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LETTER TO THE EDITOR

Predictors of the Need for Anti-TNF Alpha Drugs in Patients With Juvenile Idiopathic Arthritis-Associated Uveitis

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Dear Editor,

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory arthritis in childhood that affects children younger than 16 years of age presenting with arthritis more than 6 weeks, and diagnoses after exclusion of other causes. JIA is associated with various complications, including uveitis, inflammatory bowel disease, and skin manifestations [1]. The prevalence of uveitis in JIA ranges from 11% to 30% [2]. Uveitis is more common in patients with JIA who have oligo-articular disease course and anti-nuclear antibody (ANA) positivity. Chronic anterior uveitis accompanies oligo-articular JIA, rheumatoid factor (RF) negative poly-articular JIA, and psoriatic arthritis, and tends to be asymptomatic and has a severe disease course. On the other hand, acute anterior uveitis accompanies enthesitis-related arthritis (ERA) [1, 2]. Acute anterior uveitis associated with ERA is usually unilateral, sudden-onset, and symptomatic as erythema, pain, and photophobia [3]. Ocular complications of JIA-associated uveitis are seen in 28%–67% of the patients, such as synechiae, cataracts, band keratopathy, and glaucoma, which may lead to poor visual outcome in 12% [3–5]. Therefore, early diagnosis and appropriate treatment with good collaboration between pediatric rheumatologists and ophthalmologists and regular ophthalmologic monitoring are crucial to prevent ocular complications [6].

The aim of this study is to investigate the predictors of the requirement of anti-tumor necrosis factor (TNF) alpha treatment in patients with JIA-associated uveitis.

1 | Materials and Methods

This is a retrospective case-controlled study. The medical files of 31 pediatric patients who were diagnosed with JIA-associated uveitis under 16 years of age and were followed up for at least 6 months at the Departments of Pediatric Rheumatology and Ophthalmology of Gazi University between 2012 and 2023 were retrospectively investigated. The diagnosis of JIA was performed according to the International League of Associations for Rheumatology (ILAR) classification criteria [7]. The diagnosis of uveitis was made by an ophthalmologist who specialized in uveitis. One patient excluded due to inaccessible data, and one patient excluded due to follow-up lost. The demographics, laboratory features, and treatments were recorded for each patient. As demographics, the age, gender, age at symptom onset, subtype of JIA, age at diagnosis of JIA and uveitis, family history for uveitis, existence of consanguineous marriage, single- or double-sided eye involvement, type of uveitis, complications of uveitis, concomitant diseases; and subtype of JIA were noted. In laboratory studies, ANA, human leukocyte antigen (HLA) B27, RF, complete blood count, and biochemical parameters were noted at the first and last visits. Juvenile arthritis disease activity score 27 (JADAS27) was used to evaluate and monitor the disease severity of JIA. JADAS27 consists of the average of four parameters, including physician global assessment of disease activity, parent and/or patient global assessment of well-being, number of active joints in 27 joints (cervical spine, first-second-third metacarpophalangeal joints, proximal interphalangeal joints, elbows, wrists, hips, knees, and ankles), and degree of acute phase reactants (erythrocyte sedimentation rate). A higher JADAS27 shows severe disease activity in JIA [8].

Topical corticosteroids and topical mydriatics with or without systemic corticosteroids were initiated first in all patients with anterior uveitis. Patients whose uveal inflammation could not be suppressed or who experienced recurrent uveitis attacks or

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had ocular complications related to uveitis at the time of diagnosis were treated with methotrexate (MTX) 10–15 mg/m^2 once weekly. Anti-TNF treatment was started as adalimumab (ADA) at a dose of 20–40 mg/m^2 every other week (increased to once weekly, where necessary) or infliximab (INF) at a dose of 3–10 mg/kg at 0, 2, and 6 weeks and 8 weeks apart thereafter intravenously (increased to once monthly, where necessary) in patients who did not go into remission. If the active uveitis symptoms could not be suppressed, the anti-TNF treatment was changed to another anti-TNF treatment.

Patients were divided into two groups according to anti-TNF usage: Group 1 comprised the JIA-associated uveitis patients who did not use anti-TNF treatments, and Group 2 comprised the JIA-associated uveitis patients on anti-TNF treatments. We have evaluated the predictors of anti-TNF requirement in patients with JIA-associated uveitis.

The data were evaluated with the SPSS version 23.0 software program (Chicago, IL, USA). Descriptive data were given as numbers and percentages. According to the distribution of the data, variables were defined as median (interquartile range [IQR]) or mean ± standard deviation. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to evaluate the normality of the distribution of continuous variables. Independent sample *t*-tests for normally distributed variables or Mann–Whitney *U* test for non-normally distributed ones were used to compare the differences. Chi-squared or Fisher's exact tests were performed to compare the categorical variables. The univariate logistic regression analysis was applied to assess the relationship between each variable and anti-TNF usage. Odds ratios were calculated with 95% confidence intervals (95% CIs). A p-value < 0.05 was considered statistically significant.

2 | Results

There was a negligible female dominance ($n = 16$, 55%, $p = 0.219$). Age at diagnosis of JIA and age at symptom onset of JIA were significantly lower in patients with JIA uveitis who used anti-TNF (Group 2) compared to those who did not use anti-TNF (Group 1) ($p = 0.025$ and $p = 0.026$). Although age at diagnosis of uveitis was lower in Group 2, no significant difference was found between the groups ($p = 0.147$). ANA-positive oligo-articular JIA was the most common JIA subtype of the cohort at 62%, following ANA-negative oligo-articular JIA, ERA, and RF-negative poly-articular JIA. 86% of patients had chronic anterior uveitis, while 14% of patients had acute anterior uveitis. The rates of complications due to uveitis were higher in Group 2 than in Group 1 ($p = 0.035$). In the evaluation of the laboratory data, only ANA positivity was more common in Group 2 than in Group 1 ($p = 0.046$). When the evaluation of disease severity on the first visit, last visit, and on the diagnosis of uveitis, only JADAS27 on the first visit was significantly higher in Group 2 than in Group 1 ($p = 0.048$) (Table 1).

In univariate analysis, age at diagnosis of uveitis, consanguineous marriage, ANA positivity, and JADAS27 on the first visit were significantly associated with the use of anti-TNF ($p = 0.023$, $p = 0.004$, $p = 0.027$, and $p = 0.029$) (Table 2).

3 | Discussion

JIA-associated uveitis may cause irreversible visual loss in the long-term follow-up. Although topical/oral corticosteroids with MTX are successfully used in the treatment of such patients, sometimes these agents may be insufficient to control eye inflammation. Adding biological disease-modifying anti-rheumatic drugs (DMARDs) to the therapy, especially anti-TNF drugs, significantly improves the disease course, but clinicians may have some concerns related to the side effects of anti-TNF drugs.

Uveitis develops in more than half of the patients with JIA-associated uveitis within 6 months of the diagnosis, while uveitis preceded arthritis in approximately 10% of the patients [9], this rate was similar (7%, 2 patients) in our cohort. The recommended interval for screening uveitis is shorter in small children (< 7 years old) with JIA due to the higher risk of uveitis development [10]. In our study, we observed that younger age at the diagnosis of uveitis and ANA positivity were independent risk factors for predicting the requirement of anti-TNF drugs in pediatric patients with severe uveitis. In this context, children with early-onset ANA-positive JIA have a higher risk of developing uveitis as well as a more severe course of uveitis, so we recommend that clinicians be very careful in the follow-up of uveitis in these children.

The use of anti-TNF drugs in patients with JIA-associated uveitis varies from 38.5% to 45% in the literature [11, 12]. In our study, we observed a slightly higher rate, 58.6%. According to the recommendations of the American College of Rheumatology for JIA-related uveitis, anti-TNF therapies should be started in patients who do not achieve remission with topical/systemic corticosteroids and conventional DMARDs within 3 months or who have severe uveitis with ocular complications [13]. JIA-related uveitis may cause several ocular complications, such as macula edema, cataracts, glaucoma, posterior synechiae, and blindness [2]. Suppressing uveal inflammation with early diagnosis and treatment is important to prevent ocular complications [2, 13]. In our study, the need for anti-TNF use was high in JIA-associated uveitis patients with ocular complications. Therefore, timely initiation of anti-TNF therapies is essential to improve visual outcomes and reduce ocular complications. Osswald et al. [14] described the risk factors leading to anti-TNF therapies in 73 children with severe uveitis, including 14 (19%) with JIA-associated uveitis. 13 (18%) out of 73 patients exposed to anti-TNF drugs, while 5 out of 14 (36%) patients with JIA-associated uveitis used anti-TNF drugs due to unresponsiveness to MTX and glucocorticoids. Uveitis secondary to a systemic disease, family history of an autoimmune disease, young age at diagnosis of uveitis, eye surgery, presence of ocular complications or vision loss in the diagnosis of uveitis, ANA positivity, and HLA B27 positivity were reported risk factors for the requirement of anti-TNF drugs in pediatric patients with severe uveitis [14]. In our study, younger age of diagnosis uveitis, ANA positivity, and higher JADAS27 were found as predictors of the need for anti-TNF drugs. We believe that early initiation of anti-TNF therapy in JIA-associated uveitis patients with these clinical and laboratory predictors may result in better visual acuity, fewer complications, less exposure to topical/systemic corticosteroids, and fewer corticosteroid side effects. Among anti-TNF drugs, ADA and INF have beneficial effects on JIA-associated uveitis,

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TABLE 1 | The comparison of characteristics and demographic features of the juvenile idiopathic arthritis patients with and without uveitis.

	Total cohort	Group 1 (JIA uveitis without anti-TNF use)	Group 2 (JIA uveitis with anti-TNF use)	
	n (%)/median (IQR)	*n* (%)/median (IQR)	*n* (%)/median (IQR)	*p**
Total		12 (100)	17 (100)	
Female	16 (55)	5 (41)	11 (65)	0.219
Age	15 (12–18)	17 (16–18)	14 (9.5–17.5)	0.067
Age at diagnosis of JIA, years	8 (3.5–10)	10.5 (6.75–12)	5 (2–8.5)	*0.025*
Age at symptom onset of JIA, years	5 (3–8)	8.5 (4–11)	4 (2–8.5)	*0.026*
Age at diagnosis of uveitis, years	7 (5.5–12.5)	12 (10–14.75)	6 (5–11.5)	0.147
Family history of a rheumatologic disease	9 (31)	4 (33)	5 (29)	0.822
Consanguinity between parents	9 (31)	2 (17)	7 (41)	0.053
JIA subtype				
ANA-positive oligo-JIA	18 (62)	4 (33)	14 (82)	*0.007*
ANA-negative oligo-JIA	5 (17)	3 (25)	2 (12)	
RF-negative poly-JIA	1 (4)	2 (17)	—	
ERA	5 (17)	3 (25)	1 (6)	
Uveitis type				
Chronic anterior uveitis	24 (86)	9 (75)	16 (94)	0.053
Acute anterior uveitis	4 (14)	3 (25)	1 (6)	
Bilateral eye involvement		9 (75)	15 (88)	0.352
Complications due to uveitis	14 (48)	3 (25)	11 (65)	*0.035*
Laboratory findings				
ANA positivity	13 (45)	4 (7.5)	9 (53)	*0.046*
HLA-B27 positivity	5 (17)	2 (17)	3 (18)	0.945
WBC $\times 10^3$/uL	9.1 (7.55–11)	9.4 (7.85–11)	8.3 (6.8–12.5)	0.467
NEU $\times 10^3$/uL	5.3 (4.5–7.3)	5.8 (4.37–7.85)	4.7 (3.4–6.5)	0.274
Hb g/dL	12.3 (11.5–13.4)	12.7 (11.2–14)	12 (11.5–12.95)	0.432
PLT $\times 10^3$/uL	351 (261–389)	303 (256–375)	406 (299–469)	0.264
BUN mg/dL	12.6 (10.3–14.2)	11.6 (10.4–13.4)	14 (10.15–17.3)	0.248
Cre mg/dL	0.4 (0.3–0.48)	0.46 (0.42–0.52)	0.36 (0.28–0.46)	0.274
Albumin g/dL	4.3 (4.2–4.5)	4.24 (4.2–4.4)	4.5 (4.1–4.7)	0.130
ALT U/L	13 (11–19)	14.1 (11–19)	12 (10–19)	0.274
AST U/L	23 (17–28)	22 (16–27)	27 (21–34)	0.252
Disease activity for JIA				
JADAS27, on the first visit	3.5 (1.5–5)	3 (1–5)	5.75 (1.125–7.50)	*0.048*
JADAS27, on the last visit	1 (1–2)	1 (1–2)	1 (1–1.875)	0.703
JADAS27, on the diagnosis of uveitis	2.5 (1.5–3.5)	2 (1.625–3.50)	3 (1.4375–3.50)	0.462

Note: p values less than 0.05 are statistically significant and italicized.
Abbreviations: ALT, alanine aminotransferase; ANA, anti-nuclear antibody; AST, aspartate aminotransferase; BUN, blood urine nitrogen; Cre, creatinine; ERA, enthesitis-related arthritis; Hb, hemoglobin; HLA, human leukocyte antigen; JADAS27, juvenile arthritis disease activity score 27; JIA, juvenile idiopathic arthritis; NEU, neutrophil; PLT, platelet; RF, rheumatoid factor; TNF, tumor necrosis factor; WBC, white blood cell.
**p*-Value illustrates the comparison of Group 1 and Group 2.

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TABLE 2 | The factors associated with adding an anti-TNF to the treatment of uveitis related to juvenile idiopathic arthritis.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Female gender	0.174 (0.043–0.391)	0.090	1.843 (0.657–60.637)	0.110
Age at diagnosis of JIA, years	0.186 (0.128–0.5)	0.214	1.277 (0.076–1.320)	0.054
Age at symptom onset of JIA, years	0.025 (0.073–0.574)	0.114	1.119 (0.841–11.144)	0.090
Age at diagnosis of uveitis, years	1.124 (1.022–2.122)	*0.023*	0.562 (0.244–1.092)	0.150
Bilateral eye involvement	0.235 (0.092–0.419)	0.480	0.556 (0.086–3.812)	0.565
Family history of a rheumatologic disease	0.314 (0.252–0.817)	0.284	0.384 (0.073–6.340)	0.736
Consanguineous marriage between parents	1.435 (1.239–1.632)	*0.004*	1.638 (0.519–541.043)	0.162
ANA positivity	1.217 (1.041–1.393)	*0.027*	2.333 (0.710–149.646)	0.088
JADAS27 scores, in the first visit	1.167 (1.020–1.374)	*0.029*	0.826 (0.308–2.239)	0.226
JADAS27 scores, in the last visit	0.199 (0.072–0.343)	0.589	0.452 (0.284–3.902)	0.606
JADAS27 scores, in the diagnosis of uveitis	0.118 (0.058–0.233)	0.503	0.377 (0.273–1.539)	0.408

Note: p values less than 0.05 are statistically significant and italicized.
Abbreviations: ANA, anti-nuclear antibody; JADAS27, juvenile arthritis disease activity score 27; JIA, juvenile idiopathic arthritis; TNF, tumor necrosis factor.

whereas etanercept (ETC) may cause uveitis as a paradoxical effect, so ETC is not recommended for JIA-associated uveitis [2, 15]. Therefore, we speculate that ADA should be preferred over ETC in a young JIA patient with ANA positivity regardless of the presence of uveitis because the patient may have a severe disease course and be at a higher risk of developing uveitis.

Measuring disease activity with scoring systems like JADAS27 is important in JIA for the determination of ongoing active joints and preventing joint damage with appropriate treatment [9]. In patients with JIA, if initial treatment is delayed or inadequate during the follow-up, permanent joint damage may develop, and quality of life may decrease; therefore, when making treatment decisions, appropriate and intensive inflammation suppressive therapy should be applied in patients with active joint inflammation and high disease activity score [16]. When we evaluated the association between the disease severity of JIA and uveitis, higher JADAS27 at the diagnosis of JIA was determined as an independent risk factor for the need for anti-TNF therapy in JIA-associated uveitis. However, no statistically significant association was found in predicting the need for anti-TNF use with JADAS27 at the time of uveitis development. Although lower disease activity scores were expected in oligo-JIA compared to poly-JIA and ERA, the small number of poly-JIA and ERA patients in our study may explain the higher baseline JADAS27 in oligo-JIA patients with uveitis requiring anti-TNF. Patient/parent assessment of well-being and acute phase markers also impact the JADAS27 calculation.

Although parental consanguinity causes many genetic, metabolic, and rheumatologic diseases, there is no proven genetic inheritance in JIA-associated uveitis in the current literature [17]. The serine 11 in HLA-DRβ1 and the genotype of TRAF1-C5 should increase the risk of JIA-associated uveitis [18, 19]. In our study, parental consanguinity was found to be an independent risk factor for severe JIA-associated uveitis with a need for anti-TNF therapy. We speculated that in addition to many genetically inherited diseases severe JIA-associated uveitis may be prevented by reducing the rate of consanguineous marriages by raising public awareness. Genetic factors may influence the risk of uveitis and treatment responses, and further studies are needed.

The main limitations of our study are its retrospective nature, including one center, and the small number of patients.

4 | Conclusion

Younger age diagnosis of uveitis, ANA positivity, parental consanguinity, and higher JADAS27 at diagnosis of JIA might be the predictors of the need for anti-TNF therapy in patients with JIA-associated uveitis, and these clinical findings might guide clinicians for prompt and effective management of uveitis. Timely anti-TNF usage based on these predictors may result in better visual outcomes, earlier disease suppression, and fewer ocular complications.

Author Contributions

D.G.Y. and S.A.B. conceived the presented idea. D.G.Y. and S.A.B. designed the study methodology. D.G.Y. verified the analytical methods. D.G.Y., N.B., H.B.O., and S.A.B. contributed to the interpretation of the results. D.G.Y. and S.A.B. wrote the first draft of the manuscript. D.G.Y., N.B., and H.B.O. supervised the findings of this work. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors have nothing to report.

Ethics Statement

This study was performed in line with the principles of the Declaration of Helsinki. The present study was approved by the Ethics Committee of the Gazi University (2024, approval number: 882).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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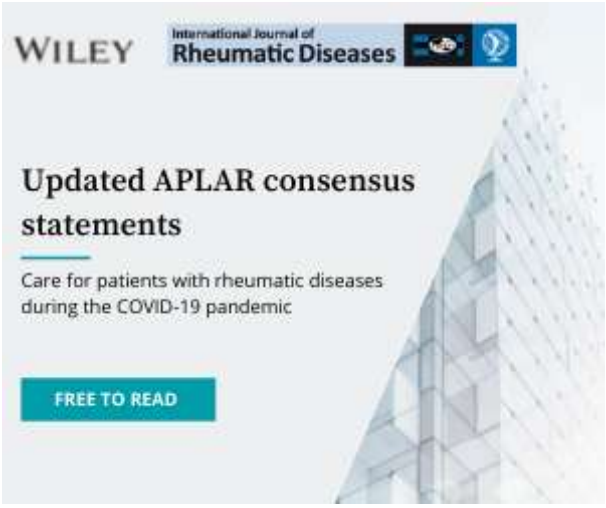
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