Original article

Effect of etanercept on refractory systemic-onset juvenile idiopathic arthritis

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Background: **Treatment of systemic-onset juvenile idiopathic arthritis (So-JIA) is challenging, and the efficacy of injectable recombinant human tumor necrosis factor type 1 receptor-antibody fusion protein (etanercept) on So-JIA has been controversial.**

Methods: **We retrospectively studied 12 patients with refractory systemic juvenile arthritis treated with etanercept at our hospital in the past 5 years. The 12 patients were divided into a corticosteroid-dependent group (*n*=7) and an ineffective group (*n*=5) on the basis of their responses to treatment before the administration of etanercept. Etanercept was added to the treatment without substantially changing the original regimens in general, and doses, and signs of efficacy including alleviation or resolution of symptoms such as high fever, inflammatory arthropathy, eruption rash, hydrohymenitis, as well as changes in the levels of laboratory inflammatory markers such as the white blood cell count, erythrocyte sedimentation rate, levels of C-reactive protein and serum ferritin were recorded.**

Results: **Etanercept was withdrawn after the first dose from one patient in the corticosteroid-dependent group because of a systemic allergic rash, and was also withdrawn from one patient in the ineffective group after 2 months of treatment owing to inefficacy; the remaining 10 patients completed the entire treatment protocol, at which point etanercept was discontinued. At that time, clinical symptoms and laboratory inflammatory markers of the remaining patients were within the normal range and the mean dose of prednisone was 0.18 mg/kg per day, an 81% decrease from the mean dose at baseline. At present, the corticosteroid has been discontinued and only methotrexate maintenance treatment is used in 3 patients; the other 7 patients are treated with prednisone and methotrexate maintenance therapy. All of the 10 patients are in a medicated remission with no recurrence.**

Conclusions: **In the treatment of patients with refractory So-JIA, the principles of individual therapy and combinations of drugs should be followed. Etanercept is an important and valid candidate for use in such combined treatment strategies.**

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Key words: **etanercept;**
juvenile idiopathic arthritis;
systemic-onset;
therapy

Introduction

Systemic-onset juvenile idiopathic arthritis (So-JIA), the most severe subtype of juvenile idiopathic arthritis (JIA),[1] accounts for about 4%-17% of the JIA cases.[2] So-JIA is unique among the subtypes of JIA. It causes inflammatory arthropathy, and its main clinical characteristics include extra-articular symptoms, such as quotidian fever, evanescent rash, serositis hydrohymenitis, and enlargement of the lymph nodes, liver, spleen, and other organs.[1] Given the yet unknown pathogenesis and extreme heterogeneity of So-JIA,[2] the progression of the disease varies among different individuals. In some cases, So-JIA progresses rapidly and the patients' lives are threatened by macrophage activation syndrome (MAS). A study[3] estimated that the risk of death among So-JIA patients is about 2.8%-14%, whereas Kahn[4] reported that the mortality from So-JIA in North America was lower than 0.3% and that the main causes of death involved MAS, infection, and cardiac complications.

The heterogeneity of So-JIA causes great discrepancies in the curative effects of the various treatments among different individuals. Less severely affected patients can show a remission in response to the traditional treatment strategy consisting of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and

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methotrexate (MTX, M).[1,5] This conventional regimen is ineffective in 40%-50% of patients with So-JIA, and these patients need to try different immunosuppressive drugs.[6-8] Unfortunately, even the curative effects of immunosuppressive agents are not satisfactory in some patients, who require a long-term and/or high dose corticosteroid therapy to keep the disease under control.[9]

The invention of biologic agents introduced new ideas and methods for the treatment of JIA. One agent, tumor necrosis factor receptor-antibody fusion protein (etanercept), has satisfactory efficacy and safety for the treatment of other subtypes of JIA;[9,10] however, its effects on So-JIA have been controversial in different studies, and many researchers believe that the curative effects are inadequate.[9-11]

Interleukin (IL)-1 and IL-6 both play important roles in the development of So-JIA.[12] Since 2004, a series of studies[13-15] have shown that blocking IL-1 activity with an IL-1 receptor antagonist (IL-1Ra, anakinra) in So-JIA is effective, and anakinra has been an important biological agent for the treatment of So-JIA, while IL-6 receptor antagonist (IL-6Ra, tocilizumab) also being reported effective for the control of So-JIA.[16-18] However, the two biological agents have not been qualified for clinical treatment and can't be obtained in China. Hence, we try to choose etanercept to treat refractory or severe So-JIA. Etanercept is a biological agent that has been approved to use for the treatment of JIA children in China currently.

The present study retrospectively analyzed the clinical data from 12 patients with So-JIA treated with etanercept in our hospital in the past 5 years, attempting to evaluate the curative effects of etanercept for the treatment of So-JIA and thereby devise some regimens for the treatment of refractory or severe So-JIA.

Methods

Patients

Between January 2008 and December 2012, twelve children were diagnosed as having So-JIA according to the criteria of the International League of Rheumatology Alliance and treated with etanercept at the Department of Rheumatism of Shanghai Children's Medical Center. They comprised 7 boys and 5 girls, and their age of onset ranged from 4 to 11 years (mean: 7 years).

Before treatment with etanercept, the 12 patients had been treated for at least 3 months with one of the following regimens: prednisone (P) combined with MTX (dosage: 10-15 mg/m^2 per week), with azathioprine (AZA, A, dosage: 1-1.5 mg/kg per day), or with cyclosporin A (CsA, Cs, dosage: 3-5 mg/kg per day). According to their responses to the previous treatment, the patients were divided into a corticosteroid-dependent group (n=7) and an ineffective group (n=5). The corticosteroid-dependent group consisted of those in whom treatment with combination therapy at sufficient doses led to resolution of the clinical symptoms of So-JIA (consisting mainly of fever, arthritis, rash, serositis, and lymphadenopathy) and normalization of laboratory inflammatory markers [especially the white blood cell count (WBC), erythrocyte sedimentation rate (ESR), levels of C-reactive protein (CRP) and serum ferritin (SF)] and in whom this medicated remission was maintained for at least 6 months.[19] However, during the subsequent gradual reduction of the dose of corticosteroids in these patients, the disease rebounded (i.e., the clinical symptoms and/or abnormalities in laboratory inflammatory markers reappeared), so the therapeutic dose of corticosteroids had to be increased to regain a medicated remission. Although some patients achieved a medicated remission after changing to a different treatment strategy [such as P combined with A or Cs (P+A or P+Cs)], their illness recurred during the subsequent process of reducing the dose of corticosteroids. Four of the patients in this group had been treated with 3 different treatment regimens (P+M, P+A, and P+Cs), 2 patients had been treated with 2 different treatment regimens (P+M and P+Cs), and 1 patient had only received the (P+M) regimen. In contrast, the ineffective group consisted of those in whom treatment with adequate doses of drugs might partially or completely alleviated the symptoms but the main laboratory inflammatory markers (blood WBC, ESR, CRP, and SF) remained abnormally elevated for at least 3 months. Although the clinical symptoms and laboratory inflammatory markers improved briefly in some individuals after high-dose methylprednisolone pulse therapy (15-30 mg/kg per dose), the disease returned rapidly when the dose of prednisone was reduced to 1.5-2 mg/kg per day, with especially rapid and severe rebounding of the laboratory inflammatory markers. Three patients in this group had been treated with 2 different treatment regimens: one patient had received P+M and P+A, and two patients had received P+M and P+Cs. Of these patients, one had received a high-dose methylprednisolone pulse therapy (20 mg/kg per dose for 3 consecutive days) and another one had tried a combined regimen including etanercept (12.5 mg twice per week; weight: 42 kg) and prednisone (15 mg/day) for 3 months at another hospital; in the latter, the disease was not effectively controlled, and the patient exhibited persistent fever and abnormally high levels of laboratory inflammatory markers. The remaining 2 patients had received either P+M or P+Cs. Demographic and clinical data at baseline are shown in Table 1.

Table 1. Demographic and clinical data at baseline

Age at onset of So-JIA (y)		7.0 (±2.0)
Sex		
Female, no. of pts. (%)		5 (41.7)
Male, no. of pts. (%)		7 (58.3)
Duration of So-JIA at the beginning of the study (mon)		17.0 (±12.8)
Systemic features (defined as fever, serositis, or rash) at the beginning of the study		
No. of pts. with fever (%)		0
No. of pts. with serositis (%)		0
No. of pts. with rash (%)		2 (16.7%)
Treatment at the beginning of the study		
P+M	(no. of pts.)	2 (16.7%)
P+Cs	(no. of pts.)	6 (50%)
P+A	(no. of pts.)	4 (33.3%)
The previous treatment strategies at the beginning of the study		
P+M	(no. of pts.)	2 (16.7%)
P+Cs	(no. of pts.)	1 (8.3%)
P+M; P+Cs	(no. of pts.)	3 (25%)
P+M; P+A	(no. of pts.)	2 (16.7%)
P+M; P+A; P+Cs	(no. of pts.)	4 (33.3%)
The previous treatment strategies in corticosteroid-dependent group at the beginning of the study (n=7)		
P+M	(no. of pts.)	1 (14.3%)
P+M; P+Cs	(no. of pts.)	2 (28.6%)
P+M; P+A; P+Cs	(no. of pts.)	4 (57.1%)
The previous treatment strategies in ineffective group at the beginning of the study (n=5)		
P+M	(no. of pts.)	1 (20%)
P+Cs	(no. of pts.)	1 (20%)
P+M; P+Cs	(no. of pts.)	1 (20%)
P+M; P+A	(no. of pts.)	2 (40%)

So-JIA: systemic-onset juvenile idiopathic arthritis; pts: patients; P: prednisone; M: methotrexate; A: azathioprine; Cs: cyclosporin A.

Study design

Etanercept treatment regimen

Because the study does not include a control group, the most recent treatment regimens and drug doses were not changed when etanercept was added, but in some individuals, the therapeutic dose of corticosteroids might have been reduced appropriately in order to prevent infection, the risk of which could be increased by the combined use of etanercept. The consistency of the treatment before and after the addition of etanercept strengthens the credibility of this study. For example, if the original regimen was P+M or P+A, the regimen and therapeutic doses were maintained. However, if the original regimen included other disease modifying anti-rheumatic drugs, such as thalidomide and/or heliopar, these drugs were discontinued, so as to keep consistent in the treatment condition among all cases in this study.

Etanercept was given at a dose of 0.4 mg/kg twice weekly by subcutaneous injection; the maximum single dose was limited to 25 mg. If etanercept treatment was effective (i.e., the clinical symptoms were relieved and the laboratory inflammatory markers tended to be improved and gradually returned to normal levels), the dose of corticosteroids was gradually reduced. If the patient remained in a medicated remission when the dose of prednisone was reduced to 0.2-0.5 mg/kg per day, CsA or AZA, if used, was changed to MTX (MTX dosage: 10-15 mg/m^2/week). After 2-3 months, the etanercept treatment was reduced from twice weekly to once weekly. In patients treated with corticosteroids and MTX at the beginning of etanercept treatment, if the patient remained in a medicated remission when the dose of prednisone was reduced to 0.2-0.5 mg/kg per day, the etanercept treatment was reduced from twice weekly to once weekly without changing the doses of prednisone and MTX, and the patient was maintained on that regimen for 1-2 months. If the patient remained in a medicated remission 1-2 months after etanercept treatment was decreased to once a week, the dose of prednisone further reduced during the second or third month. The dose of prednisone was decreased to 0.1 mg/kg per day or 2.5-5 mg/day and maintained for 2-3 months. If the patient remained in a medicated remission, etanercept was discontinued and the doses of prednisone and MTX were maintained. Eventually, the prednisone was discontinued and MTX was given alone for further maintenance. If combined treatment including etanercept did not relieve the symptoms of the disease within 3 months, etanercept was discontinued.

Assessment methods

So-JIA differs significantly from other subtypes of JIA, and its clinical manifestations are characterized by extra-articular symptoms, especially systemic inflammation. Hence, in this study, fever, rash, arthritis (tender joint count and limitation of activity count), and serositis were chosen as the clinical/symptomatic indices of JIA activity, and WBC, ESR, CRP and SF as the laboratory indices of So-JIA activity. After long-term observation, we found that these laboratory inflammatory markers could reflect So-JIA activity more sensitive and precise than symptoms and those markers in other JIA subtypes. The Childhood Health Assessment Questionnaire (Argentinean validation) and Physician's Global Assessment of Disease Activity were not used in this study because they were thought to be unsuitable for the characteristics of So-JIA. In addition, the dose of corticosteroids was also used as an indicator for evaluating the effects on So-JIA.

We adopted "inactive disease" from Wallace et al,[19] which was defined as follows: no joints with active arthritis, no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA, no active uveitis, and one of laboratory inflammatory markers being normal, but we didn't use physician's

overall assessment of disease activity (because we don't think it is quiet suitable for So-JIA). We also adopted the scheme from Wallace et al[19] for dividing the clinical remission into a medicated remission and a withdrawal remission. The medicated remission refers to inactive disease for at least 6 months in children who are still under treatment, whereas the withdrawal remission refers to inactive disease for at least 12 months after the discontinuation of all medications related to So-JIA treatment.

The data collected for statistical analysis included demographic and clinical data such as gender, age, age of onset, course of the disease before treatment with etanercept, tender joint count, limitation of activity count, and general symptoms (fever, serositis, and rash), laboratory inflammatory indicators of disease activity (ESR, CRP, WBC, and SF), the doses of corticosteroids used at different time points, and the etanercept treatment schedule. During the first month of etanercept treatment, the patients were followed up every week; after 1 month, if there were no special changes in the disease, the patients were followed up monthly. Other information included the occurrence of relapse during the treatment period, the side-effects of drugs, and whether the patient gave up the treatment and the reason.

Kimura et al[20] suggested that the best measurement of efficacy is the percent decrease in each index relative to the baseline. In the present study, the overall efficacy of etanercept was evaluated by the mean values of the percent decreases in the indices: ≥70%: excellent; 50-70%: good; 30-50%: fair; and reduced by <30%: poor. Currently, the relapse or recurrence of So-JIA has not yet been defined.[3] We defined relapse as a systemic symptom of active disease and/or an abnormality of laboratory inflammatory indices according to the points of view from others.[20] The abnormality of one of the indices (fever, rash, arthritis, serositis, WBC, ESR, CRP and SF) with exclusion of other possible causes (especially infection) was considered as no remission or relapse.

Results

Of the 12 patients, 2 discontinued etanercept treatment and 10 completed the treatment. The 7 patients in the corticosteroid-dependent group had a medicated remission before etanercept treatment but experienced relapse in the process of corticosteroid reduction after the dose of prednisone was reduced to a certain level. Under such situations, infection was excluded and the original therapy was maintained for 1-2 weeks until the relapse could be confirmed; then, etanercept therapy was instituted. In these patients, 1 discontinued etanercept treatment because of a systemic allergic skin rash after the first injection of etanercept (the patient had previously been treated with P+M, P+A, and P+Cs), and the remaining 6 patients completed etanercept therapy. In the ineffective group, 1 patient treated with P+A and etanercept, discontinued the etanercept therapy after 2 months because there was no improvement, and the patient's parents asked to stop etanercept treatment; however, the remaining 4 patients completed etanercept therapy. Among them, 1 patient had been treated with etanercept (12.5 mg twice per week) and prednisone (15 mg/day; weight: 42 kg) at another hospital for 3 months before admission to our hospital, but the treatment was ineffective and discontinued for nearly 6 months before the present etanercept treatment. Another patient had received one course of high-dose methylprednisolone pulse therapy (methylprednisolone was administered at a dose of 1 g once per day for 3 consecutive days, then reduced to 5 mg/kg per day administered in 2 intravenous infusions; weight: 45 kg) and had exhibited improvement in symptoms but no marked improvement in laboratory inflammatory indices. Both patients had good results after treatment with P+Cs in combination with etanercept.

After etanercept treatment, the results of the 10 patients were observed. Clinically, the tender joint count decreased by 67% after 1 month of etanercept treatment and decreased to 0 after 2 months of etanercept treatment. Laboratory examination revealed that the levels of WBC, ESR, CRP and SF decreased by 24%, 71%, 67%, and 61%, respectively after 1 month of etanercept treatment. It took approximately 2 months (range: 2 weeks to 3 months) for the mean CRP level to decrease to the normal range (an 82% decline), 3 months (range: 4 weeks to 9 months) for the mean ESR value to decrease to the normal range (a 74% decline), and 6 months (range: from 3 weeks to 9 months) for the mean SF level to decrease to the normal range (a 96% decline). Because corticosteroid can increase WBC, and WBC also normally changed with age (reference range: $4.0\text{-}12.0\times10^9$/L). It took 9 months for the mean WBC to decrease to the normal range (a 39% decline). Disease activity measured at baseline and follow-up visits are shown in Table 2.

The mean therapeutic dose of prednisone at baseline for all the patients was 0.93 mg/kg per day. When etanercept therapy was discontinued, the mean therapeutic dose of prednisone was 0.22 mg/kg per day, with a 76% decline. In the corticosteroid-dependent group, the mean therapeutic dose of prednisone at baseline was 0.64 mg/kg per day, and when etanercept therapy was discontinued, it was 0.18 mg/kg per day, with a 72% decline. In the ineffective group, the mean therapeutic dose of prednisone at baseline was 1.34 mg/kg per day, and after the stop of etanercept

Table 2. Disease activity measures at baseline and follow-up visits

Variables	Base-line	Mon 1 (%)	Mon 2 (%)	Mon 3 (%)	Mon 6 (%)	Mon 9 (%)	Mon 12 (%)	Mon 18 (%)
No. of patients at follow-up	12	12	10	10	10	10	10	10
No. of active joints (improvement)	9	3 (67)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)
No. of limited joints (improvement)	2	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)
No. of pts. with rash (improvement)	2	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)
WBC ($\times 10^9$/L) (improvement)	18.53±2.46	14.09±1.30 (24)	13.69±1.59 (28)	13.13±1.36 (31)	12.47±0.76 (33)	11.28±0.74 (39)	9.83±0.88 (47)	8.22±1.05 (56)
CRP (mg/L) (improvement)	92.83±35.75	30.55±18.68 (67)	20.72±16.22 (82)	12.72±16.69 (92)	4.30±4.95 (95)	<1 (99)	<1 (99)	<1 (99)
ESR (mm/h) (improvement)	87.58±29.45	25.09±17.84 (71)	20.91±17.29 (81)	18.00±15.04 (74)	9.80±5.55 (89)	9.20±7.27 (89)	9.60±6.22 (89)	9.70±3.34 (89)
Ferritin (mg/L) (improvement)	3039.17±1158.42	1172.45±1070.84 (61)	866.10±1082.57 (82)	560.90±1108.15 (93)	130.40±43.06 (96)	90.20±31.79 (97)	3.20±27.66 (97)	65.90±12.17 (98)
Patients who withdrew (cumulative)	0	1	2	2	2	2	2	2

pts: patients; WBC: white blood cell count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. Values are expressed as medians (percent improvement is in parentheses).

Table 3. Dose of prednisone at baseline and discontinuation of etanercept

Groups	Baseline	Discontinuation of etanercept (%)
All patients (*n*)	12	10
Prednisone dose [(mg/kg)/d] (improvement)	0.93±0.48	0.22±0.07 (76)
The corticosteroid-dependent group (*n*)	7	6
Prednisone dose [(mg/kg)/d] (improvement)	0.64±0.19	0.18±0.01 (72)
The ineffective group (*n*)	5	4
Prednisone dose [(mg/kg)/d] (improvement)	1.34±0.32	0.27±0.08 (80)

Values are expressed as medians (percent improvement is in parentheses).

therapy, it decreased to 0.27 mg/kg per day, with an 80% decline. Doses of prednisone used at baseline and discontinuation of etanercept are shown in Table 3.

The mean duration of etanercept treatment was 14.4 months (range: 12 months to 18 months). All the 10 children discontinued etanercept therapy, and the mean duration of follow-up after the discontinuation of etanercept therapy was 8.6 months (range: 1 month to 18 months). In the 10 patients who completed etanercept therapy, 3 stopped the use of prednisone, and the time after the discontinuation of corticosteroid ranges from 5 to 13 months. Currently, these patients are given only MTX (10-15 mg/m^2 per week) for maintenance treatment. The remaining 7 patients are being treated with P+M therapy. At present, all of the 10 patients who completed etanercept therapy are in a medicated remission, and no relapse has occurred.

Discussion

The treatment of So-JIA is challenging. More than 80% of So-JIA cases have been reported to demonstrate a prolonged recurrent process or chronic process.[3] In more than 50% of the patients with So-JIA, the prognosis was poor, and high doses of corticosteroid were required.[3,21,22] In the present study, we investigated the treatment of patients with refractory So-JIA, who were classified into two groups, corticosteroid-dependent and treatment-ineffective.

In this study, 7 corticosteroid-dependent and 5 treatment-ineffective patients with So-JIA were treated with etanercept combination therapy. One month after the etanercept combination therapy, 10 patients showed relief of symptoms, and more importantly, their laboratory inflammatory indices decreased significantly to normal levels. The other 2 patients discontinued etanercept combination therapy because of either allergy or poor response to the therapy. Therefore, this strategy is of revelatory significance. However, a further study with a larger sample size or a multi-center study should be performed to confirm our results.

Although the effect of etanercept on So-JIA has always been controversial,[10] the key issues might lie in the realization of So-JIA as well as in cognitive bias related to the expectations of its therapeutic effect. Because of the heterogeneity of So-JIA, patients with less severe disease may achieve a medicated remission after NSAIDs therapy alone or in combination with low-dose corticosteroid, whereas severe So-JIA patients may require immunosuppressive agents in combination with moderate-to-large doses of corticosteroids. Worst of all, in some patients the disease cannot be controlled, but can progress to life-threatening MAS.[3] So-JIA accounts for 85% of the patients with severe and refractory JIA who require stem cell transplantation.[8] Therefore, pediatric rheumatologists should concentrate

on how to control the disease as quickly as possible and how to use a low-dose of corticosteroids to maintain a medicated remission for the rehabilitation and development of children with So-JIA. Because of the heterogeneity of So-JIA, anakinra was reported to be only effective in 40% of the patients with So-JIA. Although the remaining patients experienced improvement in systemic symptoms, anakinra failed to control the inflammation of the joints and the whole body, and had to be discontinued or used in combination with second-line drugs and corticosteroids.[23] Therefore, So-JIA could be subdivided into 2 types according to the response to anakinra, which also supports the hypothesis of So-JIA heterogeneity.[2,23]

We found another interesting phenomenon in this study. A patient in the ineffective group (weight: 42 kg) had been treated with etanercept and prednisone for 3 months in another hospital, but the treatment was ineffective. After being transferred to our hospital, the patient was treated with P (60 mg/day)+CsA (200 mg/day)+hydroxychloroquine (0.2 mg/day) for 6 months but still showed no improvement. We thus switched to the strategy of combining P+Cs with etanercept. Before the beginning of etanercept therapy, we reduced the dose of prednisone from 60 mg/day to 45 mg/day for one week in order to reduce the side-effects of corticosteroids. This resulted in a rapid and strong curative effect immediately after the addition of etanercept, and the patient achieved a medicated remission. It is worth further investigating why the same individual had different responses to the twice etanercept treatments.

Additionally, the rate of remission reached 83% after the use of etanercept in combination strategies in our study. The 10 patients are receiving P+M therapy instead of etanercept therapy at present. Among them, 3 patients (25% of the total) are treated with MTX alone instead of prednisone. Kimura et al[20] reported that etanercept was effective for the treatment of 60% of patients with So-JIA, which is lower than the rate in our study. Clinical studies showed that P+M was the most frequently used baseline treatment strategy, but immunosuppressive drugs were rarely used. For example, Kimura et al[20] reported that P+Cs or P+cyclophosphamide as the baseline treatment strategy was used in only 36.5% of 82 patients with So-JIA. However, P+Cs or P+A was used in about 83.3% of the patients in our study, which explains the high effectiveness of etanercept combination therapy. Further in the treatment of So-JIA, especially refractory So-JIA, a strong multi-drug combination strategy targeting different inflammatory cytokines should be implemented to rapidly control the disease.

In addition, the most common adverse events reported were injection site reactions and infections after treatment with etanercept.[24,25] Murdaca et al[26] considered that irritative reactions resolve spontaneously over time and require neither discontinuation of the treatment nor particular diagnostic procedures. And antibiotics can control most of infections after treatment with etanercept. In our study, among the 12 patients but 1 discontinued etanercept treatment owing to a systemic allergic skin rash after the first injection of etanercept, no any adverse events occurred.

In summary, So-JIA is a highly heterogeneous disease, and its pathogenesis remains unclear, which prevents the selection of individualized treatment measures. Since no currently available drug or therapy is effective for patients with So-JIA, different combinations of drugs should be tried according to the clinical characteristics and responses of different individuals. Although etanercept may not be the first choice of treatment for So-JIA, it is a good choice for combination therapy strategies. At least, etanercept is an important and valid corticosteroid-sparing agent for the treatment of refractory So-JIA, especially in those countries where anakinra and tocilizumab have not been allowed to apply for pediatric patients.

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