EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2019.18180

Original Article

Evaluation of factors affecting the duration of disease-modifying anti-rheumatic drugs application in patients with enthesitis-related arthritis

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Abstract

Objective: Treatments for enthesitis-related arthritis (ERA) consist of a mono- or combination therapy with non-steroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs (DMARDs), and biological agents, and they are primarily based on adult studies and studies on other forms of juvenile idiopathic arthritis, depending on whether there is axial or peripheral involvement. We use DMARDs frequently in our daily practice, even in patients with axial involvement. The main reason for this is that the health insurance system in Turkey does not allow the use of Tumor Negrosis Factor (TNF) blockers as the first line of treatment. The aim of this study is to evaluate the factors affecting the duration of DMARDs application in patients with ERA.

Methods: Fifty-two patients with ERA were accepted in this retrospective cohort study. These patients did not have an inflammatory bowel disease, reactive arthritis or undifferentiated arthritis, psoriasis, and familial Mediterranean fever. Demographic characteristics, medical history, the initial and follow-up physical examination, initial Juvenile Spondyloarthritis Disease Activity Index (JSpA-DA), initial laboratory tests, radiographic tests, Juvenile Arthritis Damage Index-articulary (JADI-A) and extra-articulary (JADI-E) on the last admission, and data on medical treatments were recorded from the registered data. The univariate Cox proportional hazards regression analyses was used to determine factors affecting the non-response time of ERA patients to DMARDs before the biological treatment was started.

Results: Twenty-seven patients (52%) achieved remission with DMARDs, while 25 (48%) patients did not. The age at diagnosis (HR=1.12; p=0.247); gender (HR=2.53; p=0.210); family history of ankylosing spondylitis (HR=1.17; p=0.730); inflammatory back pain (HR=0.57; p=0.175); the shoulder (HR=0.75 p=0.706), hip (HR=0.45; p=0.129), and small-joint involvement (HR=1.53; p=0.439); sacroiliitis with physical examination (HR=0.90; p=0.814) and magnetic resonance imaging (MRI) (HR=2.84; p=0.110); enthesitis (HR=0.83; p=0.670); presence of uveitis (HR=2.04; p=0.342); presence of HLA-B27 (HR=1.39; p=0.524); initial high acute phase reactants levels(HR=1.89; p=0.183); initial JSpADA score (HR=0.98; p=0.944); and last JADI-A (HR=1.41; p=0.060) score did not affect the duration of DMARDs treatment before switching to biological treatments.

Conclusion: In our study, the absence of factors affecting the duration of DMARDs application in patients with ERA showed that DMARDs may still be applied as the first line of treatment.

Keywords: Enthesitis-related arthritis, biological treatments, time

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Cite this article as: Paç Kısaarslan A, Sözeri B, Gündüz Z, Zararsız G, Poyrazoğlu H, Düşünsel R. Evaluation of factors affecting the duration of disease-modifying anti-rheumatic drugs application in patients with enthesitis-related arthritis. Eur J Rheumatol 2019; 6(3): 130-5.

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Submitted: 14 October 2018
Accepted: 5 March 2019
Available Online Date: 22 April 2019

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in the world. JIA involves a heterogeneous group of diseases characterized by arthritis that begins under the age of 16 years and lasts for at least 6 weeks. Each of the JIA categories is characterized by its clinical features during the first 6 months of the disease (1). Studies from different countries have shown that the prevalence as well as the distribution of subtypes vary in different ethnic groups, with an estimated annual incidence of JIA of approximately 1 per 100,000 in Japan; 90 per 100,000 in the United States; 170 per 100,000 in Belgium; and 65 per 100,000 in Turkey (2-5).

Enthesitis-related arthritis (ERA) is classified according to the International League of Associations for Rheumatology (ILAR) criteria in the JIA subgroup as arthritis and enthesitis lasting longer than 6 weeks in

children under the age of 16, or arthritis or enthesitis plus two of the following: tenderness of the sacroiliac joint or inflammatory back pain, the HLA-B27 positivity, the onset of arthritis in boys older than 6, anterior uveitis, and a family history of ankylosing spondylitis (AS), ERA, sacroiliitis with inflammatory bowel disease (IBD), or anterior uveitis in at least one first-degree relative (1). The frequency of ERA is 15%–20% of JIA cases, and it has a peak onset at the age of 12. Boys constitute 60% of patients. The distribution of ERA is 18.9%, and the HLA-B27 positivity is 63.3% in Turkish patients with ERA (6).

The ERA category of JIA describes a heterogeneous group of patients, including those with enthesitis and arthritis, IBD associated arthropathy, and what is traditionally thought of as juvenile AS (7).ERA is similar to but not interchangeable with juvenile spondyloarthropathy (SpA). Juvenile SpA includes not only children with ERA, but also many others who do not meet the ERA criteria, such as patients with the ILAR undifferentiated and psoriatic arthritis (PsA) categories, IBD-related arthritis, juvenile AS, and reactive arthritis (8).

Treatment choices consist of a mono- or combination therapy with non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and biological agents for ERA, which are primarily based on adult studies and axial or peripheral involvement. NSAIDs are suitable for children without the features of a poor prognosis and with low disease activity (9).Methotrexate (MTX) is the most commonly used DMARDs in children with arthritis, and its efficacy and safety have been proven in JIA (9, 10). However, its efficacy for enthesitis, sacroiliitis, and inhibition of structural damage has not been determined in patients with ERA (7). For this reason, MTX is recommended for ERA patients who have peripheral arthritis without axial involvement (11). Sulfasalazine (SSZ) is another frequently used DMARD in JIA. Several studies related to the use of SSZ support its application in patients with ERA. In a randomized, double-blinded, placebo-controlled study of juvenile SpA, in terms of active joints and enthesitis counts, pain visual analog scale and spinal flexion were not significantly different between the SSZ and placebo groups. However, both the doctor and patient assessment scores were improved in the SSZ group compared to the placebo group (12). The registry results of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) reported that current treatments may not be equally effective for enthesitis or sacroiliac tenderness in ERA (9).

Treatments of ERA are based on adult and other forms of JIA studies to date. Moreover, the 2011 American College of Rheumatology (ACR) recommendations did not consider the ERA treatments separate from other JIA categories, except for sacroiliitis (13). Biological therapy is recommended for axial involvement and for peripheral involvement with no response to DMARD. In the 1/3 to half of the patients, sacroiliitis develops over the years. Factors predicting progression to axial involvement in children are not known yet (14).

Methods

Patients

A total of 52 patients with ERA who satisfied the ILAR criteria and were followed between 2010 and 2015 in Erciyes University Pediatric Rheumatology Department in Turkey were enrolled in the retrospective cohort study. Patients, apart from the 52, with psoriasis, IBD, reactive arthritis, undifferentiated arthritis, and familial Mediterranean fever were excluded from the study. Information on patients included demographic characteristics, the age at diagnosis, duration of follow-up time, duration of DMARDs application, family history of AS, presence of inflammatory back pain, presence of arthritic joints, magnetic resonance imaging findings of patients with sacroiliitis, uveitis, the HLA-B27 positivity, and initial levels of high acute phase reactants.

Patients who had not achieved the ACR 30 criteria were switched to the biological treatment options according to the health insurance system in Turkey. The disease activity score was evaluated by the Juvenile Spondyloarthritis Disease Activity Index (JSpADA) at admission and before biological treatments. This scoring index is defined below (15):

1. The number of active joints (maximum 10 joints): 0 joints: 0, 1–2 joints: 0.5, >2 joints: 1
2. The number of active enthesitis (maximum 10 tender entheses): 0 entheses: 0, 1–2 entheses: 0.5, >2 entheses: 1
3. Pain (patient visual analog scale range 0–10 over the past week): 0: 0, 1–4: 0.5, 5–10: 1
4. ESR or C-reactive protein (CRP) level increases related to the disease activity; normal: 0; 1–2 times normal: 0.5; >2 times normal: 1
5. Morning stiffness lasting longer than 15 minutes: absent: 0, present: 1
6. Sacroiliitis detected by physical examination (described as the presence of two or more of the following: tenderness of the sacroiliac joint, a positive Patrick's test or FABER test, and inflammatory back pain): absent: 0, present: 1
7. Uveitis (including acute/symptomatic and chronic/asymptomatic disease): absent: 0, present: 1
8. Abnormal back mobility is defined as the modified Schober test <20 cm: normal: 0, abnormal: 1

The score ranges between 0 and 8, where higher scores define a more disease activity.

The disease damage score was evaluated by the Juvenile Arthritis Damage Index-articulary (JADI-A) and extra-articulary (JADI-E) at the last admission. This index is defined as described below (16):

In the JADI-A, 36 joints are evaluated for the presence of damage. Each damaged joint is scored on a 2-point scale (1: partial damage, 2: severe damage, ankylosis, or prosthesis). The maximum total score is 72.

In the JADI-E, 13 items are evaluated in five different organs/systems: non-articular musculoskeletal (osteoporosis that defined fractures or vertebral collapse, significant abnormality of the vertebral curve as a result of leg-length discrepancy or hip contracture, significant leg-length discrepancy or growth abnormality of a bone segment, avascular necrosis of bone, severe muscle atrophy); cutaneous (subcutaneous atrophy as a result of the intra-articular corticosteroid injection, stria rubrae); endocrine (diabetes mellitus, growth failure, pubertal delay); secondary amyloidosis; and ocular (If the patient has had eye surgery, it was scored as 2 for each eye. If the patient developed legal blindness, the score was 3). According to whether the damage was present, each item was scored as either 0 or 1, respectively. The maximum total score is 17.

Patients were divided into two groups as DMARD responsive and non-responsive. Non-responsiveness to DMARDs was considered to exist if patients took DMARDs for at least 3 months and then were switched to the biological treatment. The duration of DMARDs application was defined as the duration of the patient on DMARDs only or the duration of the patient on DMARDs before the biological treatment.

The study was approved by the Erciyes University ethics committee (2014/657). All patients gave written informed consent.

Statistical Analysis

All statistical analyses were performed with the Statistical Package for Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA) program for Windows.

The demographical and clinical characteristics of the patients were summarized using descriptive statistics. Categorical data were summarized through frequencies and percentages, and continuous data through medians and interquartile ranges. Categorical data were compared using the chi-squared test, or Fisher's exact test, while continuous data were compared using the Mann–Whitney U and Student's t-test.

The univariate Cox proportional hazards regression analyses was used to determine factors affecting the non-response time of patients with ERA to DMARDs before the biological treatment. Hazard ratios were calculated with 95% confidence intervals. Significant variables at $p<0.05$ were admitted.

The Kaplan–Meier and log-rank tests were performed to compare the survival analysis according to the DMARDs response.

We calculated the post-power based on the duration of disease. For alpha equal to 0.05, the observed power was found as 96.72%. These analyses were conducted using the PASS 11.0 (Power Analysis Statistical System).

Results

A total of 52 ERA patients, 43 male (82.7%) and nine female (17.3%), were enrolled in the study. The median age was 16 (IQR: 13-17). The patients were diagnosed at the median age of 14 (IQR: 11–14, 75). The median follow-up time was 20 months (IQR: 12–46, 75). There was a family history of rheumatic disease in 16 (30.8%) patients. Nine of them had AS. The locations of the involved joints were as follows: the shoulder 5 (9.6%), elbow 2(3.8%), wrist 4 (7.7%), hip 15 (28.8%), knee 27 (52%), ankle 17 (32.7%), and small joints 9 (17%). The sacroiliac involvement was observed through physical examination in 28(53.8%), enthesitis in 28 (53.8%), and inflammatory back pain in 27 (52%).

The initial mean level of the erythrocyte sedimentation rate (ESR) was 33±30.7 mm/h, and the CRP level was 26±31.8 mg/L. The HLA-B27 positivity was detected in 34 (65.4%) patients. Uveitis was detected in 3 (5.8%) patients. The initial JSpADA had a mean value of 3.49±1.09 (1.5–5.5). The JSpADA was 4.00±1.02 (1.5–5.5) before biologic treatments. The JADI-A was 0.28±0.77 (0–4), and the JADI-E was 0.0 on the last admission.

In 17 of the 28 patients who had sacroiliitis based on the clinical examination, the diagnosis was confirmed with MRI. In other 11 cases, the MRI results were normal.

Table 1. Characteristics of DMARD responsive and non-responsive patients

	Responsive (n=27)	Non-responsive (n=25)	p
Age at diagnosis	14 (IQR=8–16)	13 (IQR=7–16)	0.940
Duration of disease	13 (IQR=5–76)	43 (IQR=12–84)	0.000
Gender	M=21 (48.8%) F=6 (66.7%)	M=22 (51.2%) F=3 (33.3%)	0.460
AS in family	3 (33.3%)	6 (66.7%)	0.280
Shoulder involvement	3 (60%)	2 (40%)	1.000
Sacroiliac involvement	13 (46.4%)	15 (53.6%)	0.390
Hip involvement	8 (53.3%)	7 (46.7%)	0.890
Small-joint involvement	5 (55.6%)	4 (44.4%)	1.000
Enthesitis	18 (64.3%)	10 (35.7%)	0.050
Uveitis	1(33.3%)	2(66.7%)	0.603
HLA-B 27 positivity	14 (41.2%)	20 (58.8%)	0.030
High APR	12 (40%)	18 (60%)	0.040
Sacroiliitis with MRI	6 (35.3%)	11 (64.7%)	0.130
JSpADA score	3.33±1.03	3.06±1.14	0.280
JADI-A	0±0	0.60±1.04	0.000
JADI-E	0±0	0±0	

AS: Ankylosing spondylitis; APR: Acute phase reactans; MRI: magnetic resonance imaging; JSpADA: Juvenile spondyloarthritis disease activity index; JADI-A: juvenile arthritis damage index-articulary; JADI-E: juvenile arthritis damage ındex-extraarticulary

Table 2. Factors Affecting the duration of DMARD application determined using a cox regression analysis and the hazard risk ratio

	HR	95.0 % CI	p
Age at diagnosis	1.12	0.93–1.32	0.247
Gender	2.53	0.592–10.85	0.210
AS in family	1.17	0.46–2.98	0.730
Inflammatory back pain	0.57	0.25–1.28	0.175
Shoulder involvement	0.75	0.17–3.27	0.706
Sacroiliitis by PE	0.90	0.39–2.05	0.814
Hip involvement	0.45	0.16–1.25	0.129
Small joints involvement	1.53	0.51–4.56	0.439
Enthesitis	0.83	0.36–1.921	0.670
Uveitis	2.04	0.46–8.97	0.342
HLA-B27 positivity	1.39	0.49–3.92	0.524
High APR	1.89	0.74–10.25	0.183
Sacroiliitis with MRI	2.84	0.78–10.25	0.110
JSpADA score	0.98	0.66–1.47	0.944
JADI-A	1.41	0.98–2.03	0.060

AS: ankylosing spondylitis; PE: physical examination; APR: acute phase reactans; MRI: magnetic resonance imaging; JSpADA: juvenile spondyloarthritis disease activity index; JADI-A: juvenile arthritis damage ındex-articulary

The medical treatments applied were NSAIDs in 51 (98%), systemic steroids in 16 (30.8%), MTX in 41 (78.8%), SSZ in 33 (63.5%), intra-articular steroids in seven (13.4%), and biologic treatments (etanercept, 8; adalimumab, 17) in 25 (48%) patients. Forty-seven (90%) patients were in remission, while five (10%) had active disease with treatment. Three of the patients who had active disease were on DMARDs, and two were on biologic treatments.

We evaluated the response of 52 patients with DMARDs. Twenty-seven patients (52%) achived the remission with DMARDs, while 25 (48%) patients did not achieve it (Table 1). In the remission group and non-remission group, the disease duration was 13 months (IQR, 5–76) and 43 months (IQR, 12–84), respectively. The median remission time was 14 months in the non-responsive group (IQR, 11.09–25.66).

The HLA-B27 positivity (p=0.030), a high level of APR at diagnosis (p=0.040), the JADI-A score (p=0.000), and duration of disease (p=0.000) were significantly different in the non-responsive group.

The Cox regression analysis was performed to find out the factors affecting the duration of DMARD use. The age at diagnosis (HR=1.12; p=0.247); gender (HR=2.53; p=0.210); family history of AS (HR=1.17; p=0.730); inflammatory back pain (HR=0.57; p=0.175); shoulder (HR=0.75; p=0.706), hip (HR=0.45; p=0.129), small-joint involvement (HR:1.53; p=0.439); sacroiliitis with physical examination (PE) (HR=0.90; p=0.814) and MRI(HR=2.84; p=0.110); enthesitis (HR=0.83; p=0.670); presence of uveitis (HR=2.04; p=0.342); presence of HLA-B27 (HR=1.39; p=0.524); initial high APR levels(HR=1.89 p=0.183); initial JSpADA score (HR=0.98; p=0.944); and last JADI-A (HR=1.41; p=0.060) score were found to not affect the non-response time to biological treatments (Table 2).

Using the Kaplan–Meier analysis, the number of patients who responded to DMARDs among the 17 patients who had sacroiliitis was shown to be reduced by half by the 20th month with MRI (Figure1).

Discussion

The goal of JIA treatment is to control inflammation and prevent morbidities such as vision loss, growth disturbances, joint contractures, destructions, and functional limitations. ERA is associated with a poorer quality of life, worse function, and increased pain intensity in comparison with other JIA categories (17, 18). Because juvenile spondyloarthritis continues into adulthood, pediatric and adult rheumatologists need to adapt to the differences in its presentation and outcome (10).

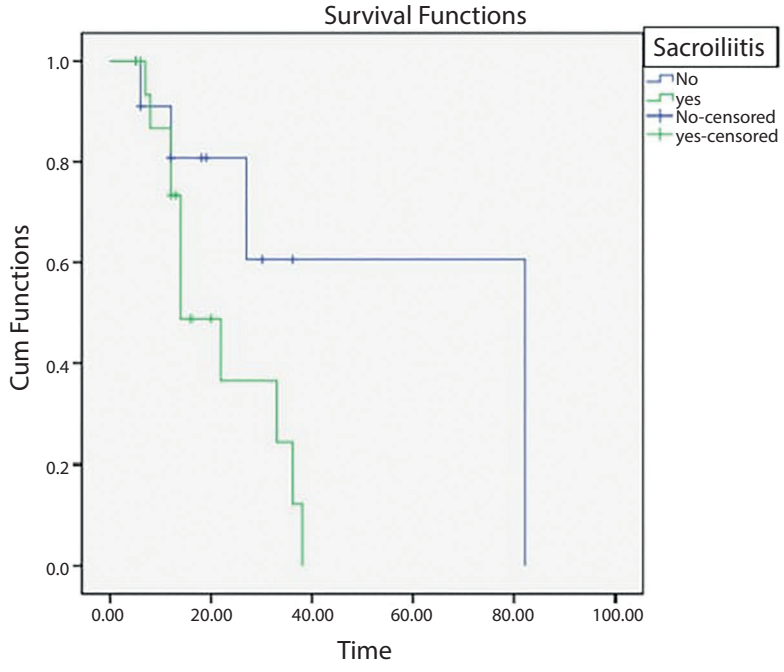

Figure 1. The Kaplan-Meier and log rank tests were performed to compare the survival analysis according to there sponse to DMARDs. Greenline: patients with sacroiliitis determined by MRI. Blue line: patients for whom MRI results did not show sacroiliitis. Time: duration of application in patients on DMARDs only or duration of application in patients on DMARDs before biologic treatments (months). Cum survival: the percentage of patients who responded to DMARDs

We evaluated the treatment of 52 patients with ERA. This group did not involve patients diagnosed with IBD, reactive arthritis, undifferentiated arthritis, psoriasis, and familial Mediterranean fever. Twenty-seven of the 52 patients (52%) achieved the remission with DMARDs, while 25 (48%) patients were switched to anti-TNFα agents. Androvic et al. (19) reported that 47.7% of Turkish juvenile spondyloarthropathies showed resistance to methotrexate and sulfasalazine. The percentage of DMARDs resistance we found was 48%.

In evaluations made in the first part of the study, the HLA-B27 positivity, a high level of APR at diagnosis, high JADI-A score, and long duration of disease were significantly different in the non-responsive group ($p<0.05$). Diagnosis at an older age, gender, family history of AS, hip arthritis, sacroiliac symptoms, tarsitis, an increased number of affected joints, positive HLA-B27 and HLA-DRB1*02, the absence of HLA-DPB1*02, and a continuing high level of APR are reported as poor prognostic factors (20-22).Our findings were consistent with the literature.

Because treatment response usually depends on the disease duration, a Cox regression analysis was performed to find out the factors affecting the duration of DMARD application in the second part of the study. Our study showed that the age at diagnosis; gender; family history of AS; hip, shoulder, small joints, and sacroiliac joint involvements; enthesitis; uveitis; an initial high level of APR; HLA-B27 positivity; initial JSpADA score; and the last examination damage score did not affect the time of the DMARDs usage. Goirand et al. (23) reported that axial involvement developed in half of the patients within 5 years. Enthesitis and SpA history in the family were considered as independent risk factors for progression to axial involvement.

TNF-alpha blocker agents have demonstrated the efficacy with regard to arthritis, enthesitis, and axial disease in JSpA (24, 25). Ineffective treatment in childhood leads to disease progression and the development of an ankylosing on axial skeleton (26). However, treatment choices in axial involvement were based on adult studies (27-29). In ACR recommendations, initiation of a TNFα inhibitor was recommended for patients with active sacroiliac arthritis who have received an adequate of NSAIDs and have high disease activity and features of poor prognosis. A TNFα inhibitor was recommended after 3-6 mounts DMARDs usage in low and moderate disease activity in patients also (level C) (13). We use DMARDs fre-

quently in our daily practice, even though patients have axial involvement. The main reason for this is that the health insurance system in Turkey does not allow the use of TNF blockers as the first line of treatment.

We found that the effectiveness of DMARDs in patients with sacroiliitis detected by MRI drops by 50% within 20 months. Clinicians should be aware of the requirement to switch to biological treatments in patients who show the HLA-B27 positivity, high APR levels at diagnosis, and high JADI-A score at the follow-up. Although biological treatments are considered as the first-line treatment for patients with axillary adult spondyloarthritis, we believe that conventional therapy can be used as the first-line treatment in ERA patients.

Our study has some limitations. First, the superiority of MTX to SSZ was not evaluated. The second is that the study has a retrospective design. Although the number of patients is limited, the fact that the psoriasis, IBD, reactive arthritis, undifferentiated arthritis, and FMF were not take into the patient group is the superiority of our study.

In conclusion, the absence of factors affecting the duration of DMARDs application of patients with ERA in our study showed that DMARDs remain may be applicable as the first line of treatment in patients with ERA. Further research is required for more conclusive results.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Erciyes University School of Medicine (2014/657).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.P.K.; Design - A.P.K.; Supervision - Z.G., H.P., R.D.; Data Collection and/or Processing - A.P.K., B.S.; Analysis and/or Interpretation - G.Z.; Literature Search - A.P.K.; Writing Manuscript - A.P.K.; Critical Review - B.S.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support

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