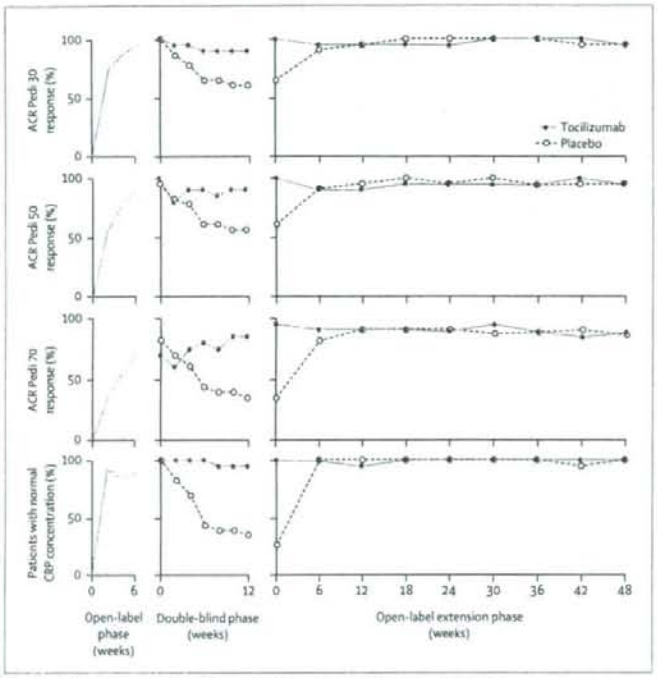

Figure 5: **Efficacy responses during the double-blind and open-label extension phases**
CRP=C-reactive protein. ACR Pedi=American College of Rheumatology Pediatric.

reaction in a patient who tested negative for IgE-type anti-tocilizumab antibodies and previously had had allergic reactions to aspirin and infliximab, and one case of gastrointestinal haemorrhage from diffuse acute or chronic colonic ulceration in a patient with a history of chronic diarrhoea and rectal bleeding.

Additionally, during the double-blind phase, two adverse events needed patients to be withdrawn from the study; one had infectious mononucleosis associated with striking increases in liver enzymes (aspartate aminotransferase 527 IU/L, alanine aminotransferase 676 IU/L, and lactate dehydrogenase [LDH] 874 IU/L) and neutropenia (963 cells per μL) 2 weeks after the fifth dose of tocilizumab. Laboratory values returned to normal 3 weeks after the onset of Epstein–Barr virus infectious mononucleosis and the patient resumed tocilizumab in the open-label extension phase. The other patient had herpes zoster during placebo administration in the double-blind phase when serum tocilizumab concentrations were below the limit of quantification. Herpes zoster was treated with aciclovir and the patient resumed tocilizumab administration in the open-label extension phase.

Most of the adverse events that arose during both the open-label lead-in and double-blind phases were mild or moderate in severity and typical of those noted with other biological agents in similar settings.[19,21] Adverse events frequently reported were symptoms of upper-respiratory-tract infections and gastroenteritis, but not of tuberculosis. In the double-blind phase, the occurrence of gastroenteritis was similar in the tocilizumab group (one [5%] of 21 patients) and placebo (one [4%] of 23 patients) groups, whereas the frequency of upper-respiratory-tract infection was increased in the placebo group (four [17%] of 23 patients) versus the tocilizumab group (two [10%] of 21 patients). Ten patients had mild infusion reactions during the open-label lead-in phase. Development of anti-tocilizumab IgE antibodies was noted in four patients.

In the open-label extension phase of the study, 13 serious adverse events were noted, which included bronchitis, gastroenteritis, and an anaphylactoid reaction (leading to patient withdrawal). The cases of bronchitis (n=2) and gastroenteritis (n=2) resolved with antibiotic treatment. The most common adverse events were nasopharyngitis (33 [59%]), upper-respiratory-tract infection (19 [34%]), gastroenteritis (16 [29%]), and bronchitis (14 [25%] of 56 patients). Increases in alanine aminotransferase (16 [29%]), aspartate aminotransferase (12 [21%]), and LDH (10 [18%]) were noted; increases of at least grade 2 in alanine aminotransferase and aspartate aminotransferase were recorded in 12 and eight patients, respectively. Transaminases tended to increase early during tocilizumab administration and then to subside during continuation of treatment. Mild increases, mostly within the normal range, in total cholesterol were noted. Tuberculosis was not reported.

Discussion

At the end of the open-label lead-in phase, the ACR Pedi 30, 50, and 70 response rates showed that tocilizumab had excellent and rapid effectiveness against systemic-onset juvenile idiopathic arthritis. After 6 weeks, the patients who did not respond—as defined in terms of both ACR Pedi 30 response and reduced CRP concentrations—were generally younger with a shorter disease duration and more severe inflammation than those who did respond to treatment. Patients who remained on tocilizumab in the double-blind phase had sustained improvements in clinical measures of effectiveness and wellbeing, whereas most of those in the placebo group needed rescue treatment.

The design of this study was chosen on the basis of counsel with the Japanese Pharmaceuticals and Medical Devices Agency because to do a standard placebo-controlled trial when there is preliminary evidence of effectiveness with a new drug would be ethically unsound.[8] The withdrawal design has the disadvantage that as patients are withdrawn for rescue treatment, the numbers of controls decrease. Therefore, the primary endpoint in the double-blind phase inevitably has to be time to early escape. However, in the open-label

extension phase the primary endpoint was the ACR Pedi 30 response rate, which was measured against baseline rather than a control population.

Active joints and systemic symptoms were not included in the inclusion criteria because refractory patients often received high-dose corticosteroids and the manifestation of joint disease and systemic features would be less obvious. To force these patients to reduce their corticosteroid dose to make their actual disease activity visible would be unethical. A necessity to start a mid to high dose of corticosteroids for a specific time and the failure to suppress inflammation as evidenced by CRP concentrations are good indicators of active disease in this patient population.

Masked assessors of joint disease were not used in this study, which might have biased the results. Since the joint assessments were done by trained paediatric rheumatologists who followed standardised methods, these assessors were thought to be unnecessary. However, interpretation of the results has some limitations.

Laboratory indicators of acute-phase reactants changed rapidly—within 2 weeks after the first infusion of tocilizumab. Median white-blood-cell, neutrophil, and platelet counts decreased in patients on active treatment, as previously described for patients with polyarticular juvenile idiopathic arthritis in response to etanercept,[4] but interleukin-6-receptor inhibition rapidly returned body temperature to normal and increased the median haemoglobin concentration. These findings accord with de Benedetti and colleagues'[18] hypotheses that interleukin 6 is causally related to the spiking fever and anaemia of systemic-onset juvenile idiopathic arthritis.

Common adverse events were gastrointestinal, nasopharyngeal, and upper-respiratory-tract infections, but they were mild. There might have been a potential absence of acute-phase reactions in response to infections because of inhibition of interleukin-6 signalling by tocilizumab. However, a mild increase in CRP concentration during infections suggested incomplete inhibition of interleukin-6 signalling or overwhelmed inflammatory responses.

Two serious adverse events—anaphylactoid reaction and gastrointestinal haemorrhage—were noted in the open-label lead-in phase. Gastrointestinal haemorrhage was presumably caused by the long-term high-dose corticosteroid treatment since the patient had previously had two similar episodes of gastrointestinal haemorrhage.

Aminotransferase concentrations tended to increase early in the tocilizumab administration, generally within the first 3–6 months and are possibly related to the pathological process unique to systemic-onset juvenile idiopathic arthritis, treatment methods such as steroid tapering, or biological effect of interleukin 6 on liver, or both.

A comparison of the time courses of ACR Pedi responses in the placebo and tocilizumab groups during the double-blind phase could not be made easily because the number of patients in the placebo group decreased rapidly because of withdrawal. Four patients in a phase II long-term study remain in remission without tocilizumab treatment or any other medications.[26] Although spontaneous disease remission can occur in these patients, the possibility exists that the interleukin-6-receptor inhibition induced long-lasting secondary changes in inflammatory and immune processes, leading to disease remission.

Effectiveness data in the extension phase were calculated against the baseline of the open-label lead-in phase because of the absence of a transition lag between the double-blind and open-label extension phases. Because the placebo periods were mostly 2–6 weeks, all patients in the double-blind phase can be discussed as one group in the extension study. The response rates at 48 weeks were almost the same between the groups.

By week 48, ESR and CRP concentrations had decreased from baseline. After completion of the initial open-label lead-in and double-blind phases, corticosteroid doses were reduced by at least 50% in most patients. Since the complications related to corticosteroid use—including growth retardation and osteoporosis—are still major problems in these children with persistent disease, the corticosteroid-sparing effect might lead to substantial benefit in the treatment of systemic-onset juvenile idiopathic arthritis.

The extension study showed that tocilizumab can be used to treat systemic-onset juvenile idiopathic arthritis and patients maintained a good response rate in terms of ACR Pedi data without flares in disease; tocilizumab had a good tolerability profile, which was much like that of other biological agents.[4]

Macrophage-activation syndrome remains the most devastating and life-threatening complication in the disease course of refractory systemic-onset juvenile idiopathic arthritis. The cause of this disorder is unknown, but the decrease has arisen after introduction of several pharmacological agents, and often follows infections.[27] Thus, macrophage-activation syndrome could develop during tocilizumab treatment.

Tocilizumab could play an important part in the treatment of systemic-onset juvenile idiopathic arthritis because interleukin 6 is directly implicated in the pathogenesis of this disease[4,9] and because tocilizumab needs less frequent administration than does anakinra. Uncontrolled studies suggest that anakinra could be effective in the treatment of both systemic symptoms and arthritis in patients with systemic-onset juvenile idiopathic arthritis, but confirmatory studies are needed. Methotrexate and anti-TNF treatments are thought to be less beneficial in this arthritis than in other subtypes of juvenile idiopathic arthritis.

Two important issues related to this class of products—namely malignant diseases and autoimmunity—were not clearly assessed because of the small sample size and the short follow-up. Longer

follow-up with a larger patient population than that in this study is needed to address these issues.

Thus, the results of this placebo-controlled and open-label extension study with tocilizumab in children with systemic-onset juvenile idiopathic arthritis show a sustained clinical improvement and a favourable risk-benefit profile. The findings of this study might represent a step forward in the control of a disease that has previously proved to be difficult to manage.

Contributors

The study protocol was developed by the authors and clinical study investigators in collaboration with the study sponsor. All data discussed in this report were interpreted by the authors in collaboration with the study sponsor. The report was written by the corresponding author in consultation with the other authors and the sponsor. The authors participated in the study procedures, including patient enrolment, screening, clinical assessments, and follow-up.

Conflict of interest statement

NN received a consulting fee from the sponsor and works as a scientific advisory board member of Hoffman-La Roche, which developed tocilizumab in collaboration with the sponsor. TK holds a patent for tocilizumab for treatment of inflammatory disorders, including rheumatoid arthritis and Castleman's disease. The other authors declare that they have no conflict of interest.

Acknowledgments

Chugai Pharmaceuticals sponsored this study. The authors thank Remi Ozawa, Rumiko Kurosawa, Yasuo Nakagishi, Junpei Kinoshita, Shu-ichi Ito (Yokohama City University), Yoshifumi Kawano, Hiroyuki Imanaka, Nobuaki Maeno, Yasuhito Nerome (Kagoshima University), Yohichi Kohno, Yuzaburoh Inoue (Chiba University), Hiroshi Tamai (Osaka Medical School), and Kazuyuki Yoshizaki (Osaka University) for helpful discussions, outpatient care, and involvement in the study procedures; and CWP Reynolds and P Langman for linguistic help with this report.

References

1 Cassidy JT, Petty RE. Juvenile idiopathic arthritis. In Cassidy JT, Petty RE, eds. Textbook of pediatric rheumatology, 5th edn. Philadelphia: WB Saunders, 2005: 291–303.

2 Billiau AD, Roskams T, Van Damme-Lombaerts R, Matthys P, Wouters C. Macrophage activation syndrome: characteristic findings on liver biopsy illustrating the key role of activated, IFN-gamma-producing lymphocytes and IL-6- and TNF-alpha-producing macrophages. *Blood* 2005; 105: 1648–51.

3 Kelly A, Ramanan AV. Recognition and management of macrophage activation syndrome in juvenile arthritis. *Curr Opin Rheumatol* 2007; 19: 477–81.

4 Cortis E, Insalaco A. Macrophage activation syndrome in juvenile idiopathic arthritis. *Acta Paediatr Suppl* 2006; 95: 38–41.

5 Grom AA, Murray KJ, Luyrink L, et al. Patterns of expression of tumor necrosis factor alpha, tumor necrosis factor beta, and their receptors in synovia of patients with juvenile rheumatoid arthritis and juvenile spondylarthropathy. *Arthritis Rheum* 1996; 39: 1703–10.

6 Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med* 2000; 342: 763–69.

7 Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002; 46: 1443–50.

8 Quartier P, Taupin P, Bourdeaut F, et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. *Arthritis Rheum* 2003; 48: 1093–101.

9 Ramanan AV, Schneider R. Macrophage activation syndrome following initiation of etanercept in a child with systemic onset juvenile rheumatoid arthritis. *J Rheumatol* 2003; 30: 401–03.

10 Pascual V, Allantaz F, Arce E, et al. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to Il-1 blockade. *J Exp Med* 2005; 201: 1479–86.

11 Irigoyen PI, Olsen J, Hom C, et al. Treatment of systemic juvenile rheumatoid arthritis with anakinra (abstract). *Arthritis Rheum* 2004; 50 (suppl): S437.

12 Henrickson M. Efficacy of anakinra in refractory systemic arthritis (abstract). *Arhtiritis Rheum* 2004; 50 (suppl): S438.

13 Verbsky JW, White AJ. Effective use of the recombinant interleukin-1 receptor antagonist anakinra in therapy-resistant systemic onset juvenile rheumatoid arthritis. *J Rheumatol* 2004; 31: 2071–75.

14 Lurati A, Teruzzi B, Salmaso A, et al. Macrophage activation syndrome during anti-IL1 receptor therapy (anakinra) in a patient affected by systemic onset idiopathic juvenile arthritis. *Paed Rheumatol Online J* 2005; 3: 79–85.

15 Buoncompagni A, Loy A, Sala I, et al. Editorial: The paradox of macrophage activation syndrome triggered by biologic medications. *Paed Rheumatol Online J* 2005; 3: 70–73.

16 Rose-John S, Scheller J, Elson G, et al. Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: role in inflammation and cancer. *J Leukoc Biol* 2006; 80: 227–36.

17 de Benedetti F, Massa M, Robbioni P, et al. Correlation of interleukin-6 levels with joint involvement and thrombocytosis in patients with systemic juvenile rheumatoid arthritis. *Arthritis Rheum* 1991; 34: 1158–63.

18 de Benedetti F, Martini A. Targeting the interleukin-6 receptor: a new treatment for systemic juvenile idiopathic arthritis. *Arthritis Rheum* 2005; 52: 687–93.

19 Lieskovska J, Guo D, Derman E. Growth impairment in IL-6-overexpressing transgenic mice is associated with induction of SOCS3 mRNA. *Growth Horm IGF Res* 2003; 13: 26–35.

20 Woo P, Wilkinson N, Prieur A-M, et al. Open label phase II trial of single, ascending doses of MRA in Caucasian children with severe systemic juvenile idiopathic arthritis: proof of principle of the efficacy of IL-6 receptor blockade in this type of arthritis and demonstration of prolonged clinical improvement. *Arthritis Res Ther* 2005; 7: R1281–88.

21 Yokota S, Miyamae T, Imagawa T, et al. Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum* 2005; 52: 818–25.

22 Petty RE, Southwood TR, Manners P, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390–92.

23 Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997; 40: 1202–09.

24 Woo P, Southwood TR, Prieur AM, et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. *Arthritis Rheum* 2000; 43: 1849–57.

25 NCI. Cancer Therapy Evaluation Program, common terminology criteria for adverse events, version 3·0. DCTD, NCI, NIH, DHHS. Bethesda: National Cancer Institute, 2006.

26 Yokota S, Imagawa T, Miyamae T, et al. Long-term therapeutic experience of humanized anti-IL-6 receptor monoclonal antibody (aIL-6R Mab) in systemic-onset juvenile idiopathic arthritis (So-JIA). *Arthritis Rheum* 2004; 50: S438.

27 Stephan JL, Zeller J, Hubert P, et al. Macrophage activation and rheumatic disease in childhood: a report of four new cases. *Clin Exp Rheumatol* 1993; 11: 451–56.