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Original Article

Biologic therapy in juvenile idiopathic arthritis-associated uveitis: Does it make a difference?

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ABSTRACT

Objective: Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease, and uveitis is its most frequent extra-articular complication. Despite advances in management, uveitis remains a major cause of morbidity.

The aim of this study was to evaluate the demographic, clinical, laboratory, and treatment characteristics of patients with JIA-associated uveitis (JIA-U), with a focus on the impact of biologic therapies and potential risk factors for ocular complications.

Material and Methods: This single-center retrospective cohort study included 49 JIA-U patients followed among 550 JIA cases at Ankara Etlik City Hospital (October 2022–November 2023). Demographics, laboratory parameters, clinical features, and treatment outcomes were collected. Patient characteristics were compared according to biologic therapy use and presence of ocular complications.

Results: The prevalence of uveitis was 8.9%. The mean age was 12.8±4.5 years; 61.2% were female. Oligoarticular JIA was the most frequent subtype (57.1%). Uveitis was asymptomatic in 81.6% of patients, and ocular complications occurred in 34.6%. All patients received methotrexate; 67% required biologic therapy, with adalimumab as the first-line agent. At last follow-up, 84% were in remission, 8% had active disease, and 8% were in drug-free remission. No significant differences were found between groups with or without biologic therapy or ocular complications.

Conclusion: Biologic therapies, particularly adalimumab, are effective in managing JIA-U, but their benefits may not be universal. Early diagnosis, regular ophthalmologic screening, and close collaboration between pediatric rheumatologists and ophthalmologists remain essential to reduce complications and improve outcomes.

Keywords: Arthritis, biologic therapy, uveitis

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease, defined by arthritis of unknown origin that begins before the age of 16 and persists for more than six weeks (1,2). Uveitis, the most frequent and severe extra-articular complication of JIA, is characterized by inflammation of the iris, choroid, and retinal tissues (3-5). Chronic anterior uveitis, which affects 10-20% of JIA patients, is often asymptomatic, bilateral, and predominantly associated with the oligoarticular and rheumatoid factor (RF)-negative polyarticular subtypes (1,6,7). In contrast, acute anterior uveitis, typically presenting unilaterally, is linked to enthesitis-related arthritis (ERA) and HLA-B27 positivity (6).

The most common ocular complications of JIA-associated uveitis (JIA-U), include cataracts, band keratopathy, posterior synechiae, macular and optic nerve edema, and secondary glaucoma (8). Systemic treatment, including conventional and/or biologic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), is essential to prevent the progression of ocular complications.

This study aimed to evaluate the demographic, laboratory, and treatment characteristics of pediatric patients with JIA-U, with a particular focus on the impact of biologic therapies and the identification of potential risk factors for complications.

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MATERIALS and METHODS

This single-center retrospective cohort study analyzed clinical data from JIA-U patients treated at Ankara Etlik City Hospital, (October 2022 - November 2023). All cases were diagnosed by pediatric rheumatologists following the International League of Associations for Rheumatology (ILAR) 2001 classification criteria. Inclusion criteria were: (1) age ≤16 years old at disease onset; (2) confirmed JIA diagnosis meeting ILAR criteria; and (3) consulted an ophthalmologist and diagnosed with uveitis. The exclusion criteria were as follows: (1) infectious uveitis (viral, bacterial, parasitic, or mycoplasma-induced); (2) ocular inflammation caused by metabolic diseases; and (3) other rheumatic diseases complicated by uveitis. All clinical data were extracted and reviewed from the hospital's electronic medical record system.

Demographic and clinical data, including gender, age at arthritis onset, affected joints, ophthalmic examination findings, and ocular complications, were recorded for all patients. Laboratory parameters such as white blood cell count (WBC), hemoglobin (HB), platelet count (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), rheumatoid factor (RF), and HLA-B27 status were collected from patient files. Information on therapeutic medications and follow-up was also documented. Patients were classified into two groups based on whether they received biologic therapy and the presence of ocular complications, and these groups were compared.

Statistical Analysis

Data were analyzed using IBM Statistical Package for the Social Sciences, version 26.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean and interquartile range and standart deviation or median (IQR) and compared using Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were presented as frequencies and percentages (%) and compared using the chi-square or Fisher's exact test. A p value <0.050 was considered statistically significant.

RESULTS

Clinical data of 49 patients diagnosed with uveitis among 550 patients followed with JIA were analyzed. At the time of analysis, the mean age was 12.8±4.5 years, and 61.2% of the cohort were female. At the time of JIA diagnosis, 81.6% of patients were asymptomatic for uveitis. The most common JIA subtype was oligoarticular JIA, identified in 57.1% of cases. Regarding uveitis symptoms, 18.3% of patients were symptomatic, whereas 81.6% were asymptomatic at the time of diagnosis. In 74% of cases, arthritis was the initial presenting complaint and uveitis developed subsequently. Uveitis preceded arthritis in 20% of patients, while both conditions were diagnosed simultaneously in 6%. Uveitis-related complications were observed in 34.6% of cases. The median follow-up duration for all patients was 72 months (min–max; 48–108).

Among the JIA subtypes, 57.1% of patients were diagnosed with oligoarticular JIA, 32.6% with ERA, and 10.2% with polyarticular JIA. Bilateral uveitis was more common than unilateral uveitis (65.3% vs. 34.7%). Chronic anterior uveitis was the most prevalent type (77.5%), followed by acute anterior uveitis (18.3%), while panuveitis was rare (4%). All cases of panuveitis occurred in female patients and involved bilateral eye involvement. ANA positivity was observed in 49% of patients, RF positivity in 2%, and HLA-B27 positivity in 14%. Asymptomatic uveitis was most frequently observed in patients with oligoarticular JIA (90%), followed by ERA (69%) and polyarticular JIA (80%).

Topical corticosteroid eye drops were used as the initial treatment in all patients with uveitis. Prednisolone acetate 1% or its equivalent (1–2 drops, administered 1–2 times daily) was prescribed. In patients who showed no response to topical therapy after three months, methotrexate (MTX; 10–15 mg/m²/week, subcutaneously) and biologic agents were added to the treatment regimen. MTX was administered to all patients (100%), while biologic agents were used in 67%. Adalimumab (20–40 mg every two weeks, subcutaneously) was employed as the first-line biologic therapy in all cases. Biologic therapy was initiated due to inadequate response to MTX in 61% of patients and due to MTX-related adverse effects in 6%. Six patients required a switch in biologic therapy, in which adalimumab was replaced with infliximab (5–10 mg/kg/month, intravenously); among these, three patients were subsequently treated with tocilizumab (8 mg/kg every 2–4 weeks, intravenously). At the last follow-up, 84% of patients were in remission with their current treatment, 8% had active uveitis, and 8% were in drug-free remission.

The demographic data, laboratory findings, and treatment characteristics are summarized in Table I. No statistically significant differences were observed between patients receiving biologic therapy and those who did not in terms of demographic characteristics, uveitis type, JIA subtype, treatment responses, or complications. Additionally, demographic data for patients with and without ocular complications are presented in Table II.

DISCUSSION

The findings of this study contribute significantly to the growing body of evidence supporting the effectiveness of biologic therapies in the management of JIA-U. The findings of this study are largely consistent with the existing literature, particularly regarding the prevalence, clinical characteristics, and treatment outcomes of JIA-U.

Table I: Comparison of patients receiving and not receiving biologic treatment

	Total	Biological treatment		
		No	Yes	p
Number of patients	49	16	33	-
Demography				
Age,* years	12.8±4.5	12.3±5.4	13±4	0.620§
Female†	30 (61.2)	7 (43.8)	22 (66.7)	0.380‖
Age in years at diagnosis of uveitis‡	6 (4-10)	6.4 (4.2-10.6)	5.8 (4-9.5)	0.410¶
Age in years at diagnosis of JIA‡	4 (2-8)	5 (2.2-11)	4 (2-7.5)	0.440¶
Follow-up period‡ months	72 (48-108)	54 (48-105)	84 (54-114)	0.460¶
Laboratory				
Hemoglobin*,g/dl	12.4±1.5	12.35 ±1.12	12.40±1.67	0.850§
White blood cell count‡/mm^3	8120 (6975-9870)	8550 (7285-9962)	7970 (6655-9695)	0.240¶
Platelet count* /mm^3	383.979±98.237	387.265±100.131	382.212±98.824	0.850§
Sedimentation‡ mm/h	22 (7.5-43)	16 (5-53)	24 (8.5-43)	0.510¶
C-reactive protein‡, g/dl	7.5 (3-16.7)	10 (3-23)	5.5 (3-11)	0.360¶
RF positivity†	1 (2)	0	1 (3)	0.480**
ANA positivity†	24 (49)	7 (43.8)	17 (51.5)	0.610‖
HLA B27 positivity†	7 (14)	4 (25)	3 (9.1)	0.130**
Type of uveitis				
Anterior uveitis†	47 (95.9)	16 (100)	31 (94)	0.600**
Panuveitis†	2 (4,1)	0	2 (6)	
Presence of symptoms				
Symptomatic uveitis†	9 (18.4)	3 (18.8)	6 (18.2)	0.960‖
Presence of ocular complications	17 (34.6)	5 (31.2)	12 (36.4)	0.720‖

:** *mean±SD,* **†:** *n (%),* **‡:** *median (IQR),* **§:** *Student's t-test,* **‖:** *Chi-square test* **¶:** *Mann–Whitney U test,* *:** *Fisher's Exact test,* ***RF:** rheumatoid factor,* ***ANA:** antinuclear antibody*

Table II: Demographic data on 49 patients who developed uveitis with and without ocular complications

	Total	Ocular complications		
		No	Yes	p
Total cases*	49 (100)	32 (65.3)	17 (34.7)	
Gender (Female)*	30 (61.2)	21 (65.6)	9 (52.9)	0.386§
Age in years at diagnosis of JIA†	4 (2-8)	5.5 (2-11.5)	3 (2-6)	0.136‖
Age in years at diagnosis of uveitis†	6 (4-10)	7 (4-11.4)	5.8 (4-7)	0.128‖
Interval in months from diagnosis of JIA to diagnosis of uveitis ‡	12 (-39-87)	6 (-39-87)	12 (-12-62)	0.574‖
Follow-up period months†	72 (48-108)	66 (48-108)	84 (48-120)	0.759‖
JIA subtype				
Persistent oligoarticular JIA	28 (57.1)	17 (53.1)	11 (64.7)	0.176§
Enthesitis related arthritis	16 (32.7)	13 (40.6)	3 (17.6)	
Polyarticular JIA	5 (10.2)	2 (6.3)	3 (17.6)	
ANA positivity*	24 (49)	13 (40.6)	11 (64.7)	0.108§
Anterior uveitis*	47 (96)	31 (96.9)	16 (94.1)	0.298§
Bilateral uveitis*	32 (65.3)	23 (71.9)	9 (52.9)	0.318§
Asymptomatic uveitis*	40 (81.6)	28 (87.5)	12 (70.6)	0.244§
Using of biological drugs*	33 (67.3)	21 (65.6)	12 (70.6)	0.724§

***:** *n (%),* **†:** *median (IQR),* **‡:** *median (min-max),* **§:** *Chi-square test,* **‖:** *Mann–Whitney U test*

In terms of treatment, this study provides further evidence supporting the use of biologic therapies, particularly adalimumab, in the management of JIA-U. The remission rate of 84% observed in this study is comparable to the rates reported in other studies evaluating adalimumab's efficacy. For example, Biester et al. (9) and Tynjälä et al. (10) demonstrated similar remission rates with adalimumab, particularly when used in combination with MTX. The study also highlights the role of alternative biologic agents, such as infliximab and tocilizumab, in cases where adalimumab was either ineffective or poorly tolerated. This finding aligns with the growing body of evidence suggesting that switching biologic agents can be an effective strategy for treatment-resistant uveitis (11-19).

The reported prevalence of uveitis (8.9%) falls within the range observed in previous studies, which typically report rates between 6% and 20% depending on the population studied and the duration of follow-up (6, 7). The predominance of oligoarticular JIA as the most common subtype associated with uveitis (57.1%) is also well-documented in the literature. For instance, studies by Saurenmann et al and Edelsten et al. (8, 20) similarly identified oligoarticular JIA as the subtype with the highest risk of uveitis, particularly in ANA-positive patients. This study further supports these findings by demonstrating that ANA positivity was observed in 49% of patients, a rate consistent with other reports linking ANA positivity to an increased risk of uveitis.

The high proportion of asymptomatic uveitis cases (81.6%) at the time of JIA diagnosis is another critical finding that aligns with prior research. Angeles-Han et al (6) emphasized that the asymptomatic nature of uveitis in many JIA patients necessitates routine ophthalmologic screening to prevent complications. This study reinforces the importance of such screenings, particularly in high-risk subgroups such as oligoarticular JIA patients, where asymptomatic uveitis was observed in 90% of cases. Additionally, the study's finding that 34.6% of patients experienced uveitic complications is consistent with the complication rates reported in the literature, which range from 20% to 40% (6, 7) These complications, including cataracts, glaucoma, and band keratopathy, highlight the need for early and aggressive treatment to preserve visual outcomes.

One unique contribution of this study is its detailed analysis of the demographic and clinical characteristics of patients with and without ocular complications. While no statistically significant differences were observed between these groups, the data provide valuable insights into the potential risk factors for complications and the overall effectiveness of current treatment strategies. Additionally, the study's finding that there were no significant differences in treatment responses or complications between patients receiving biologic therapy and those who did not raises important questions about the factors influencing treatment outcomes. This suggests that while biologic therapies are highly effective in many cases, their benefits may not be universal, and further research is needed to identify predictors of treatment success.

Another notable contribution of this study is its focus on the timing of uveitis onset relative to arthritis. The finding that uveitis preceded arthritis in 20% of cases and was diagnosed simultaneously in 6% of cases highlights the variability in disease presentation. This variability has been reported in other studies, such as those by Saurenmann et al. (8), and underscores the importance of maintaining a high index of suspicion for uveitis in JIA patients, even in the absence of arthritis symptoms.

In conclusion, this study not only corroborates existing findings in the literature but also provides new insights into the clinical characteristics, treatment responses, and outcomes of JIA-associated uveitis. By emphasizing the importance of early diagnosis, regular screening, and individualized treatment strategies, this study contributes to the ongoing efforts to optimize the management of this challenging condition. Future research should focus on identifying biomarkers for treatment response, understanding the long-term outcomes of biologic therapies, and exploring novel therapeutic approaches for refractory cases.

This study has several limitations that should be acknowledged. First, its retrospective design may introduce selection bias and limit the ability to establish causal relationships. Second, the study was conducted at a single tertiary referral center, which may not fully represent the broader population of JIA-U patients. Third, the sample size, while sufficient for descriptive analysis, may not have been large enough to detect subtle differences in outcomes between treatment groups, particularly regarding the use of biologics. Additionally, the lack of long-term follow-up data limits our ability to assess the durability of treatment responses and the long-term impact of early interventions. Finally, while we relied on clinical records for data collection, variability in documentation practices may have influenced the accuracy of certain findings, such as the exact timing of uveitis onset or the severity of complications.

Future studies with prospective designs, larger sample sizes, and multicenter collaborations are needed to validate our findings and provide a more comprehensive understanding of JIA-associated uveitis. Long-term follow-up studies would also be valuable to evaluate the sustained efficacy and safety of different treatment strategies.

CONCLUSION

The findings suggest that advancements in early diagnosis and management, rather than the use of biologic therapy alone, play a key role in minimizing complications in JIA-U. Close collaboration between pediatric rheumatologists and ophthalmologists is essential for early detection and effective management of complications.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Etlik City Hospital (10.01.2024, reference number: 2024-006).

Contribution of the authors

AA, EB, EAE analyzed and interpreted the patients data. AA was a major contributor in writing the manuscript. YO performed the examination of the eye. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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