single time-point data [1, 3, 4], but in addition they suggest that there is not a straightforward relationship between synovial fluid and plasma IL-6. A variation was reported in blood IL-6 from normal volunteers with sleep deprivation, but our blood variation is four times greater than the maximum seen in these normal volunteers [5]. Although this is a small pilot study with large confidence intervals and one volunteer was taking a low dose of glucocorticoid, the results suggest that plasma IL-6 falls substantially during the day while synovial fluid levels remain relatively unchanged. This challenges the notion that plasma IL-6 is merely a reflection of synovial IL-6 production. The true relationship between synovial fluid and plasma levels needs further investigation, in particular in relation to night-time variation. Such studies should be possible using a synovial catheter.

**Key messages**

- Sequential sampling suggests plasma and synovial IL-6 may vary independently.

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**A CCR-5 antagonist inhibits the development of adjuvant arthritis in rats**

Sir, Chemokine receptor CCR5 is preferentially expressed on Th1 lymphocytes and has been reported to have important roles in the pathogenesis of rheumatoid arthritis (RA). Yang et al. [1] demonstrated that a CCR5 antagonist inhibits the development of arthritis in the collagen-induced arthritis (CIA) model in mice. They showed that the inhibition of the development of arthritis is not caused by affecting the generation of collagen-sensitized T cells but by interfering with their migration to joint lesions. Recently, Vierboom et al. [2] reported the interesting finding that a CCR5 antagonist inhibited the development of CIA in rhesus monkeys. They showed that systemic administration of a small molecular weight antagonist of CCR5, SCH-X, suppressed the development of CIA in a monkey model of rheumatoid arthritis (RA).

Rheumatoid arthritis is a chronic, destructive, inflammatory, polyarticular joint disease, characterized by massive synovial proliferation and subintimal infiltration of inflammatory cells, followed by the destruction of cartilage and bone. In the pathogenesis of RA, inflammatory cytokines such as IL-6 and TNF-α play important roles and this chronic inflammation results in cellular damage of affected joints [3, 4]. Chemokines are involved in the process of leucocyte transmigration into sites of inflammation. CCR5 and CXCR3 are expressed on Th1 cells, and CCR4 and CCR3 on Th2 cells [5, 6]. Evidence shows that RA is a Th1-dominant disorder and that CCR5- and/or CXCR3-expressing cells are enriched in affected joints of RA patients [7, 8]. We now provide evidence showing that systemic administration of TAK-779, a non-peptide compound with a small molecular weight, inhibits the development of adjuvant-induced arthritis (AIA) in rats.

Seven-week-old female Lewis rats were obtained from Charles River Japan (Yokohama, Japan). Complete Freund’s adjuvant (CFA) was prepared by suspending heat-killed Mycobacterium butyricum (Difco Laboratories, Detroit, MI, USA) in liquid paraffin at 10 mg/ml. CFA-induced arthritis was stimulated by injection of 100 μl of the CFA emulsion intradermally at the base of the left paw. TAK-779 was obtained from Takeda (Osaka, Japan). Treatment commenced at the onset of the disease;
TAK-779 (once a day) and phosphate-buffered saline (PBS) as a control (once a day) were administered intravenously at the specified doses until 7 days after the onset of arthritis. Each group comprised 10 female Lewis rats. TAK-779 was freshly suspended in 1.0% methyl cellulose (MC) PBS. In each experiment, a group of rats was administered 1.0% MC PBS orally, which served as a control. At days 1, 7 (onset of arthritis), 8, 11 and 14 after immunization, rats were examined for AIA using two clinical parameters: paw swelling and clinical score. The footpad volume was measured with a plethysmometer (TK-101; Unicom Japan, Tokyo, Japan). For clinical evaluation of AIA, we used the following scoring system: ear, forelimb, non-treated hind-limb, and tail were scored 0–5: 0 = normal; 1 = minimal swelling; 2 = mild swelling; 3 = moderate swelling; 4 = severe swelling.

Fig. 1. Suppression of arthritis development by TAK-779 in an adjuvant-induced arthritis model. (A) TAK-779 suppressed the progression of clinical arthritis compared with control rats treated with PBS, as demonstrated by paw volume and arthritis score. The data are mean ± s.d. *P < 0.05; **P < 0.01. (B) Histological findings of the foot joint in a normal rat, a TAK-779-treated rat (1 mg/kg/day), a TAK-779-treated rat (2 mg/kg/day) and a control rat (PBS).
5 = severe and non-weight-bearing arthritis. Each limb was graded, resulting in a maximum clinical score of 20 per animal, as described previously [10]. For histological evaluation, we performed haematoxylin and eosin staining of tissue specimens of the ankle. Ethical approval was not required for this study as it was an entrusted work by Nihon Bioresearch. The Mann–Whitney U-test was used to compare non-parametric data for statistical significance.

As shown in Fig. 1, TAK-779 suppressed the progression of clinical arthritis compared with control rats treated with PBS, as demonstrated by paw volume and arthritis score (Fig. 1A).

In TAK-779-treated rats, statistically significant effects were observed with higher doses (P < 0.01). By day 18, histological analysis of the ankle joint in rats treated with TAK-779 at 1 mg/kg/day, rats treated with TAK-779 at 2 mg/kg/day and control rats (PBS) show that TAK-779 inhibited mononuclear cell infiltration and pannus formation in synovial tissue (Fig. 1B). Histology of a normal rat joint at this age is also shown in Fig. 1B. There was no mortality and no body weight loss in TAK-779-treated rats. These data suggest that TAK-779 has anti-arthritis effects in vivo.

These results further support the evidence shown by others that CCR5 plays an important role in the development of arthritis in animal models of human RA. Taken together, the results show that therapy with CCR5 antagonists may serve as a new strategy for the treatment of RA.

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IP-10/MCP-1 ratio in CSF is a useful diagnostic marker of neuropsychiatric lupus patients

Sir, Neuropsychiatric syndromes of systemic lupus erythematosus (NPSLE) is one of the major causes of morbidity and mortality in patients with systemic lupus erythematosus (SLE). NPSLE has been reported to occur in 14–75% of SLE patients and symptoms are extremely diverse, including seizures, stroke, depression and psychosis [1, 2]. Due to the multiple pathogenic mechanisms that evoke the diverse clinical manifestations of NPSLE, no single test is available for diagnosing this disease. Some reports have shown cytokines such as interleukin-6 (IL-6), IL-8 and IFN-α to be elevated in cerebrospinal fluid (CSF) from patients with NPSLE [3, 4]. Interferon-inducible protein 10 (IP-10)/CXCL10 and monocyte chemotactic protein 1 (MCP-1)/CCL2 are high-affinity ligands for the chemokine receptors CXCR3 and CCR2, respectively. To find a useful diagnostic marker of NPSLE, we measured the concentrations of IP-10/CXCL10 and MCP-1/CCL2 in CSF from NPSLE and non-NPSLE patients. A total of 202 SLE patients fulfilling the criteria defined by the American College of Rheumatology was chosen for this study. The patients (183 females and 19 males, aged 16–62 yr; average 34.7 yr) were admitted to either Tokyo Women’s Medical University or Jichi Medical School from 1992 to 2002. NPSLE was diagnosed under the American College of Rheumatology criteria for neuropsychiatric lupus syndromes [2]. Patients were divided into two groups: 101 patients were SLE patients with CNS symptoms (NPSLE) and 101 patients were SLE patients without CNS symptoms (non-NPSLE).

All procedures involving patients were performed with Institutional Review Board approval and informed patient consent was obtained for this study. CSF was collected from these patients and IP-10/CXCL10 and MCP-1/CCL2 concentrations were evaluated by enzyme-linked immunoassay (ELISA) using the Quantikine human IP-10 immunosorbent assay and Quantikine human MCP-1 immunoassay (R&D Systems, Minneapolis, MN, USA), respectively. These NPSLE patients had active NPSLE manifestations when we obtained CSF samples (the patients were treated with systemic corticosteroid alone), and we did not include samples obtained after extensive treatment, such as corticosteroid pulse and/or cyclophosphamide pulse treatment. The average concentration of MCP-1/CCL2 was 1757.68 ± 3135.09 pg/ml in NPSLE patients and 667.46 ± 1349.05 pg/ml in non-NPSLE patients (Fig. 1A). While the average concentration of IP-10/CXCL10 was 3748.78 ± 15543.68 pg/ml in NPSLE patients and 483.82 ± 1433.67 pg/ml in non-NPSLE patients (Fig. 1B).

Statistical analyses using the Mann–Whitney U-test revealed that the IP-10/CXCL10 and MCP-1/CCL2 concentrations in the NPSLE group were significantly higher than those in the non-NPSLE group (P = 0.000137 and P = 0.000150, respectively). Interestingly, the IP-10/MCP-1 ratio in the NPSLE group was significantly higher than that in the non-NPSLE group (P = 0.000014, Mann–Whitney U-test) (Fig. 1C). The