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ORIGINAL ARTICLE

Clinical features and immunosuppressive treatment results in cases of uveitis related to juvenile idiopathic arthritis: A retrospective cohort study

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Abstract

Purpose: To present the demographic and clinical characteristics and treatment management of patients who were followed with the diagnosis of juvenile idiopathic arthritis-associated uveitis (JIA-U).

Methods: Data from 66 eyes of 33 patients with JIA-U who were followed in our clinic between 2018 and 2024 were retrospectively reviewed. Demographic findings, best-corrected visual acuity (BCVA) according to the Snellen chart at the first and last visit, ocular complications, applied treatment regimens, side effects of drugs, and need for ocular surgery were retrospectively analyzed. In addition, the age, age at the time of first diagnosis, BCVA values, ocular complications, and surgical needs of patients diagnosed with uveitis before their first visit to our clinic (Group 1) and patients diagnosed with uveitis for the first time by us (Group 2) were compared.

Results: Twenty-seven of the patients were female, six were male, and the mean age was 8.8±3.9 years. All patients had chronic anterior uveitis, and the involvement was bilateral in 30 of them. The most common type was oligoarticular type JIA (84.8%). MTX was the first choice for systemic treatment in all patients. Biological treatment was started in 23 patients. The most common ocular complication was posterior synechiae (49.2%). Posterior synechiae, band keratopathy, and cataract rates were higher in Group 1 ($p=0.001$, $p=0.012$, and $p=0.026$, respectively). The mean initial BCVA value in Group 1 was statistically significantly lower than Group 2 ($p<0.05$).

Conclusion: With a timely and appropriate treatment regimen in JIA-U, the rates of sight-threatening ocular complications can be significantly reduced.

Keywords: Adalimumab; juvenile idiopathic arthritis; methotrexate; ocular complications; uveitis.

Juvenile idiopathic arthritis (JIA)-associated uveitis (JIA-U) is the most common cause of childhood non-infectious uveitis, usually occurring at an early age and having a clinically silent, chronic course. Due to the silent course of uveitis, patients may be diagnosed late and therefore may encounter serious ocular complications at presentation. In patients presenting with complications, the treatment process is long and difficult, and intraocular surgery may be required at a high rate. Untreated or resistant cases can present with serious vision loss.[1] Although the pathogenesis

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of JIA-U has not yet been fully elucidated, it is thought to be a multifactorial autoimmune disease in which many genetic and environmental parameters are intertwined.[2-7]

The primary target in the treatment of autoimmune diseases is the suppression of inflammatory activity. For this purpose, local and systemic corticosteroids, non-biological disease-modifying antirheumatic drugs (DMARDs), and biological DMARD agents are used in the treatment of JIA-associated uveitis, respectively. In this way, it is aimed to rapidly suppress intraocular inflammation, prevent relapses, and achieve clinical remission.[8,9] JIA-U may require different treatment schemes for each patient, considering the severity of the disease, response to medication, and side effects. The aim of this study is to provide a descriptive analysis of the patients we follow due to JIA-U in our clinic, which is a reference center, and to draw attention to treatment management.

Materials and Methods

This study, designed as a retrospective cohort, included data from 63 eyes of 33 patients who were diagnosed with JIA by a pediatric rheumatologist and followed up for JIA-U at the Gazi Yasargil Training and Research Hospital Eye Clinic between 2018 and 2024. Ethics committee approval was obtained for the study (2024/168), and the study was conducted in accordance with the principles of the Helsinki Declaration.

Age, gender, age at first diagnosis, uveitis type (acute/recurrent/chronic uveitis and anterior/intermediate/posterior/panuveitis), JIA subtype obtained from the Ministry of Health patient information form, and anti-nuclear antigen (ANA) positivity, best-corrected visual acuity (BCVA) according to Snellen chart at the first and last visits, presence of uveitis diagnosis before presentation to our clinic, ocular complications, applied treatment regimen, drug side effects, and need for ocular surgery were retrospectively examined. In addition, we divided patients into two groups. Patients who were diagnosed with uveitis at an external center and had a history of follow-up and treatment (just treatment with corticosteroids) when they first applied to our clinic were classified as Group 1, and those who were diagnosed with uveitis for the first time by us were classified as Group 2 and the findings were compared. In the treatment planning, topical corticosteroids and mydriatics were started in all patients in the presence of active anterior uveitis. In severe cases, systemic corticosteroids were applied at 1 mg/kg/dose and then tapered. In patients who initially presented with ocular complications and who had an anterior chamber reaction of at least 1+, a non-biological DMARD was added to the treatment. The preferred first DMARD was methotrexate (MTX) administered subcutaneously at a dose of 10–15 mg/kg/week. Oral MTX was avoided due to reduced gastrointestinal absorption and limited bioavailability at standard pediatric dosing, as well as difficulty with oral administration in younger children.[10]

In cases where adequate response was not obtained despite at least 12 weeks of MTX treatment, and/or where new ocular complications developed, and/or who required ≥3 drops of topical steroid per day to control uveitis, and who showed recurrence when the systemic steroid dose dropped below 5 mg/day, a biological DMARD was added to the treatment. The first biological agent preferred in resistant cases was adalimumab (40 mg loading dose followed by 20 mg/2 weeks in patients under 30 kg, 80 mg loading dose followed by 40 mg/2 weeks in patients over 30 kg). In cases that did not respond to the standard treatment dose and duration of adalimumab for at least 3 months, the frequency of ADA application was adjusted weekly before the biological shift. Again, in cases that did not respond or in cases with side effects, another biological agent (infliximab/tocilizumab) was switched to.

The absence of an attack requiring topical or systemic steroids during follow-up under the current immunosuppressive treatment was accepted as remission. In patients with at least 2 years of remission, the frequency of use of MTX was reduced to once every 2 weeks and then stopped. In patients using MTX and biological agents, the frequency of use of the biological agent was first reduced. If remission continued, the biological agent was stopped, and MTX treatment was continued. When remission was maintained with MTX, the aim was to gradually reduce the frequency of use and discontinue the drug.

Results

Twenty-seven patients were female (81.8%) and six were male (18.2%), and the mean age was 8.8±3.9 (2–16) years. The mean age at first presentation was 5.03±2.21 (2–11) years, whereas the mean follow-up period was 22.8±16 (6–72) months. The initial complaint of four (12.1%) patients was decreased vision, while all the remaining patients were asymptomatic, and uveitis was detected during eye examination. All patients had chronic anterior uveitis, and 30 (90.9%) patients had bilateral involvement, whereas three (9.1%) patients had unilateral involvement. Twenty-eight patients (84.8%) had oligoarticular type JIA, 5 patients (15.2%) had polyarticular type JIA, and 26 patients

(78.8%) were ANA positive. The frequency of uveitis episodes was 3.1±2.2 (1–6) during follow-ups.

All patients were started on non-steroid immunosuppressive therapy, and the first non-steroid treatment option was MTX in all our patients. However, during the follow-up period, 23 of these 33 patients (69.6%) had a biological agent added to their treatment. The mean biologic start month after the first application was 13.09±14.7 (3–60) months. Our first choice of biologic was ADA in all patients. While 18 (78.2%) of the 23 patients who were started on ADA responded to ADA treatment administered every 2 weeks, four (17.3%) patients did not respond, so ADA was switched to weekly dosing, and three patients responded to weekly ADA treatment. One (4.5%) patient did not respond to weekly MTX and weekly ADA treatment, so ADA was switched to infliximab, and remission was achieved.

On the other hand, no side effects were observed in 26 (79%) patients due to the drugs. During the follow-up period, MTX was stopped in four (12%) patients due to MTX-related elevation of liver function tests, and treatment was continued with only the biological agent. In one (3%) patient, peritoneal tuberculosis (TB) developed while using ADA, so ADA was stopped and tuberculosis treatment was started. MTX treatment was continued in this patient. In one (3%) patient, ADA was stopped and tocilizumab was started because of severe hair loss after the initiation of ADA.

The ongoing treatment schedule of the patients at the last visit is summarized in Table 1. Ocular complications observed during the follow-up period are summarized in Table 2. Surgical intervention was performed in 10 (15.8%) eyes due to ocular complications. Phacoemulsification surgery with intraocular lens implantation (PHACO+IOL) was performed in seven eyes due to cataract, and PHACO+IOL+trabeculectomy surgery was performed in three eyes due to cataract and glaucoma unresponsive to medical treatment. One eye underwent seton surgery because intraocular pressure could not be controlled with trabeculectomy or medical therapy.

The mean BCVA values at the first and last visits were 0.82±0.26 and 0.88±0.21, respectively, and there was a statistically significant improvement (p=0.013).

In Group 1, there were 15 patients (45.5%) who were diagnosed with uveitis before applying to our clinic, and in Group 2, there were 18 patients (54.5%) who were diagnosed with JIA-related uveitis for the first time by our clinic. The mean age in the groups and the age at the time of first diagnosis were 11.8±3.4 years and 5.33±2.22 years in Group 1, and 6.33±2.11 years and 4.78±2.23 years in Group 2, respectively. While the mean age was significantly lower in Group 2 (p<0.001), there was no statistically significant difference in terms of mean age at first diagnosis (p=0.429). When we look at the initial and final BCVA values, they were 0.77±0.25 and 0.85±0.26 in Group 1, and 0.86±0.27 and 0.91±0.15 in Group 2, respectively. While the mean initial BCVA value in Group 1 was statistically significantly lower than Group 2, there was no significant difference between the mean final BCVA values in the groups (p=0.021 and p=0.352, respectively). Ocular complications and surgical needs in the groups are summarized in Table 3. The rate

Table 1. Treatments used by patients at the last visit

Treatment	n (%)
MTX	10 (30.3)
MTX+ADA*	12 (36.3)
MTX+ADA$^{\&}$	2 (6.06)
MTX+ADA$^{¥}$	2 (6.06)
MTX+IFX	1 (3.03)
MTX+Tcz	1 (3.03)
MTX+AntiTuberculosis therapy	1 (3.03)
ADA*	2 (6.06)
ADA$^{\&}$	1 (3.03)
ADA$^{¥}$	1 (3.03)

n: Number of patients; MTX: Methotrexate (once a week); ADA*: Adalimumab (every 2 weeks); ADA$^{\&}$: Adalimumab (once a week); ADA$^{¥}$: Adalimumab (every 3 weeks); IFX: Infliximab (5 mg/kg/month); Tcz: Tocilizumab (162 mg/week).

Table 2. Ocular complications

	Present, n (%)	Absent, n (%)
Glaucoma	9 (14.3)	54 (85.7)
Cataract	13 (20.6)	50 (79.4)
Posterior Synechiae	31 (49.2)	32 (50.8)
Band keratopathy	18 (28.6)	45 (71.4)

n: number of eyes.

Table 3. Comparison of ocular complications and need for surgery in Groups 1 and 2

	Group 1 (n/%)	Group 2 (n/%)	p*
Glaucoma	5 (16.6)	4 (12.1)	0.396
Cataract	10 (33.3)	3 (9)	0.026
Posterior Synechiae	21 (70)	10 (30.3)	0.001
Band Keratopathy	13 (43.3)	5 (15.1)	0.012
Need for surgery	7 (23.3)	3 (9)	0.068

n: Number of eyes, *: Fisher's Exact test.

of cataract, posterior synechiae, and band keratopathy was statistically significantly higher in Group 1 (p=0.026, p=0.001, and p=0.012, respectively). Although the number of eyes requiring surgery was higher in Group 1, this difference was not statistically significant (p=0.068).

Discussion

In our study, the results have shown that even if an early diagnosis is made, we may encounter vision-threatening ocular complications more frequently in cases where the treatment protocol is not applied appropriately.

Pediatric uveitis constitutes 5–10% of all uveitis cases, whereas JIA-U constitutes the majority of pediatric uveitis cases.[1] JIA-U is usually seen as bilateral chronic anterior uveitis. However, intermediate, posterior, and panuveitis involvement has also been reported in the literature.[11,12] Uveitis is the most common extra-articular finding of JIA, and some risk factors for the development of uveitis have been identified. These risk factors are female gender, early age, oligoarticular type JIA, and ANA positivity.[13,14] It has even been reported that the combination of these risk factors increases the risk of developing uveitis.[15] In our study, all of our patients had chronic anterior uveitis, and 90.9% had bilateral involvement. 81.8% of our patients were female, 84.8% had oligoarticular type JIA, and 78.8% were ANA positive. The mean age at the time of initial diagnosis was 5 years. Our analysis results supported the literature data.

In JIA-U, diagnosis may be delayed due to the difficulty of examination in children and the child's inability to understand and express the symptoms. However, steroids are the most powerful weapons we have in the acute phase of treatment; steroid-related ocular and systemic complications are considered. The most appropriate approach would be gradual immunomodulatory treatment in these patients and biological treatment in cases of refractory uveitis.[9] These drugs are also agents used in the treatment of JIA arthritis. In fact, it has even been claimed that the overall incidence of JIA-U may have decreased in recent years due to immunomodulatory and biological drugs being a part of routine treatment in JIA.[16,17] Initial treatment of children with JIA-associated uveitis typically includes topical glucocorticoids and, in severe cases, systemic steroids. Since JIA-U mostly has a chronic course, long-term and high-dose steroid use is not suitable. If steroid treatment is insisted on, ocular and systemic side effects, especially cataract and glaucoma, will be inevitable. In the Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis published in 2019, the American College of Rheumatology/Arthritis Foundation recommends adding systemic nonbiologic DMARDs to treatment with the ultimate goal of discontinuing topical glucocorticoids in children who need continuous topical glucocorticoids to control uveitis.[9] Among nonbiologic DMARDs, MTX is usually the first choice. Although there are no randomized controlled studies on the effectiveness of MTX in JIAU, there is evidence of its effectiveness in retrospective case series in the literature.[9,18-23] 100% of our patients required non-steroidal immunosuppressive therapy, and our first choice was MTX in all patients. However, clinical remission was achieved with MTX monotherapy in only 10 of 33 patients. In addition, we had to stop MTX treatment because of increased liver function tests in four patients. Despite its known efficacy for early disease control, there are still limited data on the effects of MTX on long-term JIA-U disease activity.[18,24] Tirelli et al.[24] reported that although MTX monotherapy was effective in the early stages, it was associated with poor long-term control of JIA-U and even the emergence of new ocular complications in one-fourth of the patients. It was stated that even if uveitis initially responded well to the MTX, a biological DMARD should be added immediately in case of early relapse or long-term uveitis activity.[24] The need to add a biological DMARD in 69.6% of our patients supported this information. Among biological DMARDs, the most frequently preferred agents are anti-TNF-alpha agents developed against tumor necrosis factor-alpha, which is responsible for the pathogenesis of non-infectious uveitis.[25,26] There is no recommendation for the choice between adalimumab and infliximab as the first anti-TNF drug, but in light of the available randomized controlled studies on adalimumab, the first choice is generally ADA.[27,28] Therefore, our first biological choice was ADA. Clinical remission was achieved in 78.2% of the patients who received standard ADA treatment every 2 weeks. Only 21.8% of the patients did not respond adequately. In unresponsive cases, instead of switching to another anti-TNF, it is recommended to first increase the current anti-TNF dose and/or frequency above the standard.[9] We also switched to a weekly ADA dose in four unresponsive patients. While 75% of unresponsive cases responded to weekly treatment, one patient did not respond sufficiently, so we switched to infliximab at a dose of 5 mg/kg/month, and clinical remission was achieved in the patient. Remission was achieved with biological treatment in a large proportion of our patients, and no side effects were observed in any patient except for two patients. Biological DMARDs appear to be quite effective and reliable in the treatment of JIA-associated uveitis, but it

should not be forgotten that they are not the first choice of drugs in treatment due to their high costs and concerns about long-term reliability.[14]

An important problem with JIA-associated uveitis is the ocular complications that can be seen even at the time of initial diagnosis. Anterior segment complications such as cataract, glaucoma, posterior synechiae, and band keratopathy are more common, but posterior segment complications such as macular edema and epiretinal membrane can also be seen, although rarely.[29,30] The most common complications in our patients were posterior synechiae, band keratopathy, cataract, and glaucoma, respectively, and none of our patients had posterior segment complications. In addition, 10 eyes required surgical intervention due to ocular complications. When we classified our patients as those who received their initial diagnosis and treatment at an external center and those who received their initial diagnosis and treatment at our clinic, we found that the patients who were followed up at an external center had lower mean BCVA values at the time of their initial presentation to us, and their need for ocular complications and ocular surgery was higher. When these patients applied to us, all of them had been treated with topical steroids alone, and only one patient had a history of systemic immunosuppressive treatment. This result shows the importance of non-steroidal immunosuppressive therapy in JIA-associated uveitis.

The limitations of our study are that it is a retrospective study and that an objective assessment of clinical remission cannot be made with a flaremeter.

Conclusion

As a result, early diagnosis of JIA-U and initiation of immunosuppressive treatment as soon as possible in necessary cases can significantly reduce vision-threatening complications. In addition, the treatment of these patients should be organized by ophthalmologists with the necessary knowledge and experience.

Ethics Committee Approval: The Gazi Yasargil Training and Research Hospital Ethics Committee granted approval for this study (date: 13.09.2024, number: 2024/168).

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