pISSN: 2093-940X, eISSN: 2233-4718
Journal of Rheumatic Diseases Vol. 26, No. 3, July, 2019
https://doi.org/10.4078/jrd.2019.26.3.200

Original Article

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

Myung Hoon Bang, Kwang Nam Kim
Department of Pediatrics, Hallym University Sacred Heart Hospital, Anyang, Korea

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-

Received : March 4, 2019, **Revised** : May 17, 2019, **Accepted** : June 3, 2019

Corresponding to : Kwang Nam Kim http://orcid.org/0000-0003-4024-5128
Department of Pediatrics, Hallym University Sacred Heart Hospital, 22 Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 14068, Korea. E-mail : kwangnamkim@naver.com

thesitis-related arthritis who have an inadequate response to DMARDs for 6 months.

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 Kaplain–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
Hydrochloroquine	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.

Table 2. Duration of etanercept treatment

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

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 polyarthritis 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

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

Patients	Follow-up period					
	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 (0～3)	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)	10 (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	
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.

range, 0～20 mm/hr) was 43 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).

Table 4. Reasons for switching medication or discontinuing etanercept

Reasons	Number (%)
Reasons for switching medication	
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)

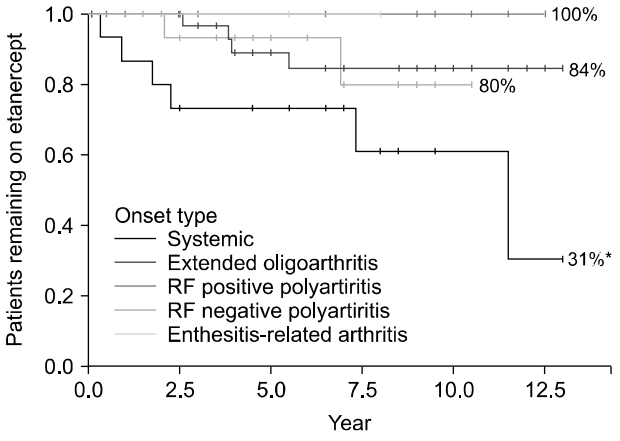

Figure 1. Drug survival of etanercept. RF: rheumatoid factor. *$p<0.01$.

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-

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

surance 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 cellulits, 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 afterr 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. Koike et al. [27] reported that injection site reaction occurred in 4.4% of patients.

This study has some limitations because it is done retrospective. 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.

REFERENCES

1. Woo P, Wedderburn LR. Juvenile chronic arthritis. Lancet 1998;351:969-73.
2. Peterson LS, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Juvenile rheumatoid arthritis in Rochester, Minnesota 1960-1993. Is the epidemiology changing? Arthritis Rheum 1996;39:1385-90.
3. Manners PJ. Epidemiology of the rheumatic diseases of childhood. Curr Rheumatol Rep 2003;5:453-7.
4. Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis why does it vary so much? J Rheumatol 2002;29: 1520-30.
5. Cai Y, Liu X, Zhang W, Xu J, Cao L. Clinical trial of etanercept tapering in juvenile idiopathic arthritis during remission. Rheumatol Int 2013;33:2277-82.
6. Petty RE. Growing pains: the ILAR classification of juvenile idiopathic arthritis. J Rheumatol 2001;28:927-8.
7. Dueckers G, Guellac N, Arbogast M, Dannecker G, Foeldvari I, Frosch M, et al. Evidence and consensus based GKJR guidelines for the treatment of juvenile idiopathic arthritis. Clin Immunol 2012;142:176-93.
8. Kuemmerle-Deschner JB, Horneff G. Safety and efficacy of once-weekly application of Etanercept in children with juvenile idiopathic arthritis. Rheumatol Int 2007;28:153-6.
9. Suffredini AF, Reda D, Banks SM, Tropea M, Agosti JM, Miller R. Effects of recombinant dimeric TNF receptor on human inflammatory responses following intravenous endotoxin administration. J Immunol 1995;155:5038-45.
10. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med 2000;342:763-9.
11. Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 1997;337:141-7.
12. Moreland LW, Weinblatt ME, Keystone EC, Kremer JM, Martin RW, Schiff MH, et al. Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. J Rheumatol 2006;33:854-61.
13. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008;58:1496-504.
14. Southwood TR, Foster HE, Davidson JE, Hyrich KL, Cotter CB, Wedderburn LR, et al. Duration of etanercept treatment and reasons for discontinuation in a cohort of juvenile idiopathic arthritis patients. Rheumatology (Oxford) 2011;50: 189-95.
15. Favalli EG, Pontikaki I, Becciolini A, Biggioggero M, Ughi N, Romano M, et al. Real-life 10-year retention rate of first-line anti-TNF drugs for inflammatory arthritides in adult- and juvenile-onset populations: similarities and differences. Clin Rheumatol 2017;36:1747-55.
16. Neovius M, Arkema EV, Olsson H, Eriksson JK, Kristensen LE, Simard JF, et al. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. Ann Rheum Dis 2015;74: 354-60.
17. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369:767-78.
18. Woo P, Southwood TR, Prieur AM, Doré CJ, Grainger J, David J, 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.
19. Halle F, Prieur AM. Evaluation of methotrexate in the treatment of juvenile chronic arthritis according to the subtype. Clin Exp Rheumatol 1991;9:297-302.
20. Prince FH, Twilt M, ten Cate R, van Rossum MA, Armbrust W, Hoppenreijs EP, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. Ann Rheum Dis 2009;68: 635-41.
21. Tzaribachev N, Kuemmerle-Deschner J, Eichner M, Horneff G. Safety and efficacy of etanercept in children with juvenile idiopathic arthritis below the age of 4 years. Rheumatol Int 2008;28:1031-4.
22. Bracaglia C, Buonuomo PS, Tozzi AE, Pardeo M, Nicolai R, Campana A, et al. Safety and efficacy of etanercept in a cohort of patients with juvenile idiopathic arthritis under 4 years of age. J Rheumatol 2012;39:1287-90.
23. Chiang YC, Kuo LN, Yen YH, Tang CH, Chen HY. Infection risk in patients with rheumatoid arthritis treated with etanercept or adalimumab. Comput Methods Programs Biomed 2014;116:319-27.
24. Ke WM, Chen LS, Parng IM, Chen WW, On AW. Risk of tuberculosis in rheumatoid arthritis patients on tumour necrosis factor-alpha inhibitor treatment in Taiwan. Int J Tuberc Lung Dis 2013;17:1590-5.
25. Lan JL, Chen YM, Hsieh TY, Chen YH, Hsieh CW, Chen DY, et al. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. Ann Rheum Dis 2011;70:1719-25.
26. Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, et al. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. Medicine (Baltimore) 2011;90:359-71.
27. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Postmarketing surveillance of safety and effectiveness of etanercept in Japanese patients with rheumatoid arthritis. Mod Rheumatol 2011;21:343-51.