other reports[1,2]. Only IL-6 has been observed to be consistently high in patients with active disease[4-6]. IL-6 is recognized as the most sensitive indicator of disease activity and course and therefore IL-6 inhibition with tocilizumab may constitute a novel strategy for treatment of PMR. As for this case, computed tomography angiography showed that there was no simultaneous occurrence of giant cell arteritis (GCA) at the onset or during followup.

In the literature, the clinical relationship between PMR and GCA has been established, since 16%–21% of patients with PMR also had GCA, and PMR was reportedly present in 40%–60% of patients with GCA[1]. Several studies of cytokines in temporal artery biopsy sections of patients with GCA also revealed overexpression of IL-6 messenger RNA and protein[2], indicating that IL-6 may play a role in the development of GCA as well as PMR. Although there have been no reports regarding treatment of GCA with tocilizumab, Nishimoto, *et al* found that treatment of a patient with Takayasu arteritis with tocilizumab improved the clinical manifestations and abnormal laboratory findings[10]. It is thus anticipated that tocilizumab may become a treatment option for GCA.

Although clinical studies are essential, for cases of PMR refractory to corticosteroids, treatment with tocilizumab can be considered a viable alternative.

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Dr. T. Kishimoto holds a patent for tocilizumab.

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