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Evaluation of Leflunomide Treatment in Patients with Juvenile Idiopathic Arthritis: A Single Center Experience

Jüvenil İdiopatik Artritli Hastalarda Leflunomid Tedavisinin Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood. Disease-modifying antirheumatic drugs (DMARD) such as methotrexate (MTX), leflunomide (LFN) are first-line treatment in JIA. MTX is the most commonly prescribed drug. Studies predominantly demonstrate the efficacy and safety of it, but the data on LFN are limited. This study aimed to present our experience with LFN treatment in JIA patients.

Material and Methods: This retrospective study included JIA patients who were followed-up regularly and had received LFN. Data on patient demographics, clinical and laboratory characteristics were obtained from medical charts.

Results: The study included 18 patients (15 female and 3 male) with a median (interquartile range) age at onset of disease 7.3 (3.1-12.0) years. Among them, 8 had oligoarticular JIA, seven had polyarticular JIA, two had systemic JIA and one had enthesitis-related arthritis (ERA). All patients received MTX as initial therapy (except one patient diagnosed with ERA was treated with sulfasalazine). MTX was discontinued and LFN treatment was started in all patients who initially received MTX due to gastrointestinal system (GIS) intolerance. Six of 7 patients with low disease activity, who had GIS intolerance while taking MTX before, were given LFN treatment because the disease activity was low. These patients achieved a complete remission with LFN. Four patients followed in remission with MTX had disease activation. These patients, who had previously experienced MTX intolerance, were given LFN treatment. Remission was achieved with LFN in 3 of 4 patients. Biological therapy was started in 6 patients with moderate or high disease activity who could not achieve remission with only MTX. These patients who did not have an adequate response were swicthed to LFN. Inactive disease was obtained in only 1 patient with the combination of LFN and biological agent. The patient with ERA was switched to LFN treatment due to inadequate response to sulfasalazine treatment. This patient achieved a complete remission with LFN.

Conclusion: LFN therapy may be beneficial in patients with low disease activity and/ or remission with other DMARDs and relapse after drug discontinuation.

Key Words: Disease-modifying antirheumatic drug, Juvenile idiopathic arthritis, Leflunomide

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ÖZ

Amaç: Juvenil idiyopatik artrit (JİA), çocukluk çağının en sık görülen kronik romatizmal hastalığıdır. Metotreksat (MTX), leflunomid (LFN) gibi hastalık modifiye edici antiromatizmal ilaçlar (DMARD) JİA'da birinci basamak tedavilerdir. MTX en sık reçete edilen ilaçtır ve çalışmalar ağırlıklı olarak MTX etkinliğini ve güvenliğini ele almaktadır. Ancak LFN ile ilgili veriler sınırlıdır. Bu çalışmada, JİA hastalarında LFN tedavisi ile ilgili kliniğimizin deneyimlerini sunmayı amaçladık.

Gereç ve Yöntemler: Bu retrospektif çalışmaya hastanemiz çocuk romatoloji polikliniğinde düzenli olarak takip edilen ve LFN tedavisi verilmiş JİA hastaları dahil edildi. Hasta demografik bilgileri, klinik ve laboratuvar özellikleri ile ilgili veriler tıbbi dosyalardan elde edildi.

Bulgular: Çalışmaya ortanca (çeyrekler arası aralık) hastalık başlangıç yaşı 7.3 (3.1-12.0) yıl olan 18 hasta (15 kadın ve 3 erkek) dahil edildi. 8 hastada oligoartiküler JİA, 7 hastada poliartiküler JİA, 2 hastada sistemik JİA ve 1 hastada entezitle ilişkili artrit (ERA) vardı. Tüm hastalara başlangıç tedavisi olarak MTX verildi (ERA tanısı konan bir hasta sulfasalazin ile tedavi edildi hariç). Gastrointestinal sistem (GİS) intoleransı nedeniyle başlangıçta MTX alan tüm hastalarda MTX kesildi ve LFN tedavisi başlandı. Daha önce MTX alırken GİS intoleransı gelişen hastalık aktivitesi düşük olan yedi hastadan altısına LFN tedavisi verildi. Bu hastalarda LFN ile tam remisyon sağlandı. MTX ile remisyonda izlenen dört hastada hastalık aktivasyonu görüldü. Daha önce MTX intoleransı olan bu hastalara LFN tedavisi verildi. Dört hastanın üçünde LFN ile remisyon sağlandı. MTX ile remisyon sağlanamayan orta ve yüksek hastalık aktivitesine sahip altı hastaya biyolojik tedavi başlandı. Yeterli yanıt alınamayan bu hastalarda MTX kesilerek LFN tedavisi başlandı. LFN ve biyolojik ajan kombinasyonu ile sadece bir hastada inaktif hastalık elde edildi. ERA tanılı bir hastada sulfasalazin tedavisine yetersiz yanıt alması üzerine LFN tedavisine geçildi ve LFN ile tam remisyon elde edildi.

Sonuç: LFN tedavisi, diğer DMARD'larla düşük hastalık aktivitesi ve/veya remisyonu olan ve ilaç kesildikten sonra nüks olan hastalarda faydalı olabilir.

Anahtar Sözcükler: Hastalık modifiye edici antiromatizmal ilaç, Jüvenil idiyopatik artrit, Leflunomid

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood (1). It is characterized by the arthritis of unknown etiology with onset before the age of 16 years and a minimum of 6 weeks duration (1). It is divided into 7 subtypes according to the International League of Associations for Rheumatology (ILAR) classification: oligoarticular (persistent or extended), polyarthritis rheumatoid factor (RF)-positive, polyarthritis RF-negative, systemic (sJIA), juvenile psoriatic arthritis, enthesitis-related arthritis, and undifferentiated JIA (2). JIA causes progressive joint destruction in untreated patients (1). The primary goals of JIA treatment are to achieve clinically inactive disease and prevent deformities. Non-steroidal anti-inflammatory drugs (NSAIDs), systemic and intra-articular glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and biological agents are treatments for JIA (3). The American College of Rheumatology recommends DMARDs (methotrexate (MTX), leflunomide (LFN), and sulfasalazine) as first-line treatments for JIA (3). As MTX is the most commonly prescribed drug, studies predominantly demonstrate the efficacy and safety of it. Although LFN is widely used in adults, it is not preferred in pediatric patients (4). In this report, we presented our experience with LFN treatment in JIA as a single center.

MATERIALS and METHODS

Patients followed in the pediatric rheumatology clinic of our hospital between January 2017 and January 2022 were included in the study. The inclusion criteria for the study were as follows: having JIA according to the ILAR criteria (2), receiving LFN treatment for at least six months, and being under the age of 21 years. According to the disease activity assessment, patients were divided into complete remission, low, moderate, and high activity groups (5).

In our clinical practice, the first-line treatment of JIA is either MTX (with a dosage of 15 mg/m^2/week) or sulfasalazine (with a dosage of 50 mg/kg/day [maximum 2.000 mg/day]). If remission is not achieved in the 3rd month of MTX or sulfasalazine therapy, biological agent is combined with DMARDs. Patients who cannot tolerate MTX are switched to LFN. LFN treatment was given to patients under 20 kg with the dose of 10 mg on alternate days. Patients with a body weight of 20-40 kg were treated with a dose of 10 mg/day. Patients above 40 kg were treated with LFN at a dose of 20 mg/day.

Demographic data (age, sex), clinical findings, affected joints, JIA subtypes, laboratory parameters ((white blood cell [WBC] count, erythrocyte sedimentation rate [ESR], c-reactive protein [CRP], anti-nuclear antibody [ANA] positivity, rheumatoid factor [RF] positivity, human leukocyte antigen [HLA]-B27) positivity), treatments were recorded.

Disease activity was evaluated by the juvenile arthritis disease activity score 71 (JADAS 71) for patients with JIA (5) and by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scoring system for patient with ERA (6). The JADAS-71 score is based on the following four parameters: 1) patient/parent's global disease assessment on a 0–10 visual analog scale (VAS), 2) physician's global disease assessment on a 0–10 visual analog scale (VAS), 3) active joint numbers (includes 71 joints), 4) ESR (5). The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) disease activity questionnaire contains six items: fatigue, spinal pain, joint pain/swelling, localized tenderness, morning stiffness severity, and morning stiffness

duration. Each item is scored from on a 0–10 VAS during the previous week (6).

Gastrointestinal system (GIS) complaints (such as nausea, vomiting) or elevated transaminase levels (more than 1.5 times the upper limit of normal) were considered MTX intolerance.

The study was consistent with the principles of the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Ankara Dr. Sami Ulus Gynecology, Obstetrics and Gynecology Training and Research Hospital (E-22/02-290). Informed consent was obtained from all patients and their parents for publication.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences ver. 21.0 (SPSS Inc., Chicago, Illinois, USA). All numerical measurements were presented with median and interquartile ranges. Qualitative data was presented with numbers and percentages.

RESULTS

General characteristics of the patients

The study included 18 patients (15 female and 3 male). Among them, 8 had oligoarticular JIA, seven had polyarticular JIA, two had systemic JIA (due to persistent chronic arthritis), and one had ERA. Only one patient had JIA-associated uveitis. The demographical, clinical, and laboratory findings of the patients are shown in Table I.

Patients' median (IQR) follow-up period during LFN treatment was 12 (6-40) months. While 17 of the patients were given MTX and NSAID as initial therapy (in addition, 15 patients received bridging steroid therapy), only one patient with the diagnosis of ERA received sulfasalazine (Figure 1). Methotrexate was discontinued because of gastrointestinal (GIS) intolerance (nausea, vomiting, elevated liver function tests) and LFN treatment was started in all 17 patients. Median (IQR) duration of MTX treatment was 12 (3-18) months. At the time of initiation of LFN treatment, four patients had a relapse after complete remission, 7 had low disease activity, and 6 had moderate-to-high disease activity. The median JADAS-71 score at the time of LFN initiation was 16.0 (7.5-25.0).

Table I: The demographical, clinical, and laboratory findings of the patients

Sex, Female,*	15 (83)
Subtypes of juvenile idiopathic arthritis	
Oligoarticular juvenile idiopathic arthritis*	8 (44)
Polyarticular juvenile idiopathic arthritis*	7 (39)
Systemic juvenile idiopathic arthritis (due to persistent chronic arthritis)*	2 (11)
Enthesitis related arthritis*	1 (5.5)
Age of symptom onset†, years	7.3 (3.1-12.0)
Age at diagnosis†, years	8 (3.8-13.3)
Current age†, years	18.5 (14.5-20.0)
Laboratory parameters	8.230 (7.185–11.100)
White blood cell†, /mm^3	8 (4-33)
Eritrocyte sedimentation rate†, mm/hour	
C-reactive protein†, mg/l	3 (3–5)
Anti-nuclear antibody positivity*	4 (22)
Human leukocyte antigen B-27 positivity*	1 (5.5)
Rheumatoid factor positivity*	3 (17)
Anti-cyclic citrulline peptideantibody*	1 (5.5)

**n (%), †Median (IQR)*

Responses to treatments of JIA patients with low disease activity

Six of 7 patients with low disease activity, who had GIS intolerance with MTX, achieved a complete remission at three months with LFN. Median (IQR) follow-up period of these patients was 8 (6-18) months. Since remission was not achieved in only one patient, biological agent treatment was started. Four patients who achieved complete remission with MTX and were followed up without treatment. These patients followed without medication relapsed after 24 (12-36) months. These patients, who had previously suffered from GIS intolerance while taking MTX, were given LFN therapy as they had low disease activity. Complete remission was achieved with LFN in 3 patients.

Responses to treatments of JIA patients with moderate to high disease activity

Complete remission could not be achieved with MTX and biologic agents (2 adalimumab, 1 tocilizumab, 2 etanercept, 1 canakinumab) in 6 patients with moderate to high disease activity and GIS intolerance during the median (IQR) follow-up of 10 (3-36) months. MTX was discontinued and LFN therapy was started instead. Complete remission was achieved at three months with LFN treatment in only one of these six patients. Other biological agent treatments were applied in the other five patients because disease activation could not be controlled. Three of five patients were in remission with tocilizumab treatment, with a median (IQR) of 2 (1-3) years of follow-up. In two patients, complete remission was still not achieved despite multiple biologic agent changes.

Response to leflunomide treatment of the patient with enthesitis-related arthritis

The patient with ERA was switched to LFN treatment at six months due to inadequate response (morning stiffness and enthesitis) to sulfasalazine treatment. Remission was achieved at six months with LFN treatment. This patient, who received LFN treatment for three years, has been followed for two years without medication and is in remission.

Adverse effects

No adverse effects related to LFN were observed in any of the patients.

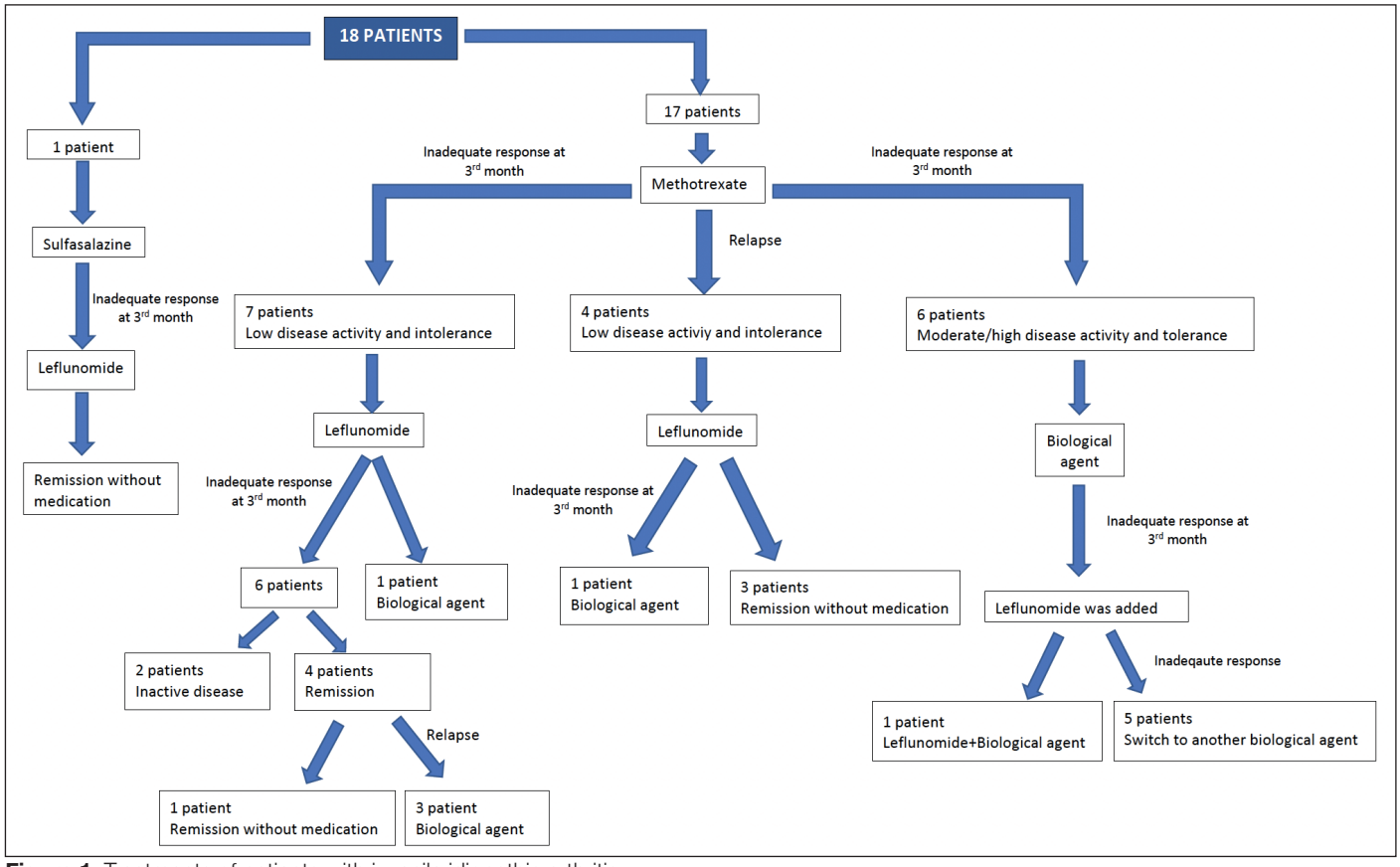

Figure 1: Treatments of patients with juvenile idiopathic arthritis

DISCUSSION

This study revealed that LFN treatment can be safely preferred in JIA patients with mild disease activity. According to our results, complete remission was achieved with LFN in 61% (n=11) of 18 patients. Seven patients did not benefit from LFN treatment. Pediatric rheumatologists prefer LFN treatment less than MTX treatment. There are few studies evaluating the efficacy of LFN treatment in JIA. In an observational study, LFN treatment was given to 32 patients with polyarticular JIA who did not respond to MTX treatment (7). At 3 months, 68% of the patients had an American College Rheumatology (ACR) 30 response, and 85% had an ACR 30 response. Only 2 patients had LFN side effects (7). In a multicenter, multinational, randomized controlled trial, the MTX group had a better ACR 30 response than the LFN group at 16 week (8). Foeldvari and Wierk evaluated 58 patients diagnosed with JIA who received LFN. They showed that 30% of patients achieved remission with LFN. They demonstrated that it may be a safe and effective agent for JIA patients who cannot tolerate or respond to MTX monotherapy (9). LFN, isolated or combined with MTX, has been found to be safe and effective in patients with JIA unresponsive to MTX (10). Aktay Ayaz et al. (11) demonstrated in their study involving 38 patients that LFN is an effective treatment in patients with MTX intolerance and low disease activity. Our results also suggest that LFN therapy can be used in JIA patients with low disease activity in the presence of MTX intolerance.

Studies addressing the safety of LFN are also limited. Abdominal pain, gastritis, dyspepsia, diarrhea, nausea, vomiting, anorexia, alopecia, weight loss, rash, elevated liver transaminases, can be seen as side effects of LFN therapy (7, 8, 12). Aktay Ayaz et al. (11) reported side effects in 2/38 (lymphopenia in 1 patient and elevated liver enzymes in 1 patient) patients in their study. Alcântara et al. (10) reported the intolerance with LFN in 7/43 patients (nausea and abdominal pain in 3 patients, elevated liver enzymes in 4 patients). In an observational study, LFN-related side effects were seen in 2/32 children with polyarticular JIA (gastritis in 1 patient and elevated liver enzymes in 1 patient) (7). In a controlled study comparing the efficacy and safety of MTX and LFN therapy in 94 patients with polyarticular JIA, the rates of side effects were similar in both groups (8). In our study, no side effects related to LFN were recorded in our patients.

The most important limitation of our study is the small number of patients. Another limitation is that the study design is retrospective. The present report may be useful for pediatric rheumatologists, as data on LFN in children with JIA are still limited.

On conclusion, LFN therapy may be beneficial, especially in patients with low disease activity and/ or remission with other DMARDs and relapse after drug discontinuation. More pediatric data are needed on the efficacy and safety of LFN therapy.

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