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CASE REPORT

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Switching the therapy from etanercept to infliximab in a child with rheumatoid factor positive polyarticular juvenile idiopathic arthritis

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Abstract Tumor necrosis factor α (TNFα)-blocking agents have been used increasingly in the treatment of severe refractory juvenile idiopathic arthritis (JIA). However, some patients have been forced to discontinue these agents because of the lack of efficacy or adverse events. In these situations, cases of switching from one TNF-blocking agent to another are reported in rheumatoid arthritis, but there are few cases in JIA. This report documents the case of a patient with JIA who improved following a switch from etanercept to infliximab.

Key words Etanercept · Infliximab · Juvenile idiopathic arthritis

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disorder of childhood. Persistent destructive arthritis occurs in many patients with polyarticular-course JIA. Over the past few years, tumor necrosis factor α (TNFα)-blocking agents have been increasingly used in the treatment of severe refractory JIA[1,2] and rheumatoid arthritis (RA).[3,4] Two such agents, etanercept and infliximab are widely used to treat patients with RA. However, the discontinuation of these agents is occasionally required because of the lack of efficacy or adverse events. In these situations, several studies on the efficacy of switching between TNFα-blocking agents have been reported in RA.[5–9] The authors conclude that patients who failed to respond to one TNF-α antagonist may thus possibly respond to the other. However, there is little information on switching therapy in JIA.[10] This report documents the case of a patient with RF-positive polyarticular JIA who improved remarkably after switching from etanercept to infliximab.

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Case

A 14-year-old female patient who experienced right knee arthralgia developed polyarticular-course JIA. She was treated with a nonsteroidal anti-inflammatory drug for 2 months following the diagnosis. She visited our hospital 3 months from the onset because the number of joints with tenderness and swelling had increased. Following the failure of a weekly treatment of 17.5 mg methotrexate (10 mg/m^2), we decided to administer 0.4 mg/kg etanercept twice a week subcutaneously for a course of 5 months. Her disease activity score 28 (DAS 28) values improved from 7.1 to 5.1 at 4 weeks after starting etanercept. However, her clinical findings gradually deteriorated thereafter, and the DAS28 values increased up to 7.5 following 12 weeks of etanercept therapy.

Therefore, it was necessary to switch the treatment from etanercept to infliximab at 12 weeks following the initiation of etanercept therapy. She received infliximab intravenously at a dosage of 3.9 mg/kg of body weight (total 300 mg) at weeks 0, 2, and 6 and every 4 weeks thereafter, with a combination of oral 17.5 mg methotrexate once a week and 10 mg prednisolone.

Remarkable improvements were observed at 33 weeks of treatment, with a jump from 7.5 to 3.9 in DAS 28, from 7.5 to 1.88 in the Children Health Assessment Questionnaire (CHAQ),[11] from 4.75 mg/dl to <0.05 mg/dl in C-reactive protein, from 2040 U/ml to 241 U/ml in MMP-3, and from 414 IU/ml to 27 IU/ml in rheumatoid factor. She also achieved a 50% improvement in the JIA score set[12] in the 16th week of treatment and a 70% improvement in the 24th week (Figs. 1, 2). Enhanced magnetic resonance imaging with Gad demonstrated that active arthritic findings such as increased joint fluid, proliferating synovitis, and erosions in her right knee joint at the baseline had remark-

ably improved following treatment at 33 weeks (Fig. 3). However, infliximab was infused every 4 weeks thereafter, and the infusion interval could not be extended because of a flare-up of inflammation.

Discussion

Several studies on switching between TNFα-blocking agents have been reported in RA,[5–9] whereas only one article addresses this action in JIA.[10] In that report, 14 of the 15 patients (8 RA and 7 JIA) were initially treated with infliximab, then switched to etanercept. Only one patient was treated with etanercept first and then changed to infliximab; however, it is uncertain whether this patient had RA or JIA. It appears that this is the first report of a successful switching therapy from etanercept to infliximab in JIA. Both etanercept and infliximab bind with high affinity to soluble TNF-α, but the binding of infliximab to cell expressing transmembrane TNF can lead to lysis.[13] This may explain in part the different ability of infliximab to be effective despite a failure of etanercept.

Here, this patient was switched to infliximab without increasing the dosage of etanercept. There is a report that an increasing dosage of etanercept may not offer any additional benefit to children with unsatisfactory response to a standard dosage of etanercept.[14]

Infliximab is usually administered intravenously at 3 mg/kg at 0, 2, and 6 weeks, and every 8 weeks thereafter; however, a higher dosage of infliximab and frequent infusions were required to achieve disease control in this patient. We hypothesize two reasons for this as noted below.

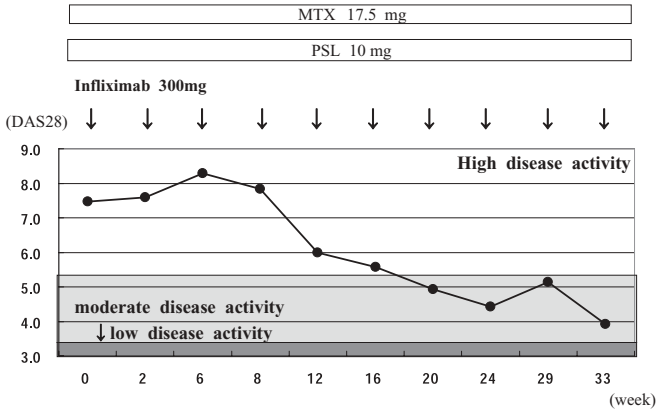

Fig. 1. Remarkable improvements were obtained in the disease activity score 28 at 24th week, so the infusion schedule was extended. However, it was necessary to shorten the interval from 5 weeks to 4 weeks at the 29th week because of a flare of inflammation

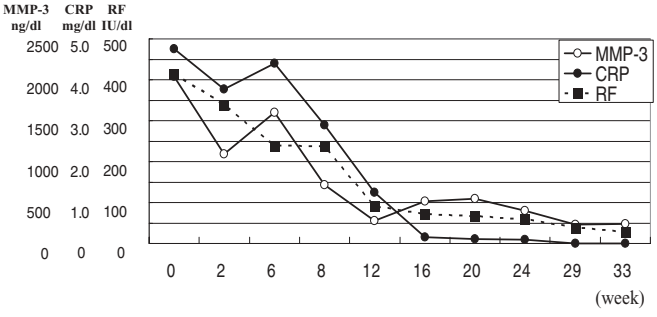

Fig. 2. Improvements were obtained in MMP-3 (2040 U/ml at baseline, 241 U/ml at 33 weeks), C-reactive protein (4.75 mg/dl at baseline, <0.05 mg/dl at 33 weeks) and rheumatoid factor (414 IU/ml at baseline, 27.2 IU/ml at 33 weeks)

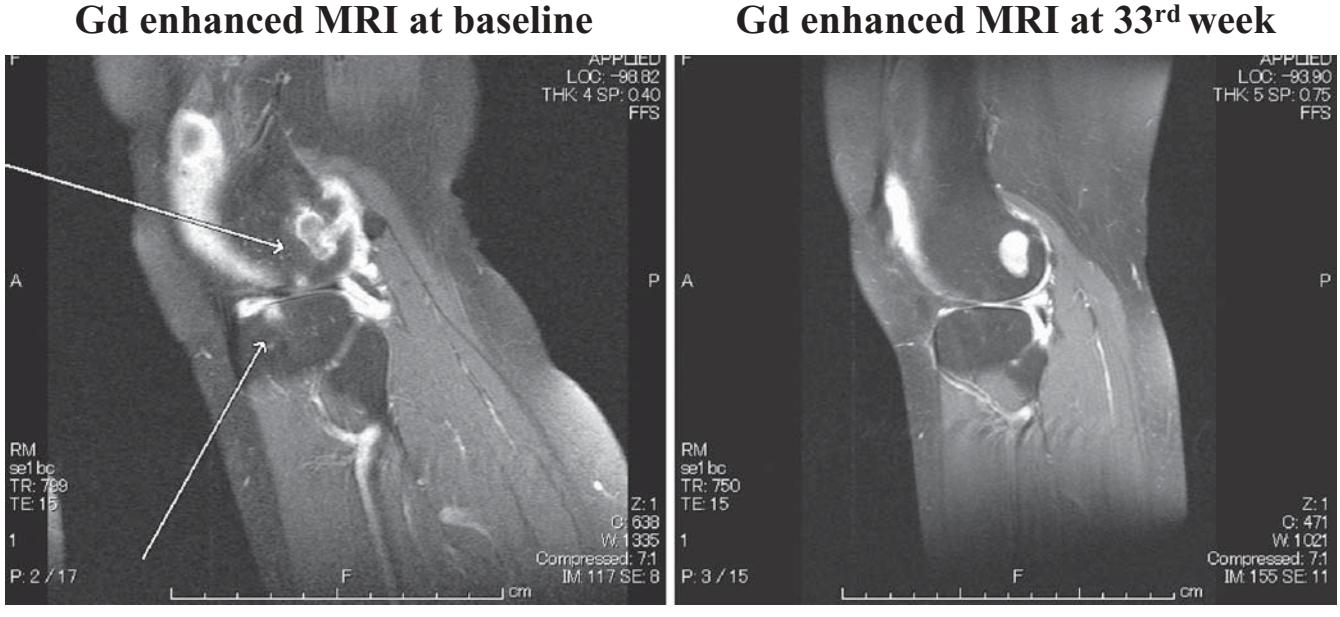

Fig. 3. Enhanced magnetic resonance imaging with Gad demonstrates active arthritic findings such as an increased amount of joint fluid, proliferating synovialis, and erosions in her right knee joint at the baseline remarkably improved after treatment at 33 weeks

First, this case had to be switched from etanercept to infliximab. Hansen et al.[9] performed a retrospective study of 93 patients who had been administered infliximab in addition to leflunomide. Of these patients, 20 had undergone treatment with etanercept earlier, which had been discontinued mostly because of the lack of efficacy. Comparing these 20 patients with the 73 patients for whom infliximab was administered as the first biological treatment, no differences in the clinical efficacy were observed, but the dosages of infliximab required for the patients who switched from etanercept were significantly higher. In contrast, Yazici and Erkan reported in a letter that patients with unsuccessful etanercept therapy showed lower response to infliximab than patients who were naïve to TNF-α blockers. van Vollenhoven et al.[7] treated 18 patients with infliximab after etanercept had failed and 12 of them achieved an American College of Rheumatology for 20% (ACR20) response. Brocq et al.[6] treated six patients who switched from etanercept to infliximab with dosing regimens as 3 mg/kg every 4 or 8 weeks and 10 mg/kg every 4 or 8 weeks, and three of them achieved an ACR20 response.[6] In addition, Ang and Helfgott[8] treated 24 patients who switched from etanercept to infliximab and 12 of them achieved ACR20 response but they described no dosing regimen of infliximab.[8] Therefore, the usage and dosage of infliximab upon switching from etanercept is not clear, so higher dosage and/or shorter interval of infliximab administration may be required to achieve better results.

Second, she is younger than the adult RA patients treated with infliximab. In our hospital, we treated five rheumatoid factor-positive polyarticular JIA patients who needed a higher dosage of infliximab and frequent infusions to achieve sufficient disease control except for one adult-age patient. The clinical improvement from infliximab therapy is related to the serum concentration.[15] There have so far been no reports on the serum concentrations of infliximab in JIA; however, pharmacologic half-life of infliximab may differ between children and adults. As a result, further investigations are needed.

In conclusion, switching to infliximab may be beneficial to patients with polyarticular JIA when etanercept has failed. However, a prospective multicenter study is therefore required to evaluate the efficacy of a switching therapy between TNFα-blocking agents.

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