Disease activity score in 28 joints at 3 months after the initiation of biologic agent can be a predictive target for switching to the second biologic agent in patients with polyarticular juvenile idiopathic arthritis

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Abstract

Objective: To clarify polyarticular juvenile idiopathic arthritis (pJIA) patients who failed to maintain prolonged remission with the first biologic agent.

Methods: Fourteen pJIA patients were observed for 47.5 months (median) after initiating the first biologic agent.

Results: Eight maintained sustained clinical remission (median 47 months) with the first biologic agents, while the six switched to the second one due to lack of efficacy, thereafter. Receiver operating characteristic (ROC) analysis revealed that disease activity score in 28 joints (DAS28) of 2.37 at 3 months could distinguish between the two patient groups (p = 0.001).

Conclusion: pJIA patients with DAS28 ≥ 2.37 at 3 months of the initial biologic therapy may be considered to switch to the second biologics.

Keywords
Biologic agent, DAS28, Juvenile idiopathic arthritis, Polyarticular-type, Switching

Introduction

Juvenile idiopathic arthritis (JIA; onset prior to age 16 years, present with joint pain, stiffness and swelling that persists for longer than 6 weeks) is the most common rheumatic disease in children and the prevalence rate worldwide is up to 1 in 1000 children [1]. The International League Against Rheumatism (ILAR) categorizes JIA into seven subsets according to clinical and laboratory features [2]. Chronic childhood arthritis that affects more than four joints during the first six months of the disease is defined as polyarticular JIA (pJIA).

Recent major advances in treatment, especially the advent of biologic agent, have greatly improved the outcome for children with JIA. Inactive disease and remission are now the therapeutic targets for JIA, and biologic agents are considered to be important drugs for this purpose [3,4].

Although biologic agents have improved disease activity, up to 75% to 85% of patients show significant responses to these biologic agents [4,5]. Therefore, some patients have to change to the second biologic agent due to lack of an effect or adverse events. For these patients, the switch to another biologic agent can be beneficial [6,7]. However, to the best of our knowledge, there is no reliable criterion for deciding when or how to switch to the second biologic agent. The aim of this pilot study was to clarify the differences between pJIA patients who could or could not maintain clinical remission with the first biologic agent in the early period of treatment.

Patients and methods

Study design

The study was designed as a retrospective observational study. The following data were obtained from the medical records of all enrolled patients: C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), number of swollen joints, number of tender joints, visual analogue score (VAS), and disease activity score in 28 joints (DAS28). The term “clinical remission” was defined so as to reflect at least a moderate response according to the EULAR response criteria every other month or to maintain DAS28 ≤ 2.6 [8]. The patients were classified into a remission group and a switching group. The remission group was defined as pJIA patients who remained in clinical remission with the first biologic agent, and the switching group was pJIA patients who received the second biologic agent because the first biologic agent was ineffective. The efficacy of biologic agent was evaluated in terms of DAS28, the number of active joints, the number of painful joints on pressure or motion. This study was approved by the Kagoshima University Hospital Ethical Committee (No. 26-137).

Patients

A total of 14 pJIA patients (5 boys and 9 girls) who were refractory to conventional methotrexate (MTX) therapy were enrolled in this study. They fulfilled the Edmonton 2001 review
criteria of pJIA [2] and had received MTX at 10 mg/m²/weekly for more than 3 months before the initiation of the first biologic agent. Patients were evaluated clinically in follow-up examinations every month by a pediatric rheumatologist at Kagoshima University Hospital in Japan. However, 2 patients in switching group at 1 and 2 month, and 1 patient in remission group at 2 month could not be evaluated for clinical features because they were treated in other hospital at the time. We performed Welch’s t-test at each month except 3 patients who could not be evaluated at 1 and 2 month. The patients who enrolled in this study were treated with biologic agents from April 2004 to February 2014. Three patients in remission group and 3 patients in switching group were treated with NSAIDs and PSL as initial treatment, but PSL was discontinued when biologic agent was initiated.

Patients who were treated with the first biologic agent for at least 6 months were included in this study due to the failure of primary elimination. Biologic agents were considered to be ineffective and switched when the number of active joints and VAS increased for more than consecutive 2 months.

Statistical analysis

Welch’s t-test and Fisher’s exact test were used to evaluate the each characters of the 2 groups. Although 3 patients could not be evaluated at 1 and 2 month in this retrospective study, we performed Welch’s t-test at each month. To calculate the cut-off point for DAS28, Receiver Operating Characteristic (ROC) curves were computed and the respective AUC values were determined at every month after the initiation of biologic agents. AUC values ≥0.9 were considered to have outstanding classification ability [9]. Statistical analyses were performed using the statistical software R i386 version 3.0.1 (A Language and Environment for Statistical Computing, Vienna, Austria), and a p value of less than 0.05 was considered statistically significant.

Results

Characteristics of the patients at the initiation of biologic agents

The remission group (eight patients) remained in clinical remission for a median of 45.3 ± 28.6 months with the first biologic agent, while the switching group (six patients) switched to the second biologic agent at a median of 11.5 ± 18.0 months after initiation of the first biologic agent. In the remission group, four patients (50%) were treated with TCZ, three (38%) with Etanercept (ETA) and one patient (12%) with Adalimumab (ADA). In the switching group, two (33%) received ETA, two (33%) ADA, one (17%) TCZ and one (17%) Infliximab (IFX).

Six patients (75%) in the remission group and five (83%) in the switching group were RF-positive (p = 0.6), and there were no significant differences between the two groups with regard to the median age at disease onset, the median disease duration before the initiation of the first biologic agent, active joint count or the median DAS28; the only difference was found in the median duration of treatment with the first biologic agent (Table 1).

No patient in the switching group achieved DAS28 remission (<2.6) at 3 months, whereas seven patients (87.5%) in the remission group did (p = 0.005, 95%CI 2.5-Inf). (Supplementary material Figure 3).

ROC curves for DAS28 were used to determine the most appropriate cut-off values at every month after the initiation of the first biologic agent (Figure 1). With these cut-off points, we performed Fisher’s test to predict whether the patient should continue with the first biologic agent. At 3 months after the initiation of the first biologic agent, pJIA patients who did not achieve DAS28 ≥ 2.37 should have switched to the second biologic agent (sensitivity 100%, specificity 87.5%, AUC 0.963, 95%CI 2.92-Inf, OR:Inf) (Figure 2).

Regarding to other data, there is significant difference between the 2 groups in the number of active joint count at 3 month (p = 0.04) (Supplementary material Table 2). The cut-off point is only one joint and its area under the curve is 0.854 (Supplementary material Figure 4). With this cut-off point, we performed Fisher’s exact test between the two groups and there is no significant difference (p = 0.1).

Discussion

A growing body of evidence suggests that disease control in the early stage affects the long-term outcome of patients with arthritis [10]. It is important to determine what kind of “suitable” treatment should be applied in each patient in the early period [11,12]. The use of biologic agents is recommended for children with pJIA who are refractory to MTX for 3 months [13]. Previous reports on the effectiveness of biologic agents for pJIA have shown no significant difference among ETA, ADA, IFX and TCZ [14,15]. In our hospital, we treat pJIA patients with ETA at 0.4 mg/kg 2×/w (maximum 25 mg/dose), ADA at 40 mg every other week (if patient’s body weight >30 kg), IFX at 3–5 mg/kg/dose at 0, 2, 6, and 14 weeks and then every eight weeks, or TCZ at 6 mg/kg every four weeks. In the case of self-injection treatment, patients or their parents performed self-injection with their doctors at least three times to keep good adherence. Therefore, we checked their adherence and procedure again in the case of poor clinical responder.

Many studies have reported that a delay in the initiation of biologic agents can lead to a poor outcome [13,16]. However, the switching group in our study failed to continue the first biologic agent even they began to receive biologic agent sooner after onset than the remission group. The switching group might have had more progressive disease activity in the early period contrary to remission group, although there was no significant difference in DAS28 at the start of treatment with biologic agents between the two groups.

If the first biologic agent is ineffective, a switch to another biologic agent at 3 months has been recommended [13]. Compared to the ease of switching biologic agents in patients who show primary failure, it is difficult to predict patients who will become secondary failure in the early period. In our study, only one patient

| Table 1. Characteristics of pJIA patients treated with biologic agents. |
|-----------------|-----------------|-----------------|-----------------|
| Remission group | Switching group |
| Number of patients | 8 | 6 | 0.80 |
| Number of female | 4 | 5 | 0.29 |
| Number of RF positive | 6 | 5 | 0.60 |
| Disease duration from onset (month) | 22.4 ± 12.5 | 15.1 ± 12.9 | 0.17 |
| CRP | 1.78 ± 2.4 | 2.1 ± 2.3 | 0.81 |
| ESR(1h) | 35.4 ± 36.4 | 27.0 ± 21.9 | 0.60 |
| MMP-3 | 309.0 ± 222.3 | 177.5 ± 126.6 | 0.17 |
| Active joint count | 6.8 ± 3.6 | 7.8 ± 4.8 | 0.49 |
| DAS28 | 4.9 ± 0.9 | 4.9 ± 0.6 | 0.56 |
| Treatment period with the first biologic agent (month) | 49.4 ± 27.5 | 16.5 ± 16.0 | <0.05 |
| RF: rheumatoid factor, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, MMP-3: matrix metaprotease3, DAS28: disease activity score in 28 joints. |
(27%) fulfilled the criteria for high disease activity with a history of five or more joints at 3 months.

In our study, the switching group changed to the second biologic agent at a mean of 16.5 months after the initiation of treatment with the first biologic agent (range 6–18). We were unable to switch from the first biologic agent to the second biologic agent in the early period in the switching group, because those patients still had a moderate response to the first biologic agent then. However, significant difference was revealed between the two groups in the frequency of achieving DAS28 remission ($5_{2.6}$) at 3 months after the initiation of the first biologic agent ($p = 0.001$).

To concern with the number of active joint count, we did not show any statistical difference due to the small number of patient in this study. More patient numbers are needed.

For clinicians who care for patients with JIA, it is essential to choose effective and suitable treatments in the early period based on a ”target of treatment” policy. Our results suggest that pJIA patients who are treated with the first biologic agent should be evaluated at 3 months by DAS28 to assess the probability of which will keep effective. In this study, two patients out of six (33%) switched to the second biologic agent and one patient out of three (33%) switched to the third biologic agent could attain their DAS28 score were lower than 2.37 at 3 month after switching in each biologic agent. Therefore, total three out of six patients (50%) could attain their DAS28 score <2.37 at 3 month after switching to the second or third biologic agent and all of them maintained clinical remission.

Figure 1. Cut-off points, sensitivities and specificities were calculated for every month. DAS28:2.37 is the cut-off point in the remission group at 3 months after the initiation of biologic agents, and the AUC is 0.958.

Figure 2. DAS28 plots for pJIA patients for every month after the initiation of the first biologic agents. Based on the cut-off point in Figure 1, patients with DAS 28 scores below 2.37 remained in clinical remission (sensitivity 100%, specificity 87.5%). The percentage of patients with DAS28 scores below 2.37 at 3 months in the remission group was significantly higher than that in the switching group ($p = 0.001$, Fisher’s exact test).
thereafter. From these favorable results, it seems valuable to consider switching the biologic agent based on DAS 28-ESR score at 3 month after initiating the first biologic agent. However, the number of patients was too small to evaluate the efficacy of the second or third agent. Moreover, the kind of the biologic agents approved for JIA was limited. Long term follow up will be needed to evaluate the outcome of the patients treated with the second or third biologic agents after switching from the first one.

Although our study were limited by the retrospective design and small number of patients, DAS 28 remission (<2.6) at 3 months after the initiation of the first biologic agents should be considered to evaluate the efficacy of treatment.

Conclusion
Polyarticular JIA patients with DAS 28 >2.37 at 3 months after the initiation of the first biologic agents may be considered for switching the biologic agent. DAS28 at 3 months after the initiation of the first biologic agents could be a target of treatment in pJIA patients.

Conflict of interest
The authors have no conflicts of interest to declare.

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Supplementary material available online

DOI: 10.3109/14397595.2015.1083147

Polyarticular juvenile idiopathic arthritis 361