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Determining Predictive Factors for Refractory Disease in Oligoarticular Juvenile Idiopathic Arthritis

Oligoartiküler Juvenil İdiopatik Artritte Dirençli Hastalığı Öngörücü Faktörlerin Belirlenmesi

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ABSTRACT

AIM: This study aims to compare the clinical and demographic characteristics of patients diagnosed with oligoarticular juvenile idiopathic arthritis (JIA) treated with conventional disease-modifying antirheumatic drugs (cDMARDs) versus those requiring additional biologic DMARDs (bDMARDs). Additionally, it aims to identify the factors that necessitate the inclusion of bDMARDs in the treatment regimen and to determine predictors of long-term treatment resistance.

MATERIAL AND METHOD: Patients diagnosed with oligoarticular JIA were classified into two groups based on their response to cDMARDs: responders and resistant.

RESULTS: The study included 71 patients with oligoarticular JIA on cDMARDs. Knee joint complaints were most common (83.1%), followed by ankle joint (29.6%). All patients were started on non-steroidal anti-inflammatory drugs (NSAIDs) at diagnosis, and cDMARDs were initiated at a median of one month (IQR: 3 months). The most commonly initiated treatment in these patients was methotrexate (MTX) (97.2%). cDMARDs were effective in 21 patients (29.5%), while 50 patients (70.4%) were resistant to cDMARDs and required the initiation of bDMARDs. In comparing cDMARD-responsive and resistant groups starting bDMARDs, family history was more common in responders (23.8%, p=0.044), while ankle involvement was higher in resistant group (38%, p=0.016). Univariate analysis highlighted ankle/toe joint involvement as a risk factor for resistance (p=0.027, CI 95%), and family history as protective (p=0.043, CI 95%). When multivariate analysis was performed with the variables that were significant in univariate analysis, there was statistical significance only in the involvement of ankle/toe joints (ankle/toe joints OR=5.29 CI 95% (1.08-25.83), p=0.040, family history OR=0.24 CI 95% (0.05-1.19), p=0.080).

CONCLUSION: In patients with oligoarticular JIA, the involvement of ankle/toe joints at diagnosis increases the risk of resistance to cDMARDs therapy. Therefore, careful monitoring of these patients is warranted during follow-up.

Keywords: Disease-modifying antirheumatic drugs, oligoarticular juvenile idiopathic arthritis, predictive factors, refractory disease

ÖZET

AMAÇ: Bu çalışma, oligoartiküler jüvenil idiyopatik artrit (JİA) tanısı almış ve konvansiyonel hastalık modifiye edici antiromatizmal ilaç (kDMARDs) tedavisi alan hastalar ile biyolojik DMARDs (bDMARDs) tedavisine ihtiyaç duyan hastaların klinik ve demografik özelliklerini karşılaştırmayı amaçlamaktadır. Ayrıca, tedavi rejimine bDMARDs eklenmeyi gerektiren faktörleri ve uzun vadeli tedavi direncinin öngörücülerini belirlemeyi hedeflemektedir.

GEREÇ VE YÖNTEM: Oligoartiküler JİA tanısı almış hastalar, kDMARDs yanıtlarına göre iki gruba ayrıldı: yanıt verenler ve dirençli olanlar. İki grup arasında klinik ve demografik özellikler karşılaştırıldı.

BULGULAR: Çalışmaya, kDMARDs kullanan 71 oligoartiküler JİA hastası dahil edildi. Hastalar en sık diz eklemi (%83,1) ardından ayak bileği eklemi (%29,6) şikayetleri ile başvurdu. Tüm hastalara tanı anında nonsteroid antiinflamatuar ilaç (NSAİİ), ortanca birinci ayda (ÇAA: 3 ay) ise kDMARDs başlandı. Bu hastalarda en sık başlanan tedavi metotreksat (MTX)(%97,2) idi. kDMARDs 21 hastada (%29,5) etkili olurken, 50 hasta (%70,4)'nın kDMARDs tedavisine direnç gösterip bDMARDs'a ihtiyaç duyduğu saptandı. kDMARDs'a yanıt veren grup ile dirençli grup karşılaştırıldığında, aile öyküsü yanıt verenlerde daha yaygındı (%23,6, p=0,044), ayak bileği tutulumu ise dirençli grupta daha sıktı (%38, p=0,016). Tek değişkenli analizde, ayak bileği/ayak parmağı eklemi tutulumu kDMARDs tedavisine direnç açısından risk faktörü (p=0,027, %95 GA), aile öyküsü olması ise koruyucu faktör olarak (p=0,043, %95 GA) belirlenmiştir. Tek değişkenli analizde anlamlı olan değişkenlerle çok değişkenli analiz yapıldığında, sadece ayak bileği/ayak parmağı eklemi tutulumu istatistiksel olarak anlamlı bulunmuştur (ayak bileği/ayak parmağı eklemi OR=5,29 %95 GA (1,08-25,83), p=0,040, aile öyküsü OR=0,24 %95 GA (0,05-1,19), p=0,080).

SONUÇ: Oligoartiküler JİA'lı hastalarda, tanı anında ayak bileği/ayak parmağı eklemi tutulumu, kDMARDs tedavisine direnç riskini artırmaktadır. Bu nedenle, bu hastaların takiplerinde dikkatli izlem gerekmektedir.

Anahtar Kelimeler: Hastalık modifiye edici antiromatizmal ilaçlar, oligoartiküler jüvenil idiyopatik artrit, öngörücü faktörler, dirençli hastalık

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease of childhood. This term encompasses a heterogeneous group of arthritis types in terms of genetic factors, etiopathogenesis, age of onset, and outcomes.[1]Oligoarticular JIA is the most common subtype, affecting fewer than five joints and accounting for approximately 50% of JIA cases, and it is divided into two subgroups. Persistent oligoarticular JIA is defined as having no additional joint involvement after the first six months of disease, whereas extended oligoarticular JIA starts with four or fewer joints affected within the first six months but involves five or more joints over time.[2]

In the management of active oligoarthritis, initial treatment typically involves non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular corticosteroid injections (IACS). If these options prove insufficient, conventional disease-modifying antirheumatic drugs (cDMARDs) are introduced. However, if there's still inadequate response or intolerance to NSAIDs and/or IACS despite cDMARDs therapy, transitioning to biological DMARDs (bDMARDs) becomes necessary. It's noteworthy that certain cases of oligoarticular disease may progress to chronic destructive arthritis. Factors such as involved joints, presence of erosive disease or enthesitis, delayed diagnosis, elevated inflammatory markers, and symmetrical disease are critical indicators for prognosis and influence treatment strategies.[3]

Recent advancements in targeted therapies for JIA have led to improved disease outcomes both in the short and long term. Over the past decade, evidence has demonstrated that early and aggressive treatment of the disease with a targeted approach increases the likelihood of achieving and maintaining clinical remission.[1]Anticipating patients who will be transitioned to bDMARDs also enables more rigorous and precise monitoring of these patients. Therefore, there is a need for biomarkers that can predict resistance to cDMARDs in oligoarticular JIA. Until biomarkers for determining the risk of resistant disease become available, it is useful to identify markers that can be employed in clinical practice.

In this study, our objective is to compare the clinical and demographic characteristics of patients diagnosed with oligoarticular JIA treated with cDMARDs to those who received additional bDMARDs. Additionally, we aim to determine the factors that require the inclusion of bDMARDs in the treatment plan and to identify the predictors of long-term disease resistance.

MATERIAL AND METHOD

This retrospective study included 71 pediatric patients aged 0-18 years who were diagnosed with oligoarticular JIA according to ILAR (International League of Associations for Rheumatology) criteria [2] and followed up in the Pediatric Rheumatology Clinic of Ankara Etlik City Hospital between October 2022 and April 2024. Inclusion criteria included patients who received cDMARDs for at least three months and were followed up for one year. The study excluded other subtypes of JIA and patients with concurrent rheumatologic conditions (e.g., familial Mediterranean fever). The data were sourced from patient medical records. Parameters recorded included patient demographics (age, gender), clinical findings, symptom duration, oligoarticular JIA subtype (persistent or extended), complications, presence of concomitant uveitis, laboratory findings at diagnosis (complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), rheumatoid factor, HLA-B27), treatments (NSAIDs, IACS, cDMARDs and bDMARDs) and disease activity assessed using the Juvenile Arthritis Disease Activity Score 27 (JADAS 27) at diagnosis, 3 months, 6 months and 12 months.

The JADAS was calculated using the following components: 1. Physician's global assessment of disease activity (scored on a 10-cm VAS where 0 represents no activity and 10 represents maximum activity), 2. Parent's global assessment of well-being (scored on a 0-10 VAS), 3. Number of active joints (either 71, 27, or 10 joints), 4. ESR (mm/hour)-20/10 or CRP (mg/L)-10/10. Based on this parameter, JADAS is classified as follows: JADAS ≤1 indicates inactive disease, JADAS between 1.1 and 2 indicates low disease activity, JADAS between 2.1 and 4.2 indicates moderate disease activity, JADAS ≥4.2 indicates high disease activity[4].

Clinical remission was defined based on Wallace criteria, which evaluate remission under three conditions: clinically inactive disease, characterized by the absence of active arthritis, systemic symptoms, and uveitis, normal ESR and/or CRP levels, optimal physician's global assessment, and morning stiffness lasting less than 15 minutes; remission on medication, defined as the maintenance of clinically inactive disease for at least six months while continuing anti-rheumatic and/or anti-uveitis medication; and remission off medication, which requires sustained inactive disease for 12 months without any medications[5].

The initiation of bDMARDs treatment for patients diagnosed with oligoarticular JIA is defined as resistant disease when there is no achievement of an ACR30 response despite a minimum of three months of treatment with at least one cDMARDs. Treatment response is evaluated using the ACR Pediatric criteria, where ACR Pediatric 30 indicates at least 30% improvement in three or more core set criteria, with no more than one component worsening by more than 30%. Similarly, ACR Pediatric 50, 70, and 90 represent 50%, 70%, and 90% improvement in three or more core set criteria, respectively[6].

Permission for the current study was received from our hospital's ethics committee on June 05, 2024, with decision number 2024/379.

Statistical analysis

SPSS version 21 software (SPSS, Chicago, USA) was used to analyze the data. Categorical data were presented as numbers and percentages, and quantitative data were presented as median and interquartile range (IQR) (non-normally distributed). When comparing the groups with and without biologic therapy in patients with oligoarticular JIA, the Chi-Square test or Fisher's Exact test was used to compare categorical data. Mann-Whitney U test was used to compare quantitative data. Factors associated with the use of biological therapy in oligoarticular JIA patients were evaluated by binary logistic regression analysis, and multivariate analyses were performed with variables considered statistically significant in univariate analyses. Odds ratios (ORs) calculated as a result of these analyses were presented using 95% confidence intervals. $p<0.05$ was considered statistically significant.

RESULTS

The study included 71 patients with oligoarticular JIA receiving DMARDs. Forty-two (59.2%) of the patients were female. Median age at diagnosis was 56 (IQR:75) months and median age at symptom onset was 53 (IQR:73) months. Family history was present in 11.3% and 9.9% of the patients had concomitant uveitis. Joint swelling was the presenting complaint in 64 (90.1%) patients, while 61 (85.9%) patients had morning stiffness. The most common complaints were in the knee joint (83.1%), followed by the ankle joint (29.6%). Laboratory characteristics revealed ANA positivity in 26 (36.6%) patients. At the time of diagnosis, the median ESR was 21 mm/h (IQR: 34 mm/h) and the median CRP was 7.1 mg/L (IQR: 15.5 mg/L). When the disease activities of the patients at presentation were evaluated, the median value of the number of active joints was 2 (IQR:1). The median values of physician global assessment score and patient/parent VAS (visual analogue scale) at the time of diagnosis were 6 (IQR:1) and 6 (IQR:2), respectively, and the median value of JADAS 27 was 13.7 (IQR:5.7)

Table 1. Characteristics of oligoarticular JIA patients at the time of diagnosis

	N=71 Oligoarticular JIA
Gender, female†	42 (59.2)
Age at diagnosis, months‡	56 (75)
Age at symptom onset, months‡	53 (73)
Clinical characteristics	
Family history †	8 (11.3)
History of uveitis†	7 (9.9)
Extended oligoarticular JIA	2 (2.8)
Complaint/findings at diagnosis	
Arthritis †	64 (90.1)
Arthralgia †	7 (9.9)
Morning stiffness †	61 (85.9)
Affected joints at the time of diagnosis	
Knee†	59 (83.1)
Ankle†	21 (29.6)
Fingers†	6 (8.5)
Wrist†	4 (5.6)
Hip†	2 (2.8)
Toes†	1 (1.4)
Elbow†	1 (1.4)
Assessment of disease activity	
Number of active joints‡	2 (1)
Number of active enthesitis‡	0 (0)
Physician global assessment score‡	6 (1)
Patient/parent VAS‡	6 (2)
JADAS 27 (at diagnosis) ‡	13.7 (5.7)
Serological, genetic, and laboratory/radiological features	
ANA positivity†	26 (36.6)
HLA B27†	1 (1.4)
Hb, gr/dL‡	12.2 (2)
WBC, $10^3/\mu L$‡	8360 (3810)
ESR, mm/hour‡	21 (34)
CRP, mg/L‡	7.1 (15.5)

ANA antinuclear antibody, CRP C-reactive protein, ESR erythrocyte sedimentation rate, HLA B27 Human Leukocyte Antigen B27, JADAS 27 Juvenile Idiopathic Arthritis Disease Activity Score 27, JIA juvenile idiopathic arthritis, VAS visual analogue scale

†Data presented as numbers and percentages.
Values are presented as median and interquartile range.

At the time of diagnosis, all patients were started on NSAIDs, and cDMARDs were initiated at the median one month (IQR: 3). Of these patients, 69 (97.2%) were on methotrexate, 4 (5.6%) on leflunomide, and 1 (1.4%) on sulfasalazine. Glucocorticoids were used as bridge therapy in 36 patients (50.7%) and IACS in 41 patients (57.7%). cDMARDs were effective in 21 patients (29.5%), while 50 patients (70.4%) were resistant to cDMARDs and required the initiation of bDMARDs. The reasons for transitioning to bDMARDs treatment included an inadequate response to cDMARDs in 32 patients (64%), disease flare after remission in 13 patients (26%), and adverse effects from cDMARDs in 5 patients (10%). These adverse effects included gastrointestinal intolerance in 3 patients and elevated liver function tests in 2 patients.

Among patients receiving bDMARDs, 34 (68%) used etanercept, 20 (40%) used adalimumab, 2 (4%) used tocilizumab, 2 (4%) used infliximab, and 1 (2%) used tofacitinib

Table 2. Comparison of Response and Resistance to Conventional DMARD Therapy

	Responsive OligoJIA N=21	Resistant OligoJIA N=50	
Gender, female	11 (52.4)	31 (62)	0.452*
Age at onset of symptoms, months	55 [69.5]	52 [74.25]	0.480†
Age at diagnosis, months	56 [71]	57 [75.75]	0.724†
Duration of follow-up, months	39 [41.5]	57 [56.5]	0.108†
Family history	5 (23.8)	3 (6)	**0.044****
ANA positivity	5 (23.8)	21 (42)	0.146*
HLA B27 positivity	0	1 (2)	>0.999**
Disease activity markers (at presentation)			
Morning stiffness	19 (90.5)	42 (84)	0.712**
Uveitis	1 (4.8)	6 (12)	0.665**
Number of active joints	1 [1]	2 [1]	0.129†
JADAS 27	12.4 [6.2]	13.5 [5.45]	0.148†
CRP, mg/L	6 [16.2]	8.2 [15.9]	0.355†
ESH, mm/hour	16 [28]	22 [33]	0.098†
Affected joints			
Knee	20 (95.2)	39 (78)	0.094**
Ankle	2 (9.5)	19 (38)	**0.016***
Toe	0	1 (2)	>0.999**
Finger	1 (4.8)	5 (10)	0.662**
Wrist	0	4 (8)	0.312**
Hip	1 (4.8)	1 (2)	0.507**
Elbow	0	1 (2)	>0.999**
Treatments (cumulative)			
Glucocorticoid	12 (57.1)	24 (48)	0.482*
İntraarticular steroid	9 (42.9)	32 (64)	0.100*
Methotrexate	21 (100)	48 (96)	>0.999**
Leflunomide	1 (4.8)	3 (6)	>0.999**
Sulfasalazine	0	1 (2)	>0.999**
Etanercept	0	34 (68)	-
Adalimumab	0	20 (40)	-
Tocilizumab	0	2 (4)	-
İnfliximab	0	2 (4)	-
Tofacitinib	0	1 (2)	-

ANA antinuclear antibody, CRP C-reactive protein, DMARD disease-modifying anti-rheumatic drug, ESR erythrocyte sedimentation rate, HLA B27 Human Leukocyte Antigen 27, JADAS 27 Juvenile Idiopathic Arthritis Disease Activity Score 27, JIA juvenile idiopathic arthritis

*Chi-square test was employed.

**Fisher's exact test was utilized.

†Mann-Whitney U test was conducted.

When the groups that responded to cDMARDs therapy and those that were resistant to cDMARDs therapy and started bDMARDs therapy were compared, family history was more common in the DMARDs-responsive group (23.8%) (6%) (p=0.044), while ankle involvement was more common in the resistant group (38%) (9.5%) (p=0.016).

Univariate analysis was performed with clinical and laboratory findings that may be associated with resistant disease. Involvement of the ankle/toe joints at presentation increased the risk of resistant disease (p=0.027, CI 95%), while the presence of a family history decreased the risk of resistant disease (p=0.043, CI 95%)

Table 3. Univariate and multivariate analysis of factors associated with refractory disease

	Univariate Analysis (95% CI)	P value	Multivariate Analysis (95% CI)	P value
Gender, male	0.67 (0.24-1.89)	0.453	-	-
Age at diagnosis, months	0.99 (0.98-1.01)	0.704	-	-
Age at symptom onset, months	0.99 (0.98-1.01)	0.461	-	-
Family history	0.20 (0.44-0.95)	**0.043**	0.24 (0.05-1.19)	0.080
Knee	0.18 (0.02-1.47)	0.109	-	-
Ankle/toe involvement	5.82 (1.22-27.85)	**0.027**	5.29 (1.08-25.83)	**0.040**
Wrist/finger involvement	3.81 (0.45-31.57)	0.222	-	-
Uveitis	2.73 (0.31-24.17)	0.367	-	-
Number of active joints	2.04 (0.89-4.68)	0.091	-	-
Physician global assessment	1.00 (0.67-1.50)	0.979	-	-
Patient/parent VAS	1.11 (0.72-1.69)	0.639	-	-
JADAS 27 (at diagnosis)	1.09 (0.94-1.27)	0.246	-	-
ANA positivity	2.32 (0.73-7.32)	0.152	-	-
ESR, mm/hour	1.02 (0.99-1.04)	0.211	-	-
CRP, mg/L	0.99 (0.98-1.01)	0.677	-	-

ANA antinuclear antibody, CRP C-reactive protein, ESR erythrocyte sedimentation rate, JADAS 27 Juvenile Idiopathic Arthritis Disease Activity Score 27, VAS visual analogue scale

CI; confidence interval, OR: odds ratio

When multivariate analysis was performed with the variables that were significant in univariate analysis, there was statistical significance only in the involvement of ankle/toe joints (ankle/toe joints OR=5.29 CI 95% (1.08-25.83), p=0.040, family history OR=0.24 CI 95% (0.05-1.19), p=0.080).

DISCUSSION

This research is one of the notable studies in the literature that examines the factors predicting resistance to cDMARDs therapy in patients with oligoarticular JIA. Through multivariate analysis, we identified that the involvement of the ankle/toe joints is the only significant predictor of refractory disease.

Oligoarticular JIA is more prevalent in females at a ratio of 3:1, with the disease peaking between the ages of 1 and 3. In oligoarticular JIA, the affected joint typically exhibits swelling and sometimes increased warmth, but there is generally little pain or tenderness. The lower limbs are predominantly affected in this type.[7, 8] In a study conducted with 64 patients diagnosed with oligoarticular JIA, it was reported that the most commonly affected joints were one or both knees (89%), with the ankles affected in 36% of cases.[9] In our research, the majority of the patients were female. The most common presentation involved morning stiffness following joint swelling, with the knee being the most frequently affected joint, followed by the ankle.

The therapeutic approach in patients with oligoarticular JIA typically follows a stepwise progression. Initial treatment with NSAIDs and/or IACS is administered, and for those who do not achieve an adequate response, cDMARDs are initiated. Among cDMARDs therapy options, MTX is known to be superior to leflunomide, sulfasalazine and hydroxychloroquine.[3] In prior studies, the initiation rates of cDMARDs in patients with oligoarticular JIA were reported to range from 64.7% to 75%. MTX was identified as the most frequently initiated cDMARDs, with initiation rates between 89% and 94%, followed by sulfasalazine and leflunomide.[10-12] In our research, while the initiation of MTX as the most frequently prescribed cDMARDs aligns with previous findings, we observed a notably higher overall rate of cDMARDs initiation compared to earlier studies.

In the treatment of oligoarticular JIA, when patients exhibit either a lack of response or intolerance to cDMARDs, the recommendation is to transition to bDMARDs.[3] An investigation determined that 45% of oligoarticular JIA patients received biologic DMARDs, with 96% of these patients commencing treatment with tumor necrosis factor inhibitors (TNFi). Etanercept was the most commonly used TNFi, followed by adalimumab and infliximab.[11] Another study indicated that bDMARDs therapy was initiated in 34.2% of 187 oligoarticular JIA patients, with etanercept being the most frequently prescribed biologic agent.[12] In addition, a different research found that bDMARDs therapy was started in 10% of 574 oligoarticular JIA patients, with etanercept again being the most commonly used agent.[13] The use of biologic agents (70.4%) is significantly higher in our study compared to previous studies. This may be due to differences in clinical approaches and the increasing adoption of biologic therapies in recent years. Consistent with previous studies, etanercept was the most frequently initiated bDMARDs in our research, followed by adalimumab and infliximab. Etanercept, approved in 2001 as the first biologic therapy for JIA.[14] Probably for this reason, it remains the most frequently used agent by clinicians, as observed in our clinic.

Uveitis, one of the most serious complications of oligoarticular JIA, develops in 20-25% of patients.[15, 16] Additionally, approximately 50% of JIA patients present with the oligoarticular type, and among this group, 50% develop extended oligoarticular JIA over time.[17] It is well known that extended oligoarticular JIA has a poorer prognosis. In these patients, initiating DMARDs therapy in the early stages of the disease may be considered.[18] In our study, the observed rates of uveitis (9.9%) and the progression to extended oligoarticular JIA (2.8%) were significantly lower compared to the rates reported in the literature.[11, 12] We believe that the low frequency of complications and the reduced progression to extended oligo JIA, can be attributed to the initiation of cDMARDs and bDMARDs therapies in the majority of our patients.

In patients with oligoarticular JIA, ankle involvement, wrist involvement, symmetrical joint involvement, and elevated acute phase reactants at presentation are known poor prognostic factors.[19] In a cohort of 440 JIA patients, ankle involvement was observed in 57% during the first eight years of the disease. This manifestation was most prevalent in extended oligo JIA and RF-negative polyarticular JIA. Patients with ankle involvement within the first year exhibited lower remission rates and increased physical disability. Consequently, assessing ankle involvement is recommended for determining prognosis and tailoring treatment strategies.[20] According to Al-Matar et al., an evaluation of the initial six months' characteristics of 205 oligoarticular JIA patients revealed that ankle and/or wrist involvement predicted joint extension and erosion, indicating disease progression.[21] Further research involving 88 oligoarticular JIA patients examined predictors of inactive disease and relapse. Ankle involvement at disease onset was identified as a significant risk factor for relapse.[22] In our study, ankle/toe joints involvement was identified as a predictor for transitioning to biologic agents. In contrast to prior investigations [12, 19] wrist joint involvement, symmetric joint involvement, elevated acute phase reactants and high JADAS values at diagnosis were not identified as predictive factors for refractory disease.

Our study had some limitations, including its single-center and retrospective design. However, a notable strength of our study is its contribution to the existing literature on predicting the initiation of biologic agents in oligoarticular JIA, despite the extensive research on prognosis in this subgroup. Our findings provide valuable insights for the management of these patients.

CONCLUSION

In conclusion in patients diagnosed with oligoarticular JIA, the involvement of ankle/toe joints at the time of diagnosis increases the risk of resistance to cDMARDs therapy. Therefore, careful monitoring of these patients is warranted during follow-up.

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Author Contributions

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