Efficacy of Methotrexate Treatment in Children with Polyarticular Juvenile Idiopathic Arthritis

Aysun A. Tekeli* and Ayse Oner

Department of Pediatric Nephrology, Dr. Sami Ulus Maternity and Children’s Education and Research Hospital, Ankara, Turkey

Abstract

Objective: This study aims to evaluate the efficacy of methotrexate (MTX) use in the treatment of patients with polyarticular Juvenile Idiopathic Arthritis (JIA).

Materials and Methods: Forty-nine patients with polyarticular JIA who didn’t respond to NSAIDs and therefore underwent the MTX treatment were analyzed retrospectively. The joint involvements were evaluated through systemic and extra-articular findings while the laboratory findings were assessed in terms of remission, deformity, and relapse rates.

Results: Twenty-eight patients with polyarticular JIA received MTX therapy. The majority of our MTX patients ages (46.4%) ranged between 8–11 years. While 18 patients were girls, 10 were boys. The most frequent joint involvements were observed in knee, ankle, wrist, and finger. Extra-articular findings were observed in 17 patients. The laboratory findings highlighted that; increase in C-reactive protein (CRP) 25 (92.5%), leukocytosis 2 (7.1%), thrombocytosis 21 (75%) and anemia 22 (78.5%) were observed in patients. The remission rate of the patients with MTX treatment at regular controls was 83.3%, the deformity rate 20.8% and the relapse rate was 45.8%.

Conclusion: MTX treatment is successful for patients with polyarthritis-induced JIA with poor prognostic factors, not having responded to NSAIDs.

Keywords: Children; Efficiency; Juvenile idiopathic arthritis; Methotrexate; Polyarticular

Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatologic disease in the childhood. JIA is a disease that varies individually and may produce benevolent results with the appropriate treatment; but may otherwise lead to an important morbidity, such as disability [1–3]. Progressed with chronic joint involvement, the disease is a systemic disease producing extra-articular findings other than arthritis; such as fever, rash, nephritis, carditis, and uveitis. The treatment of JIA, a chronic systemic disease, aims to control inflammation in acute period, to reduce complications of disease and treatment in the long term, as well as to provide normal growth and development, rehabilitation and family training [4,5]. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are the mainstay treatment of JIA patients which are used in initial treatment for many children. MTX treatment is recommended for patients who are not responding to NSAIDs, with polyarthritis and systemic onset who have poor prognostic factors [6]. MTX is a folate antagonist which inhibits cell proliferation and antibody synthesis, interleukin-1 activity and leukotriene production and is the most commonly-used drug in all JIA cases, after Naproxen sodium [7]. Polyarticular is the most common form in JIA [8]. It has been observed that MTX have serious clinical responses with patients with JIA up to 80% and lead to delay in radiological progression. Generally, the recommended dose is 10 mg/m²/week. Methotrexate is started as 0.3 mg/kg/week and can be increased up to 1 mg/kg/week. In severe cases, doses may range from 20–30 mg/m² in a week. It reduces the progression of disease and bone damage. Intramuscular use is preferred because it is less painful than subcutaneous usage. The generally preferred dose of 10 mg/m²/week is applied orally. If the weekly dose exceeds over 20 mg/m², then the parenteral route is preferred. Subcutaneous route is more effective than oral route, but the efficacy of 15 mg/m²/week is observed [9,10]. The most common side effects are increased risk of gastrointestinal toxicity, pulmonary toxicity, elevation of liver enzymes, stomatitis, leukopenia, rash, headache and lymphoproliferative malignancy [11]. Unlike steroids, it doesn’t affect the bone mineralization negatively. Liver enzymes and complete blood count tests are recommended every 4–6 weeks [12]. Folic acid supplementation appears to reduce the gastrointestinal tract and mucocutaneous side effects without altering the therapeutic effect. 1 mg/kg/day folic acid should be added to the treatment [13].

The optimal time for discontinuing the MTX treatment is unknown. A relapse is observed in approximately 50% of the patients after the treatment is finished. It is suggested that the drug may be released after a long period of recovery [14]. Another proposal for when to leave methotrexate treatment for rheumatic diseases is that the drug can be discontinued one year after the active disease [15]. When the disease and laboratory parameters are completely normalized, MTX is gradually reduced. The medicine is to be discontinued decreasing by the same dose for the first two to three months and using once in two weeks, followed by a 2.5 mg per week for a period of three to six months. In case of malnutrition, viral hepatitis and other liver diseases, obesity and in particular viral diseases such as varicella the drug should be discontinued or be replaced with another drug [16].

Methods

During the seven-year period between 2002 and 2008, clinical and laboratory features, treatment, side effects of medicines, remission, deformity and relapse rates of 49 patients who were diagnosed with polyarticular JIA and followed up at the same clinic were retrospectively evaluated. According to laboratory findings, those whose hemoglobin levels were below standard deviation two were accepted to be anemic [7]. Leucocytes and thrombocytes have been determined according to the gender and age group whether it was leukocytosis or thrombocytosis [17]. Erythrocyte sedimentation rate (ESR) > 20 mm/hour, CRP > 5 mg/L were considered to be high. Rheumatoid Factor (RF) was determined by latex agglutination method and nephelometric method [18]. Bone mineral densitometry was evaluated through the use of long bone and all joint graphs, as well as the DEXA method.

The patients were evaluated according to the poor prognostic
Side effects were observed in 33 (44%) patients due to the drugs used. Anemia occurred in 4 patients, leukopenia in 2, pancytopenia in 1 and elevation of liver enzymes were detected in two patients and the treatment was interrupted for a while. Drug dose was reduced in 1 patient having received MTX treatment because of nausea. While 24 (85.7%) of our patients used MTX regularly, 18 (85.7%) take their medication irregularly. The remission rate of the patients who received MTX treatment and came to the regular follow-up was 83.3%, the deformity rate was 20.8% and the relapse rate detected was 45.8%.

Discussion

Until now, many agents were used in the treatment of JIA, but definite treatment couldn’t be provided for the disease. In patients who didn’t respond to NSAIDs, MTX is recommended as a second option [7,19,20]. When all types of the disease were considered, the rate of girl/boy was 2/1 [21,22]. Contrary to the literature, of the 49 patients in our study, 26 (53%) were girls and 23 (47%) were boys and the rate of girls to boys was quite equal to each other. This suggests that more attention was attached to boys in our society because of cultural habits and that boys may have been brought to the reference centers much more than girls. According to previous studies, the rate of girl/boy in our study was equal to that of girls and this can be explained by the increase in socio-cultural level and taking them to advanced health institutions. There was no gender difference between two groups (p > 0.05). Although the disease may occur at any age in childhood, age distribution according to sex and sub-groups was reported [7]. The symptoms were observed in children under five years more frequently, especially between 1–3 years, and a slight increase was re-observed towards the puberty. This distribution was more obvious especially amongst girls and oligo-articular cases [23,24]. In boys, it peaks at around two and nine years. In our study, 77.5% of the patients ranged between 2–7 and 8–11 years. These results were consistent with the other studies [7,22,24] and there was no significant difference in terms of age amongst the groups (p > 0.05). RF positivity was reported as 5–25% amongst JIA patients. In our cases, RF was examined through latex fixation technique. RF (+) polyarticular group constituted 73.5% and the RF (+) group constituted 26.5% of the patients. Our results were consistent with the literature [7,17]. While 21 patients (58.3%) from the RF (+) polyarticular group received MTX treatment, 7 patients (53.8%) from the RF (-) group received the therapy. There was no significant difference between the groups regarding MTX treatment (p > 0.05).

The most frequent finding of the disease was the joint pain and swelling in the joints for JIA. Restriction of mobility may be progressed with pain or tenderness through movement and local increase of warmth and redness might be present. Arthritis was initially observed in all our patients. This type of arthritis tends to be symmetrical and any joint in the body may be involved. Smaller joints, especially proximal interphalangeal joints, metacarpophalangeal joints and wrists were characteristic of the hands. Major joint involvement knee, elbow, ankle joints were also common. The most frequently involved joints were knee 92.8%, ankle 85.7%, and wrist 67.8% and fingers 85.7%. Laboratory findings highlighted that CRP was high in 25 (92.5%), leukocytosis 2 (7.1%), thrombocytosis 21 (75%) and anemia 22 (78.5%) were present in all patients who received MTX treatment. RF positivity was observed in 7 patients (25%). According to the radiographic findings of patients who received MTX treatment, osteopenia was detected in 19 patients, swelling of soft tissue in 16, osteoporosis in 10 and reduction of joint distance in 4. Osteoporosis was detected in 16 patients (57.1%) in bone mineral densitometry.

Poor prognostic factors were observed in 13 patients receiving the treatment and in six patients who didn’t get MTX. 27 (55.1%) with polyarticular JIA patients had received treatment in other centers and their treatment was maintained. At first, NSAIDs were initiated at 11 (50%) of the patients who were admitted to our hospital. Six of the patients (54.5%) were treated with slow-acting antirheumatic drugs and corticosteroids according to clinical and laboratory responses. Treatment schemes with MTX were started for 14 of the 22 patients for the first time and it was added to the treatment of 7 patients afterward.
CRP was used in the same way. Although CRP was less affected by showing the active disease course and response to the treatment and data in the literature [30,31]. There was no significant difference in was detected in 73.5% of our patients. This ratio is consistent with the patients (4%). The rates in our study were found to be consistent with the literature. Generalized lymphadenopathy (LAP) was reported as 5% in patients with polyarticular JIA and most commonly involved sites were the anterior cervical, axillary, and inguinal lymph nodes [28]. Hepatosplenomegaly commonly occurs in the systemic-onset group, which may occur within a few years after the onset of the disease [29]. In literature, polyarticular is reported as 10% in JIA [15]. In our cases, hepatosplenomegaly was detected in 3 (6.1%) patients.

Anemia in JIA is a common finding especially in systemic patients but is common in all forms of JIA as chronic disease anemia with decrease in serum iron and iron binding capacity [7]. Serum ferritin levels may increase due to disease activity. Gastrointestinal blood loss due to the intake of NSAIDs or iron deficiency anemia may also be observed due to underlying malabsorption of iron and inflammatory disease. In polyarticular JIA patients, 71.4% of mild-to-moderate anemia was detected. There was no significant difference between the groups (p > 0.05). Leukocytosis is often observed in systemic-onset of JIA. In literature, leukocytosis rate in systemic JIA is reported as 80% [30]. The leukocytosis rate was detected 8.2% in our patients. The reason can be attributed to the fact that 55.1% of our patients have been treated at the centers before admitted to our hospital. There was no significant difference in leukocytosis between the patients (p > 0.05). Thrombocytosis was detected in 73.5% of our patients. This ratio is consistent with data in the literature [30,31]. There was no significant difference in thrombocytosis between the groups (p > 0.05). ESR was useful to show the active disease course and response to the treatment and CRP was used in the same way. Although CRP was less affected by anemia and other factors [18,32], increase in ESR in 93.8% and CRP 93.7% of our patients were observed. These findings were consistent with the literature [7]. There was no significant difference between the groups (p > 0.05).

JIA is a systemic disease that leads to osteoporosis [33]. Radiological examinations were used to evaluate the pathologies related to the disease and the complications related to the disease and treatments used. In a study, the reduction in bone density in the lumbar vertebra and femur neck was found to be 50–60% [8]. Osteoporosis was detected in 13 (36.1%) of the patients with polyarticular JIA as a result of bone mineral densitometry study. These ratios were compatible with the literature. All our patients diagnosed with osteoporosis were taking steroid therapy. NSAIDs are the basis of treatment in a large proportion of patients with JIA. Using an initial treatment in many children ensures important success.

Generally, the recommended dose of MTX is 10 mg/m²/week. Methotrexate is started as 0.3 mg/kg/week and can be increased up to 1 mg/kg/week. In severe cases, doses may range from 20–30 mg/m²/week in a week. When the disease and laboratory parameters are completely normalized, MTX is gradually reduced. The medicine is to be discontinued decreasing by the same dose for the first two to three months and using once in two weeks, followed by a 2.5 mg per week for a period of three to six months. The effectiveness of the MTX is performed by Giannini and his colleagues they used 5 mg/m²/week MTX for one of the groups and 10 mg/m²/week for the other was supplemented as the second drug for the treatment. Both groups were compared with the placebo group not having been supplemented with 2nd drug treatment. While 65% efficacy was ensured with 10 mg/m²/week treatment, 36% efficacy was observed in the placebo group [11]. Polyarticular JIA was 28 (57.1%) of our patients and MTX was used at a dose of 7.5–10 mg/m²/week. This dose was consistent with classical information [34]. Remission was observed in 20 (83.3%) of our patients which was compatible with the literature [24]. MTX therapy ensures significant success in slowing cartilage damage, but inadequate treatment response was obtained in a considerable amount of patients [35]. There was no significant difference between MTX treated patients and those who did not, in terms of remission (p > 0.05).

Systemic onset and RF (+) cases in JIA are at risk for joint destruction. In all JIA patients’ severe functional limitation rate was reported as 25% [4,5], 10–15% in the RF (-) polyarticular group, 50% in the RF (+) polyarticular group [23,32]. In our cases, the deformity rate was found as 18.3%. In the MTX group, this rate was detected as 20.8% and there was no significant difference between the groups (p > 0.05).

In patients with JIA, relapse may occur after the remission. The relapse rate was found as 31.5% in our followed-up patients. While relapse rate was 45.8% in patients receiving MTX and it was 5.8% in not receiving MTX group. There was an important significance between two groups (p < 0.05). Relapse rates were found to be high because of the poor prognostic factors, delayed admission to the hospital, inappropriate treatment at the epicenters, and non-compliance with treatment.

In juvenile idiopathic arthritis as a chronic disease, compliance with follow-up and treatment of patients is very important. JIA is a disease that is difficult to diagnose and treat; it should be followed for a life-time. Even if remission rates are high, fairly high rates of deformity occur in patients and their life standard reduces. Apart from the drug treatment, patients should be provided with physical and occupational therapy and psychosocial support. JIA treatment is a team work that includes children, family, pediatric rheumatologist, physical therapist, physiotherapist, psychologist, ophthalmologist, dentist, orthopedist, nurse, occupational therapist, nutritionist and social workers. All members of the team must work in conjunction with each other.

Conclusion
Consequently, JIA is a chronic disease with a high rate of recurrence and active arthritis that leaves deformation. In case of the poor prognosis criteria in the treatment and if arthritis progresses rapidly, it is suggested that the treatment pyramid is reversed and MTX and other second-line drugs should be initiated immediately since MTX is a useful and successful treatment option in polyarticular JIA.

Conflict of Interest
The authors declared there is no conflict of interest.

References


