Long Term Safety and Efficacy of Etanercept in Juvenile Idiopathic Arthritis in a Single Center

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Objective. Our aim was to investigate the long term safety and efficacy of etanercept in children with juvenile idiopathic arthritis (JIA). Methods. The study subjects were the 90 JIA patients treated with etanercept in the Department of Pediatrics, Hallym University Medical Center between January 2004 and December 2017. We retrospectively reviewed their medical records for age at diagnosis, duration of etanercept treatment, number of active joints, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and adverse events during treatment. Results. Among the 90 patients, 38 (42.0%) were male and 52 (58.0%) were female; 15 (16.7%) had systemic onset, 41 (45.6%) had extended oligoarticular, 14 (15.6%) had rheumatoid factor-positive polyarticular, 18 (20.0%) had rheumatoid factor-negative polyarticular, and 2 (2.1%) had enthesitis-related arthritis. The median age at the start of etanercept treatment was 9 years (range, 3 ~ 18 years), and the median duration of etanercept treatment was 6 years (range, 0.5 ~ 13 years). The median number of active joints decreased from 9 to 0 after 6 months of etanercept treatment. The median CRP and ESR were within normal range after 3 months of treatment. Six patients experienced recurrence, 9 switched to other medications and 3 discontinued etanercept. Of the 14 reported adverse events, 1 was serious, and there were no tuberculosis infections or malignancies. Conclusion. Long-term treatment with etanercept is efficacious and safe for children with JIA. However, those with the systemic onset subtype appear to have low drug survival rate compared to those with other types of JIA. (J Rheum Dis 2019;26:200-205)

Key Words. Juvenile idiopathic arthritis, Etanercept

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is one of the most common autoimmune diseases with an incidence of about 10 ~ 20/100,000 children and a prevalence of 80 ~ 100/100,000 children [1-4]. It is defined as inflammatory arthritis occurring in patients under 16 years of age for over 6 weeks without other known etiologies or diseases [5]. The International League of Associations for Rheumatology (ILAR) has grouped JIA into 7 subsets based on the clinical and laboratory features: systemic arthritis, oligoarthritis (persistent type and extended type), rheumatoid factor (RF)-positive polyarthritis, RF-negative polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis [6,7]. Although the overall prognosis is good, some types are refractory to conventional therapies, such as non-steroidal anti-inflammatory drugs (NSAID) and disease-modifying antirheumatic drugs (DMARDs) [8]. These refractory disease outcomes have been dramatically improved by the development of the tumor necrosis factor (TNF) antagonists [5]. Etanercept is a dimeric fusion protein that contains the extracellular portion of the human p75 TNF receptor linked to the Fc portion of human IgG1, so it can neutralize TNF activity [9]. It has been established as a safe and highly efficacious agent in treating refractory arthritis and related autoimmune disorders [10-12]. Healthcare Insurance Review & Assessment in Korea only approves treatment with etanercept in JIA patients with polyarticular, extended oligoarticular, or en-
Long Term Safety and Efficacy of Etanercept in JIA

Among the biological products available for treating JIA, etanercept has been approved in Korea since 2004, while adalimumab and tocilizumab were approved later in 2013 and 2017, respectively. Hence, given etanercept’s relatively long history of use, our aim was to investigate its long-term safety and efficacy.

MATERIALS AND METHODS

Patients and study protocol
A total of 90 JIA patients were treated with etanercept (Enbrel; Pfizer, New York, USA) in the Department of Pediatrics, Hallym University Medical Center between January 2004 and December 2017. All patients were diagnosed before the age of 16 years by a pediatric rheumatologist and the JIA subtype was assigned according to the criteria of the ILAR classification [6].

We retrospectively reviewed the patients’ medical records to analyze age at diagnosis, duration of etanercept treatment, number of active joints, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and adverse events during treatment.

The study subjects were JIA patients who had polyarticular disease irrespective of onset type. Patients received subcutaneous injections of etanercept at a dosage of either 0.4 mg/kg twice weekly (maximum dose 25 mg per injection) or 0.8 mg/kg once weekly (maximum dose 50 mg per week). During etanercept therapy, patients were evaluated every 3 to 6 months. Patients taking NSAIDs, such as acetaminophen or naproxen, and DMARDs, such as methotrexate, hydroxychloroquine or sulfasalazine, maintained their medicines until symptoms improved.

The study protocol was approved by the Ethics Committees of Hallym University Sacred Heart Hospital (IRB no. 2018-08-014-001).

Efficacy
We evaluated efficacy by analyzing the number of active joints, ESR (mm/hr), and CRP levels (mg/L), and the presence of clinical findings such as fever, rash, serositis, splenomegaly, generalized lymphadenopathy, and active uveitis. Active joints were defined as joints with swelling or joints with limited of motion and pain or tenderness.

Safety
Adverse events reported by patients throughout the course of treatment with etanercept were recorded. These were classified as non-serious or serious adverse events. Serious adverse events were defined as adverse events that were fatal or resulted in hospitalization.

Statistical analysis
Descriptive statistics were reported as medians and ranges for continuous variables and as absolute frequencies and percentages for categorical variables. The drug survival rate was analyzed by Kaplan–Meier curves. All statistical analyses were performed using a software program (SPSS for Windows, Version 20.0; IBM Co., Armonk, NY, USA), and a p-value of <0.05 was considered statistically significant.

RESULTS

Among the 90 patients, 38 (42.0%) were male and 52 (58.0%) were female; 15 (16.7%) had systemic onset, 41 (45.6%) had extended oligoarticular, 14 (15.6%) had RF-positive polyarticular, 18 (20.0%) had RF-negative polyarticular, and 2 (2.1%) had enthesitis-related arthritis. The median age at start of etanercept was 9 years (3 ~ 18 years), and the median period of etanercept treatment was 6 years (0.5 ~ 13 years). Fever was present in 3 patients, and lymphadenopathy and hepatomegaly were

Table 1. Clinical characteristics of patients treated by etanercept

| Characteristics                          | All patients (n = 90) |
|------------------------------------------|----------------------|
| Female                                   | 52 (58.0)            |
| Age at start of etanercept (yr)          | 9 (3 ~ 18)           |
| Disease duration before etanercept (yr)  | 5.5 (0 ~ 13)         |
| Duration of etanercept therapy (yr)      | 6 (0.5 ~ 13)         |
| JIA onset type                           |                      |
| Systemic onset arthritis                 | 15 (16.7)            |
| Extended oligoarthritis                  | 41 (45.6)            |
| RF-positive polyarthritis                | 14 (15.6)            |
| RF-negative polyarthritis                | 18 (20.0)            |
| Enthesitis-related arthritis             | 2 (2.1)              |
| DMARD before etanercept treatment        |                      |
| Methotrexate                             | 84                   |
| Hydroxychloroquine                       | 77                   |
| Sulfasalazine                            | 7                    |

Values are presented as number (%) or median (range). JIA: juvenile idiopathic arthritis, RF: rheumatoid factor, DMARD: disease-modifying antirheumatic drug.
observed in 1 patient each. The patients’ demographic and clinical characteristics are described in Table 1. The
duration of etanercept treatment in all patients is shown in Table 2 and the number of patients at baseline and follow-up are shown in Table 3.

Clinically, the median number of active joints was 9 (range, 5–24) at baseline, decreased to 2 (range, 0–26) after 3 months of etanercept, and further decreased to 0 (range, 0–11) after 6 months. The median number of active joints at baseline was largest in the RF-positive arthritis group (17; range, 6–22) and smallest in the enthesitis-related arthritis group (7; range, 5–8). No patients had other symptoms attributable to JIA after 6 months of treatment, including fever, splenomegaly, and lymphadenopathy. The median CRP level (reference range, 0.0–5.0 mg/L) was 22.4 mg/L (range, 0.5–180.0 mg/L) at baseline, decreased to 1.8 mg/L (range, 0.5–157.0 mg/L) after 3 months and remained within normal range thereafter. The median CRP level at baseline was highest in the systemic onset group (82.2; range 0.5–180.0) and lowest in RF-negative polyarthritis group (8.8; range, 0.5–64.3). The median ESR (reference

| Duration | Number of total patients | Medication switching | Medication discontinuation |
|----------|--------------------------|----------------------|---------------------------|
| 6 mo ~ 1 yr | 8 | 2 | 0 |
| 1 ~ 2 yr | 6 | 1 | 0 |
| 2 ~ 3 yr | 13 | 3 | 0 |
| 3 ~ 4 yr | 8 | 2 | 0 |
| 4 ~ 5 yr | 6 | 0 | 0 |
| 5 ~ 6 yr | 4 | 0 | 1 |
| 6 ~ 7 yr | 5 | 1 | 0 |
| 7 ~ 8 yr | 9 | 0 | 1 |
| 8 ~ 9 yr | 5 | 0 | 0 |
| 9 ~ 10 yr | 8 | 0 | 0 |
| 10 ~ 11 yr | 7 | 0 | 0 |
| 11 ~ 12 yr | 3 | 0 | 1 |
| 12 ~ 13 yr | 5 | 0 | 0 |
| 13 ~ 14 yr | 3 | 0 | 0 |
| Total | 90 | 9 | 3 |

Table 3. Number of patients, active joints, CRP, and ESR levels at baseline and follow-up periods

| Patients | Baseline | 3 mo | 6 mo | 1 yr | 5 yr | 10 yr |
|----------|----------|------|------|------|------|-------|
| All patients | n=90 | n=90 | n=90 | n=82 | n=49 | n=18 |
| No. of active joints | 9 (5–24) | 2 (0–26) | 0 (0–11) | 0 (0–4) | 0 (0–3) | 0 (0–2) |
| CRP | 22.4 (0.5–180.0) | 1.8 (0.5–157.0) | 1.6 (0.5–79.0) | 1.5 (0.5–67.2) | 1.5 (0.5–24.7) | 1.1 (0.5–15.1) |
| ESR | 43 (2–130) | 12 (1–80) | 12 (2–65) | 11 (2–65) | 11 (2–59) | 9 (2–48) |
| Systemic onset | n=15 | n=15 | n=15 | n=13 | n=10 | n=2 |
| No. of active joints | 13 (5–24) | 3 (0–10) | 0 (0–11) | 0 (0–4) | 0 (0–1) | 0 (0) |
| CRP | 82.2 (0.5–180.0) | 3.6 (0.5–103.0) | 3.5 (1.0–79.0) | 1.6 (0.6–67.2) | 1.5 (0.5–24.7) | 1.2 (1.2) |
| ESR | 69 (2–130) | 21 (2–58) | 15 (4–57) | 13 (2–50) | 9 (4–58) | 4 (4) |
| Extended oligoarthritis | n=41 | n=41 | n=41 | n=39 | n=21 | n=10 |
| No. of active joints | 8 (5–14) | 2 (0–26) | 0 (0–3) | 0 (0–2) | 0 (0–1) | 0 (0–1) |
| CRP | 26.7 (0.5–130.0) | 1.2 (0.5–47.7) | 1.1 (0.5–36.9) | 1.5 (0.5–13.9) | 1.5 (0.5–12.9) | 1.2 (0.5–5.0) |
| ESR | 45 (6–120) | 12 (1–55) | 9 (2–65) | 9 (2–59) | 10 (5–14) | 10 (5–14) |
| RF(+) polyarthritis | n=14 | n=14 | n=14 | n=11 | n=8 | n=4 |
| No. of active joints | 17 (6–22) | 4 (0–14) | 1 (0–3) | 0 (0–2) | 0 (0–1) | 0 (0–2) |
| CRP | 14.1 (2.3–46.7) | 2.4 (0.5–13.2) | 2.3 (0.5–62.2) | 1.1 (0.5–8.5) | 2.1 (0.5–4.5) | 1.1 (0.5–15.1) |
| ESR | 32 (11–89) | 9 (3–49) | 13 (4–43) | 13 (3–23) | 9 (4–33) | 5 (2–48) |
| RF(−) polyarthritis | n=18 | n=18 | n=18 | n=17 | n=8 | n=2 |
| No. of active joints | 11 (7–24) | 3 (0–24) | 0 (0–3) | 0 (0–2) | 0 (0) | 0 (0) |
| CRP | 8.8 (0.5–64.3) | 1.6 (0.5–15.7) | 1.7 (0.5–15.6) | 2.1 (0.5–9.7) | 1.0 (0.5–5.0) | 0.5 (0.5) |
| ESR | 33 (2–87) | 11 (2–80) | 13 (2–51) | 14 (3–21) | 16 (6–28) | 9 (9) |
| ERA | n=2 | n=2 | n=2 | n=2 | n=2 | n=2 |
| No. of active joints | 7 (5–8) | 0 (0) | 0 (0) | 1 (0–1) | 1 (0–1) | |
| CRP | 48.5 (2.7–94.3) | 1.9 (1.2–2.7) | 2.0 (1.2–2.7) | 6.5 (3.4–9.6) | 10.7 (9.7–10.7) | |
| ESR | 56 (10–102) | 7 (3–10) | 8 (6–10) | 15 (10–20) | 33 (24–33) | |

Values are presented as median (range). CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, RF(+): rheumatoid factor positive, RF(−): rheumatoid factor negative, ERA: enthesitis-related arthritis.

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range, 0 ~ 20 mm/hr (range, 2 ~ 130) at baseline, decreased to 12 mm/hr (1 ~ 80) after 3 months, and remained within the normal range thereafter. The median ESR at baseline was highest in the systemic onset group (69; range, 2 ~ 130) and lowest in the RF-positive group (32; range, 11 ~ 89). The changes in the number of active joints, ESR, and CRP level are shown in Table 3.

During etanercept treatment, 6 patients experienced recurrence. Three patients had good drug compliance, 2 had poor drug compliance, and 1 was tapering the dosage. The 3 patients with good drug compliance had DMARDs added to their treatment regimen. Two patients with poor drug compliance were re-educated about the importance of the injections. One patient who experienced a flare while tapering returned to the original dose.

Of the 90 patients, 9 switched to other biologics (Table 4): Six patients switched to adalimumab (2 patients), abatacept (3 patients), and tocilizumab (1 patient) due to lack of efficacy. Four of the patients had systemic onset type JIA, 1 had extended oligoarticular type, and 1 had RF-negative polyarticular type. Three patients switched to adalimumab due to uveitis flare: 2 had extended oligoarticular arthritis and 1 had RF-negative polyarticular arthritis. Three patients discontinued etanercept after 5 years, 7 years, and 11 years, respectively, after achieving satisfactory results (Tables 2 and 4).

The lowest drug survival rate was observed in the patients with systemic onset JIA compared to those with other subtypes (p < 0.05). After 5 years of etanercept treatment, the drug survival rate in systemic onset JIA patients was 73%, while in the extended oligoarticular group it was 89% and in the RF negative polyarticular group, it was 93%. After 10 years, the drug survival rate was 61% in systemic onset JIA patients, 84% in those with extended oligoarticular subtype, and 80% in those with the RF-negative polyarticular subtype. The drug survival rate after 13 years was 31% in systemic onset JIA patients, and 84% in those with extended oligoarticular subtype. None of the patients with RF-positive arthritis or enthesitis-related arthritis discontinued treatment. The drug survival rates of etanercept by JIA subtype are shown in Figure 1.

All patients were taking NSAIDs or DMARDs at the beginning of etanercept treatment, and 7 patients discontinued other medications except etanercept due to poor compliance; none of the seven patients discontinued etanercept.

Fourteen adverse events were reported (Table 5). Non-serious adverse events were localized pain at the injection site (n=6, 6.7%) and dysmenorrhea (n=2, 2.2%). No rashes or allergic reactions were noted. Serious adverse events were uveitis and a case of cellulitis needing hospitalization. Three of the 5 patients with uveitis switched to adalimumab, but the other 2 patients were not able to switch medications because Korea health in-

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**Table 4. Reasons for switching medication or discontinuing etanercept**

| Reasons for switching medication | Number (%) |
|----------------------------------|------------|
| Recurrent or severe uveitis       |            |
| Adalimumab (Humira)              | 3 (3.3)    |
| Lack of efficacy                 |            |
| Adalimumab (Humira)              | 2 (2.2)    |
| Abatacept (Orencia)              | 3 (3.3)    |
| Tocilizumab (Actemra)            | 1 (1.1)    |
| Reasons for discontinuing        |            |
| Satisfactory result              | 3 (3.3)    |

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**Table 5. Adverse events**

| Adverse events                        | Number (%) |
|---------------------------------------|------------|
| Non-serious adverse event             |            |
|Localized pain of injection site       | 6 (6.7)    |
|Dysmenorrhea                           | 2 (2.2)    |
|Serious adverse event                  |            |
|Uveitis                                | 5 (5.6)    |
|Recurrent cellulitis                    | 1 (1.1)    |
|Tuberculosis                           | 0          |
|Malignancy                             | 0          |

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Figure 1. Drug survival of etanercept. RF: rheumatoid factor. *p < 0.01.
survance did not cover adalimumab. However, these 2 patients were effectively treated by adding topical or systemic corticosteroids, so etanercept was continued. One case of cellulitis necessitating hospitalization did not occur at the etanercept injection site, and the patient did not have any other underlying diseases. When the patient first developed cellulitis, she was treated with oral antibiotics. However, cellulitis recurred afterward, so she was admitted for more than 10 days, treated with intravenous antibiotics, and advised to temporarily discontinue etanercept while admitted for treatment of cellulitis. No patients were diagnosed with tuberculosis infections or malignancies.

**DISCUSSION**

In this study, we investigated the long-term safety and efficacy of etanercept in 90 patients who had been treated with etanercept for at least 6 months and up to 13 years. Etanercept treatment reduced the number of active joints and reduced the ESR and CRP to their normal ranges in all subtype groups other than the enthesitis-related arthritis group, possibly due to the small number of patients with this subtype. Also, the highest values of ESR and CRP in each period remained above the upper limit of normal despite treatment, which can be explained by the fluctuation of disease activity over time.

Nine of the 90 patients (10%) switched to another medication and 3 patients (3.3%) discontinued etanercept (Tables 2 and 4). Lovell et al. [13] reported that 7% of patients discontinued etanercept when observed up to 8 years and studies in adult patients with rheumatoid arthritis reported failure rates from 25% to 38% [11,12]. Southwood et al. [14] reported that 100 of 483 patients (20.7%) discontinued etanercept. These discordances may be due to the differences in patient population.

The drug survival rates after 5 years were 73% in the systemic onset JIA group, 89% in the extended oligoarticular group, 93% in the RF-negative polyarticular group, and 100% in the RF-positive polyarticular and enthesitis-related arthritis group. After 10 years, the drug survival rates were 61% in the systemic onset JIA group, 84% in the extended oligoarticular group, 80% in the RF-negative polyarthritis group, and 100% in the RF-positive polyarthritis and enthesitis-related arthritis groups. Southwood et al. [14] reported a 20.7% discontinuation rate of etanercept after 5 years, and Favalli et al. [15] reported the drug survival rate of etanercept as 38.1% after 10 years. Neovius et al. [16] reported drug survival rate of etanercept as 55% after 5 years of rheumatoid arthritis treatment in adults.

The treatment failure rate was highest in the systemic onset JIA group. This may be due to the heterogeneity of the systemic onset type [17], which has also shown relative resistance to methotrexate treatment in studies reported by Woo et al. [18] and Halle and Prieur [19].

Adverse events were reported in 14 patients; 8 were non-serious and 6 were serious (Table 5). However, no cases of malignancy, tuberculosis or varicella zoster infections were reported. Prince et al. [20] reported 65 adverse events during 312 patient-years of etanercept. Tzaribachev et al. [21] reported one case of varicella zoster virus infection and one case of fever up to 39.5°C that spontaneously resolved, both non-serious. Bracaglia et al. [22] reported 2 cases of varicella zoster infection.

Varicella zoster infection may have been prevented in our patients due to the national immunization program in Korea, which includes vaccination against varicella zoster virus at one year old. Also TNF targeting therapies are known to increase the risk of tuberculosis [23,24] and to reactivate hepatitis B virus infection [25,26] in adults.

This study has some limitations because it is done retrospectively. Also, since this is a single center study, selection bias may be present. Finally, some patients’ data were lost during the long follow up period. Additional multicenter studies should be performed in the future.

**CONCLUSION**

In this study of long term etanercept treatment for JIA in Korea, we found that etanercept is efficacious and can be safely used in children with this condition. After 13 years, the drug survival rate was 31% in systemic onset JIA patients and 84% in those with the extended oligoarticular subtype; after 10 years, it was 100% in those with the RF-positive and 80% in those with the RF-negative polyarticular subtype; and after 5 years it was 100% in those with the enthesitis-related arthritis subtype. There were 6 serious adverse events (6.7%) during the 13-year period, consisting of 5 cases of uveitis and 1 case of cellulitis.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article.
was reported.

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