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Original Article

Clinically inactive disease status with tocilizumab every 4 weeks in refractory systemic-onset juvenile idiopathic arthritis

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Abstract: Objective: Tocilizumab, an anti-IL-6 receptor antibody, was shown efficacious and safe in persistent systemic-onset juvenile idiopathic arthritis (SoJIA) when infused every 2 weeks, which generated financial burdens in developing countries. This study is to evaluate the curative effects of tocilizumab every 4 weeks (8 mg/kg) in the treatment of refractory SoJIA. Methods: This prospective intervention study was conducted for 1.5 years. The refractory SoJIA patients with 1-year and more illness courses were treated with tocilizumab every 4 weeks (8 mg/kg/dose). We assessed the effects of tocilizumab on clinical symptoms, inflammatory indicators, number of patients achieving the Wallace criteria for inactive disease, and the corticosteroids dosage before each infusion. Adverse events were reported throughout the treatment process. Continuous variables were compared using the Mann-Whitney U test. Results: All clinical symptoms of 12 patients disappeared except fevers in 2 patients after 3 infusions. Inflammatory indicators all declined gradually to normal levels. Percentage of patients meeting the Wallace criteria increased from 8% at baseline to 100% after 4 doses. The prednisone dosage significantly reduced after 5 infusions. The 2 patients not attaining inactive disease status were precisely who discontinued cyclosporine immediately after the first tocilizumab. All adverse events disappeared when we stopped tocilizumab and gave symptomatic treatments. Conclusions: We concluded that 8 mg/kg every 4 weeks was a suitable dosage for tocilizumab in refractory SoJIA in developing countries, based on effectiveness, safety, and financial factors. Simultaneously administered disease modifying anti-rheumatic drugs (DMARDs) should be reduced gradually based on the dose-dependent half-life of tocilizumab.

Keywords: Systemic-onset juvenile idiopathic arthritis (SoJIA), interleukin 6 (IL-6), tocilizumab, wallace criteria for inactive disease, prospective intervention study

Introduction

Systemic-onset juvenile idiopathic arthritis (SoJIA), manifested by chronic arthritis, systemic manifestations (quotidian fever, rash, hepatosplenomegaly, lymphadenopathy, and serositis), and obviously elevated inflammatory markers, is the most severe subtype of JIA [1]. A number of patients have an unremitting course of spiking fever and chronic arthritis; some children even progress to macrophage activation syndrome (MAS) [2, 3]. Therefore, effective and tolerable treatments are needed. However, disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) and leflunomide (LEF), and tumor necrosis factor α (TNF-α) inhibitors have limited efficacy [4, 5]. Besides, long-term use of systemic corticosteroids and DMARDs leads to various side effects. Therefore, the treatment for SoJIA remains challenging.

In SoJIA, increased interleukin 6 (IL-6) and IL-6 receptor in serum and synovium play a part as inflammatory mediators, and are related to many clinical and laboratory features [6, 7]. Tocilizumab is a recombinant, humanized, anti-human IL-6 receptor monoclonal antibody, which could block soluble and membrane-bound receptors. There have been double-

blind, placebo-controlled, randomized phase III trials showing that tocilizumab is efficacious and safe in persistent SoJIA [8, 9]. The United States Food and Drug Administration (FDA) has approved tocilizumab for the treatment of active SoJIA in patients of 2 years and older. The recommended dosage is 12 mg/kg for patients weighing less than 30 kg and 8 mg/kg for those more than 30 kg intravenously every 2 weeks. In Japen, tocilizumab is also approved for the treatment of SoJIA, and the recommended dose is 8 mg/kg intravenously at 2-week intervals.

However, in some developing countries like China, a number of families of SoJIA patients could not afford the huge expenses in consideration of the high price of tocilizumab and the fact that this drug was not covered by insurance. The aim of this study is to evaluate the curative effects of tocilizumab every 4 weeks for the treatment of refractory SoJIA, which could obviously reduce the financial costs.

Methods

Patients

This prospective intervention study was conducted in the Department of Pediatrics in Peking Union Medical College Hospital (PUMCH) from May 1st 2014 to October 30th 2015 (1.5 years). The diagnosis of SoJIA was established according to the International League of Association for Rheumatology (ILAR) diagnostic criteria [1]. The patients with refractory SoJIA, who experienced relapses and persistent inflammation, but whose conditions could not be sufficiently controlled by glucocorticoids, immunosuppressants, and even TNF-α inhibitors, were given tocilizumab. Those were also included, who suffered from great side effects of multiple medications even if their conditions were stable. The patients whose illness courses were less than 1 year, or who were being complicated with MAS, were excluded. Demographics, clinical and laboratory data, and medications were collected.

Treatment and assessments

Tocilizumab was administered intravenously every 4 weeks (8 mg/kg of body weight per dose) for 6 doses, and the intervals between dosing were extended to 6-8 weeks from the 7th infusion if this medication had good effects and the conditions were stable. We defined that the first tocilizumab was given at 0 week (the second dose given at 4th week, and so on), and patients were followed up from the first to the last infusions. Treatment plans of corticosteroids and DMARDs were adjusted based on their disease activities. This study was approved by the Ethic Committee of PUMCH, Peking Union Medical College, Chinese Academy of Medical Sciences. Written informed consent was obtained from the participants and their parents.

We assessed the effect of tocilizumab on patients' clinical conditions before each dose from 0 week to 20th week (when the 6th tocilizumab was given) or to the time point when tocilizumab was withdrew for adverse events or other possible reasons: fever, rash, number of active joints, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin (Fer) levels, white blood cell (WBC) count, hemoglobin (HGB), and platelet (PLT) count. Efficacy was assessed by the proportion of patients achieving clinically inactive disease before each dose according to the preliminary Wallace criteria for inactive disease of JIA [10]. The Wallace criteria defines inactive disease of SoJIA as no joints with active arthritis, no features (fever, rash, serositis, splenomegaly, and generalized lymphadenopathy) attributable to SoJIA, normal ESR and CRP, and physicians' global assessment of disease activity indicating no disease activity [10]. The corticosteroids dosages were recorded before each infusion. Meanwhile, adverse events, such as infusion reactions, anaphylactic reaction, liver damage, infections and respiratory disorders, and so on, were reported throughout the course of the therapy process.

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges (IQR), and compared using the Mann-Whitney U test. ESR, CRP, and Fer before the 3rd infusion (at the 8th week) were compared with those at baseline (at the 0 week); WBC, HGB, and PLT before the 4th infusion (at the 12th week) were compared with those at baseline. The doses of prednisone before the 6th infusion (at the 20th week) were compared with those at baseline. In this analysis, *p* values less than 0.05 were considered as

Table 1. Demographics and baseline characteristics of the 12 patients. Values are median (IQR) unless otherwise specified

Characteristics	Values
Demographic features	
Female, n (%)	7 (58)
Age at disease onset, yrs	4 (2.9-4.8)
Age at receiving tocilizumab, yrs	9.2 (6.5-11.7)
Number of active arthritis (any time point), n (%)	8 (67)
Number of no obvious arthritis symptoms (any time point), n (%)	4 (33)
MAS before tocilizumab administration (any time point), n (%)	2 (17)
Previous biologics, n (%)	4 (33)
Baseline features	
SoJIA related systemic symptoms, n (%)	9 (75)
SoJIA related arthritis, n (%)	5 (42)
Heart involvement, n (%)	1 (8)
Interstitial lung disease, n (%)	1 (8)
Concomitant glucocorticoids, n (%)	12 (100)
Concomitant DMARDs, n (%)	12 (100)
Concomitant CsA, n (%)	6[++] (50)
Concomitant FK506, n (%)	1[+] (8)
Concomitant MTX, n (%)	1 (8)
Concomitant LEF, n (%)	1[+] (8)
Concomitant CsA + MTX, n (%)	1 (8)
Concomitant CsA + LEF, n (%)	1[+++] (8)
Concomitant MTX + LEF, n (%)	1 (8)

[+]The patients also took hydroxychloroquine (HCQ) simultaneously. [++]One of the patients also took HCQ simultaneously. [+++]The patient was also given HCQ and tripterygium wilfordii simultaneously. CsA, cyclosporine; DMARDs, disease modifying anti-rheumatic drugs; FK506, tacrolimus; IQR, interquartile ranges; LEF, leflunomide; MAS, macrophage activation syndrome; MTX, methotrexate; SoJIA, systemic-onset juvenile idiopathic arthritis.

statistically significant. The software SPSS version 19.0 was used for data analysis.

Results

Study population

Demographic features, clinical manifestations, and medications (corticosteroids and DMARDs) at baseline were shown in **Table 1**. Clinical symptoms, laboratory indicators, and the doses of prednisone at baseline are shown in **Table 2**, which also showed tocilizumab treatment schedules. We evaluated 12 patients (5 boys, 7 girls) with a median age at disease onset and at tocilizumab treatment of 4 years (IQR 2.9-4.8) and 9.2 years (IQR 6.5-11.7) respectively. All patients experienced repeatedly systemic features (particularly fever and rash), but 4 patients had no obvious arthritis features in the course of disease. Two patients had been complicated with MAS before receiving tocilizumab. Twelve patients were all refractory SoJIA, who were treated by kinds of DMARDs and corticosteroids; 4 patients had received anti TNF-α agent.

At baseline, there were 9, 3, 5, 1, and 1 patients having fever, rash, active arthritis, heart disease, and interstitial lung disease respectively. Inflammatory indicators of disease activity (ESR, CRP, Fer, WBC, and PLT) all increased. All 12 patients received glucocorticoids and DMARDs treatments simultaneously, and the dose of prednisone was 0.77 mg/kg/day (IQR 0.36-1.21). Cyclosporine (CsA) was the most common DMARD; other DMARDs included tacrolimus (FK506), MTX, and LEF. Three patients even had two or more DMARDs, one of whom received 4 DMARDs and achieved clinically inactive disease.

Tocilizumab treatment schedules

Among 12 patients at follow-up, only 5 patients received 6 and more doses of tocilizumab every 4 weeks; 3 patients were given 4 doses at the study endpoint. Four patients withdrew tocilizumab because of great side effects or financial burden: 2 of them received 2 doses, and the other 2 were given 3 doses. One patient withdrew after 6 doses for financial burden; the other 4 patients extended the intervals between doses to 6-8 weeks. One patient suffered from disease flare when infused every 8 weeks, who withdrew after 8 doses (altogether). The second one experienced increased ESR and CRP when infused every 8 weeks, who could achieve inactive disease status every 6-7

Table 2. Disease activity measures and prednisone dosage at baseline and follow-up visits before each tocilizumab. Values are median (IQR) unless otherwise specified

Characteristics	Baseline (0th week)	4th week	8th week	12th week	16th week	20th week
Patients at follow-up, n	12	12	10	8	5	5‡‡
Fever, n (%)	9 (75)	5 (42)	2 (20)	2† (25)	0	0
Rash, n (%)	3 (25)	2 (17)	0	0	0	0
Number of active joints, n (%)	5 (42)	3 (25)	1 (10)	0	0	0
ESR (mm/h)	69 (34-83)	16 (6.8-24.5)	5 (3.3-9.5)	2.5 (1.8-7)	2 (1-2)	2 (1-2)
CRP (mg/L)	84.5 (44-95.3)	20.5 (3.8-88.3)	7 (1.5-14)	1 (1-8.3)	1 (1-1)	1 (1-1)
Fer (ng/ml)	1529 (182-2033)	131 (41-397.5)	36 (24.5-130)	38 (14-50.5)	35 (13-60)	48 (33-92)
WBC ($\times 10^9$/L)	16.15 (14.44-17.85)	15.13 (9.67-18.63)	10.61 (7.31-17.25)	8.18 (5.88-11.34)	7.71 (6-8.83)	7.53 (6.02-7.94)
HGB (g/L)	112.5 (104.5-125.5)	129 (117-133)	133 (128.8-136)	135.5 (127.3-140.5)	137 (132-143)	145 (140-148)
PLT ($\times 10^9$/L)	387.5 (323.8-539.5)	325 (255.8-381.5)	230 (198-404.5)	279.5 (207.8-321.5)	229 (212-262)	217 (215-241)
Patients who achieved inactive disease, n (%)	1‡‡‡ (8)	3 (25)	7 (70)	6 (75)	5 (100)	5 (100)
Prednisone dosage, mg/kg of body weight	0.77 (0.36-1.21)	0.61 (0.35-0.8)	0.52 (0.32-0.58)	0.46 (0.22-0.63)	0.38 (0.14-0.58)	0.29 (0.1-0.38)
Patients who withdrew, n	0	0	2*	2**	0	0

†These 2 patients received 4 doses of tocilizumab, but still suffered from fevers and increased inflammatory indicators preceding the 4th dose. ‡‡These 5 patients received 6 doses of tolicizumab every 4 weeks. ‡‡‡The patient achieved inactive disease status before the use of tolicizumab on condition that she received prednisone (25 mg/d) and 4 disease modifying anti-rheumatic drugs (DMARDs), which produced many side effects. *Two patients withdrew tocilizumab after 2 doses: one suffered from aminotransferase increase; one experienced allergic reaction (urticaria). **Two patients withdrew tocilizumab after 3 doses: one suffered from aminotransferase increase; one experienced financial difficulty. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Fer, ferritin; HGB, hemoglobin; IQR, interquartile ranges; PLT, platelet count; WBC, white blood cell.

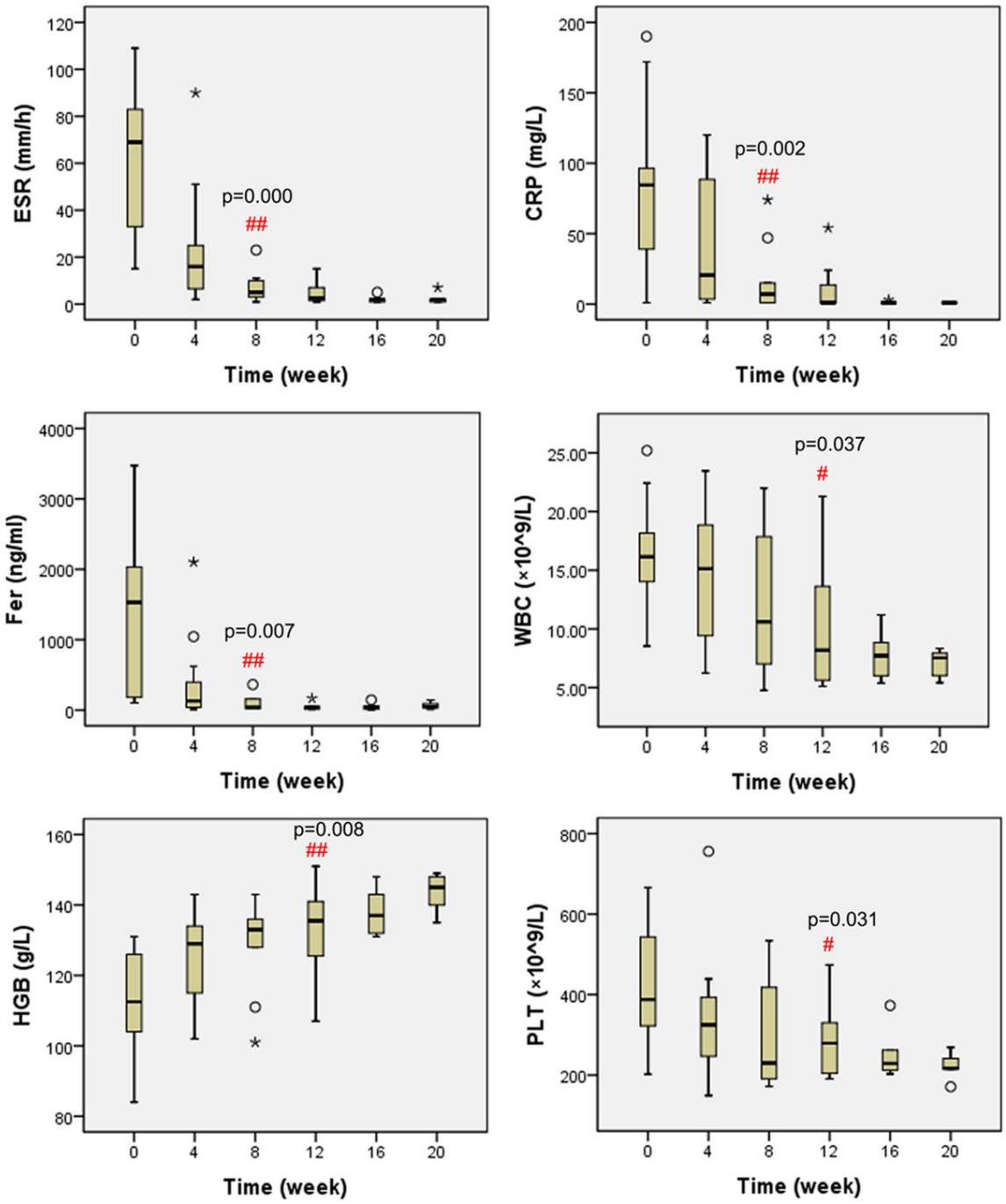

Figure 1. Laboratory inflammatory indicators of disease activity (ESR, CRP, Fer, WBC, HGB, and PLT) at baseline and follow-up visits before each tocilizumab. #P<0.05, ##P<0.01 compared with the inflammatory indicators respectively at baseline (before the first tolicizumab). CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Fer, ferritin; HGB, hemoglobin; PLT, platelet count; WBC, white blood cell.

weeks (13 doses at the study endpoint). Another 2 patients could still keep clinically inactive when infusion intervals were extended to 6 weeks: one of them withdrew for financial burden after 7 doses; the other could still keep stable when the intervals were prolonged to 7-8 weeks gradually (10 doses at the study endpoint).

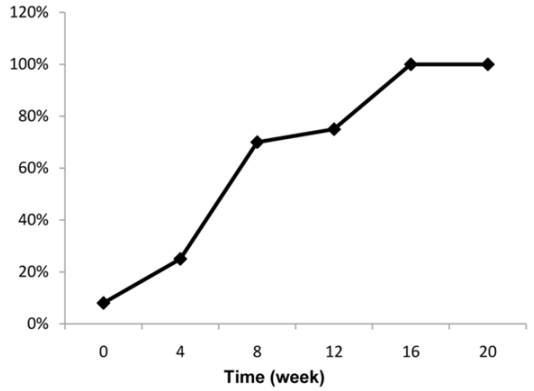

Figure 2. Percentage of patients who achieved the criteria of inactive disease at baseline and follow-up visits before each tocilizumab. The effects of the last dose of tolicizumab were not evaluated here.

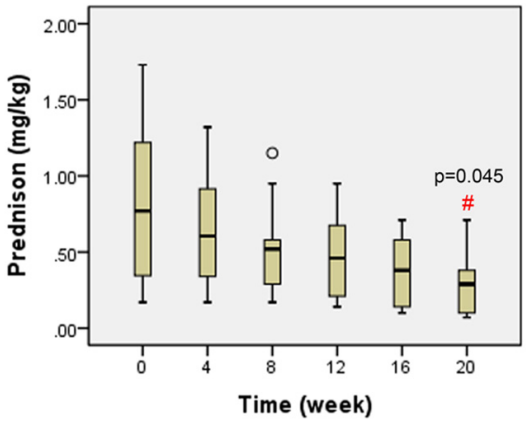

Figure 3. Doses of prednisone (mg/kg/day) at baseline and follow-up visits before each tocilizumab. #P<0.05 compared with the prednisone dosage at baseline (before the first tolicizumab).

Efficacy

Clinical symptoms, laboratory indicators, number of patients achieving inactive disease, and the doses of prednisone at follow-up visits before each tocilizumab were shown in **Table 2**. Proportion of patients who suffered from fever, rash, or active arthritis all fell gradually when tocilizumab was given. All features disappeared except fevers in 2 patients after 3 doses. As shown in **Figure 1**, inflammatory indicators including ESR, CRP, Fer, WBC, and PLT all declined gradually to normal levels, and HGB increased gradually. After 2 tocilizumab infusions, the changes of ESR, CRP, and Fer were statistically significant (P<0.01, P<0.01, and P<0.01 respectively); after 3 infusions, WBC, HGB, and PLT were significantly changed (P<0.05, P<0.01, and P<0.05 respectively). In **Figure 2**, percentage of patients who met the criteria for inactive disease increased from 8% at baseline to 100% after 4 doses. There were 70% and 75% of patients achieving inactive disease after 2 and 3 infusions respectively, and the proportion remained 100% after 5 doses.

Tocilizumab infusions could help the dosage reduction of systemic glucocorticoids. As shown in **Figure 3**, the doses of prednisone were decreased gradually from 0.77 mg/kg/day (IQR 0.36-1.21) at baseline to 0.29 mg/kg/day (IQR 0.1-0.38) after 5 infusions, which was statistically significant (P<0.05). Among the 10 patients given more than 2 tocilizumab infusions, 2 patients receiving 4 infusions did not attain clinically inactive disease after 3 doses. One patient stopped CsA immediately after the first tocilizumab and experienced very fast prednisone reduction, who received MTX after the second infusion. The other stopped CsA immediately after the first dose, who still received MTX. They changed for the better after each infusion both in clinical symptoms and laboratory indicators, but could only keep clinically stable for 3 weeks. In general, their inflammatory indicators decreased gradually at follow-up visits. However, fevers and slightly increased inflammatory indicators always happened about 1 week before each infusion.

Safety

Upper respiratory tract infections (URTI) were the most common adverse events in our study, which were not more frequent than those when tocilizumab was not given. URTI were not so serious that symptomatic treatments and sometimes antibiotics could cure. Other recorded events were aminotransferase increase and anaphylaxis (urticaria), because of which 3 patients withdrew tocilizumab. They returned to normal when tocilizumab was stopped and symptomatic treatments were given.

Discussion

As we all know, patients with SoJIA are variable in disease course and severity, which range from a benign monocyclic course to a relapsing and persistent course with severe articular and

extra-articular damage [11]. More than 50% of SoJIA patients develop severely persistent inflammation, who need continuous application of high-dose corticosteroids and prolonged immunosuppressants [12]. To date, only 2 kind of biologicals, anti-IL-1 agents (anakinra, canakinumab, and rilonacept) and anti-IL-6 agents (tocilizumab), have been demonstrated effective in the treatment of SoJIA [8, 13-15]. Improvement in SoJIA course and achievement of the inactive disease status allow the tapering and even discontinuation of corticosteroids and DMARDs. Unfortunately, in some countries such as mainland China, the IL-1 blockers are still unavailable and tocilizumab is the only option of biologicals in the treatment of refractory SoJIA. We attempted to lighten the financial burden of patients in developing countries by means of lower dosage or longer dosage intervals. To our knowledge, this study is the first prospective intervention study about the effectiveness of tocilizumab in the treatment of refractory SoJIA every 4 weeks (8 mg/kg).

We chose 8 mg/kg of body weight every 4 weeks as the dose of tocilizumab in refractory SoJIA mainly for the successful experience of tocilizumab in the treatment of refractory adult-onset Still's disease (8 mg/kg every 4 weeks in 22 patients) [16]. What is more, in Japen, another east Asian country, 8 mg/kg (not 12 mg/kg) is chosen for SoJIA patients of all body weights [9]. There has been one study that evaluated the effectiveness of tocilizumab in SoJIA every 4 weeks, but this schedule was only applied to mild SoJIA (lower disease activity group) [17]. Our study paid attention to patients with refractory SoJIA, 70% of which achieved inactive disease after 2 tocilizumab infusions every 4 weeks, and the proportion increased to 100% after 4 infusions. Furthermore, no serious adverse events were reported during the follow-up visits.

It is known that achievement of the inactive disease status allows the tapering of glucocorticoid and DMARDs. However, we should clarify a fact that DMARDs should be reduced step by step after tocilizumab infusions, in consideration of the fact that the half-life of tocilizumab was dose-dependent and prolonged when the number of doses increased through repetitive treatments [18]. Otherwise, the clinical symptoms and/or inflammatory indicators of SoJIA might flare less than 4 weeks. The results of our study demonstrated this point of view: the only 2 patients who did not attain clinically inactive disease were precisely who discontinued CsA immediately after the first tocilizumab infusion. Another viewpoint worth being noticed was that the dosage intervals of tocilizumab might be extended to 6-8 weeks after 6 infusions. However, this process should be realized step by step in order to ensure the inactive disease status.

This was a prospective intervention study that did not include control groups. After all, nearly all the refractory SoJIA patients suffered from persistent systemic inflammation and/or adverse drug reactions, and it is against ethics that some refractory SoJIA patients were grouped as controls and did not receive tocilizumab (the only probably effective therapy in China). Comparing the effects of different usage of tocilizumab (once every 4 weeks and every 2 weeks) was not the key point of our study. What is more, we did have a relatively small sample size. Therefore, we just evaluated the effectiveness of tocilizumab every 4 weeks (8 mg/kg) in the treatment of refractory SoJIA patients, and we only conclude whether this usage was suitable in consideration of effectiveness and financial factors, but not whether this was the best usage.

In the statistical analysis, we compared ESR, CPR, and Fer after 2 tocilizumab infusions with those at baseline, WBC, HGB, and PLT after 3 infusions, and the doses of prednisone after 5 infusions. In fact, the choice of different time point was just based on our clinical observations and clinical experience: inflammatory indicators often changed faster than blood routine indicators after tocilizumab infusions, and the doses of prednisone changed more slowly. We had described the change trend of these indicators, and we just wanted to show that the changes were statistically significant. As we all know, multiple comparisons would increase the odds of statistical mistakes, therefore, we made only one comparison for each variable. We proposed several separately statistical hypotheses and verified them. In fact, if statistical analysis was given, there was the possibility that ESR and Fer were significantly decreased after one tocilizumab in **Figure 1**, and that HGB was significantly increased after 2 doses.

Our study is a single-center study about refractory SoJIA, and the majority of patients have more severe fevers than arthritis at baseline. There is no doubt that clinical symptoms, including fever, rash, and active arthritis, could all recover as soon as tocilizumab was given [8, 9]. However, the improvement of active joints was not shown as fully as fever was in our study. The other limitation of our study is that the effects of the last dose of tocilizumab were not evaluated. We assessed patients' clinical symptoms, laboratory indicators, percentile of patients achieving the status of inactive disease, and the prednisone dosage before each tocilizumab, all of which were impacts of the previous infusions. We did not evaluate patients in this study once they discontinued infusions, because they were not at follow-up visits any more.

We have shown that the dose of prednisone tapered when tocilizumab was given. However, we did not evaluate the reduction or discontinuation of DMARDs, which was another weakness of our study. The follow-up period was relatively not long enough to obviously reduce the dose of DMARDs. The SoJIA patients were only able to achieve the tapering of glucocorticoid, or discontinuation of the weaker DMARDs when more than two categories were given, or occasionally slight reduction of DMARDs. What is more, some patients did not achieve inactive disease when CsA was stopped after the first tocilizumab infusion. Therefore, it is inappropriate to estimate the tempering of DMARDs in our study. A multi-center study with a larger simple size and a longer follow-up period need to be performed to assess more comprehensively the reduction or discontinuation of DMARDs when tocilizumab was given every 4 weeks (8 mg/kg) in refractory SoJIA.

Conclusions

In our study, we concluded that 8 mg/kg every 4 weeks was a suitable dosage and usage for tocilizumab in the treatment of refractory SoJIA patients in the developing countries, based on the effectiveness, safety, and financial factors. DMARDs should be reduced step by step after tocilizumab was administered in consideration of the dose-dependent and prolonged half-life of tocilizumab through repetitive infusions.

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Disclosure of conflict of interest

None.

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