Risk factors associated with the relapse of uveitis in patients with juvenile idiopathic arthritis: a preliminary report

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PURPOSE To identify risk factors associated with relapse of uveitis in patients with recurrent uveitis associated with juvenile idiopathic arthritis (JIA) after treatment with immunomodulatory therapy (IMT) and durable remission of 1 year.

METHODS The medical records of 30 patients with JIA-associated uveitis who were successfully treated with IMT to a state of corticosteroid-free remission and subsequently remained in remission after discontinuation of IMT for a period of at least 1 year were retrospectively reviewed. In subsequent follow-up, some patients had relapse of uveitis, whereas others continued to be in remission. Remission was defined as <1 + cells in the anterior chamber and <1 + vitreous haze grading; relapse was defined as ≥1 + cell in the anterior chamber or ≥1 + vitreous haze grading.

RESULTS A total of 30 patients were included. Of these, 17 (56.7%) patients remained in uveitic remission, whereas 13 (43.3%) relapsed. The patients in remission received IMT earlier in the course of disease compared with patients who relapsed (median, 12 months vs 72 months; $P = 0.002$ [Mann-Whitney test]). Patients in remission had received treatment with IMT at a younger age compared with the relapse group (median age, 7 years vs 13 years; $P = 0.02$ [Mann-Whitney test]). None of the other factors studied revealed a statistically significant association.

CONCLUSIONS Patients with JIA-associated uveitis who were treated with IMT earlier in the course of disease and at a younger age were associated with a lower rate of relapse of uveitis after durable remission and 1 year of quiescence, compared with similar patients who relapsed. (J AAPOS 2013;17:460-464)

Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown etiology of at least 6 weeks duration and with the onset before the age of 16 years.[1] Uveitis is the most common extra-articular manifestation of JIA and is seen in up to 30% of patients positive for antinuclear antibody (ANA).[2] Various risk factors have been studied for uveitis associated with JIA, including female sex, type of oligoarticular arthritis, young age at arthritis onset, ANA seropositivity, and rheumatoid factor seronegativity.[3,4] JIA-associated uveitis often has a chronic course and over time may lead to complications, including cataract, glaucoma, band keratopathy, posterior synechiae, pupillary membranes, and hypotony, which all contribute to compromised visual acuity. The goal of treatment in these patients should be corticosteroid-free remission and prevention of recurrences to avoid sight-threatening complications. Recently, there have been reports of improved outcomes in children with JIA-associated uveitis with the increasing use of various immunomodulatory therapies (IMTs).[5-7] Although IMT has been shown to be effective in treating inflammation in these patients, little is known about the risk of relapse after withdrawing IMT and risk factors associated with increased relapse. The purpose of this study was to examine the risk factors associated with relapse of uveitis once the patients are treated with IMT and are in durable remission off all immunomodulatory and corticosteroid therapy for at least 1 year.

Methods

The medical records of all patients with JIA-associated chronic or recurrent uveitis who were treated with IMT by the author (CSF)

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during the period from 1990-2011 were retrospectively reviewed. Those patients who were followed at the Massachusetts Eye Research and Surgery Institution after its establishment in 2005 were included. New England Institutional Review Board approval was obtained. Inclusion criteria for the study were as follows: disease onset from the age 1-16 years, diagnosis of JIA by a rheumatologist, presence of intraocular inflammation consistent with the signs and symptoms of JIA-associated uveitis, successful treatment with IMT to a state of corticosteroid-free remission, and subsequent maintenance of durable remission for ≥1 year. Durable remission was defined as control of ocular inflammation in the absence of systemic IMT and after cessation of all corticosteroid treatment.[8] Uveitis was diagnosed as per criteria defined by the International Uveitis Study Group.[9] Patients who were diagnosed with JIA but were free of uveitis, patients not using IMT, and patients seen on a one-time basis for consultation and patient education were excluded, as were patients currently taking IMT, those in remission for <12 months although not taking IMT or treated with corticosteroid-based intravitreal implants.

The disease was considered chronic if the duration of active ocular inflammation was >3 months. Recurrent disease was defined as repeated episodes separated by periods of inactivity without treatment for ≥3 months in duration. All patients were referred either by their rheumatologist, pediatrician, or primary ophthalmologist. Subsequent follow-up was performed in close conjunction with the referring physician. Immunomodulatory treatment was initiated if there was chronic or recurrent inflammation despite conventional therapy with topical corticosteroids, mydriatics, and nonsteroidal anti-inflammatory drugs. Before initiation of IMT, patients and their parents were educated about possible side effects and the necessity for close monitoring. The following data were noted for each patient: sex, age of uveitis diagnosis, age of arthritis diagnosis, subtype of arthritis, ANA positivity, family history of JIA, age at which IMT was started, duration of uveitis before starting IMT, the various immunomodulatory drugs used, total duration of IMT, duration of quiescence of inflammation before stopping IMT, reason for withdrawal of IMT, side effects, and time to relapse after withdrawal, if applicable. It is a standard protocol at the Massachusetts Eye Research and Surgery Institution to continue IMT for at least 2 years once the disease is in remission, unless there are significant intolerable side effects or lack of motivation for continuation on the patient's part. Remission was defined as <1 + cell (6-15) in the anterior chamber and <1 + vitreous haze grading; relapse was defined as ≥1 + cell in the anterior chamber or ≥1 + vitreous haze grading. Active inflammation in the anterior and posterior chambers on the slit-lamp examination was evaluated as recommended by the Standardization of Uveitis Nomenclature Working Group.[10] Anterior chamber inflammation assessment was consistently made by 1 observer (CSF). Patients in remission were compared with those who relapsed to evaluate risk factors associated with the relapse.

Treatment protocols vary by patient, medication, and clinical response. The overall philosophy in treatment is the achievement of remission; thus, similar practice of therapy was used for all the included patients across the study period, although small differences existed because of referral and the previously mentioned factors. Table 1 shows IMT used by patient. Adverse events and high-risk blood monitoring were captured every 6 weeks for patients on IMT. Additionally, vital signs and measures of growth were captured to verify correctness of medication dosage. Therapy was rarely, if ever, delayed; in most cases, treatment began immediately, and the length of time required to start therapy was recorded. As mentioned previously, IMT treatment is continued for approximately 2 years once remission is achieved and no corticosteroids are simultaneously taken (unless the patient was prescribed chlorambucil treatment). Duration and dosage of chlorambucil treatment were titrated based on clinical response, patient tolerance, and hemodynamic profile.

Table 1. Comparison of various factors in remission and relapse group

Factor	Remission (n = 17)	Relapse (n = 13)	*P* value
Female	16 (94.11)	11(84.61)	0.39[a]
Initial manifestation			
Arthritis	13	9	0.66[a]
Uveitis	4	4	
Age of diagnosis of arthritis: median (range), y	4 (3-7)	4 (2-8)	0.83[b]
Age of diagnosis of uveitis: mean ± SD, y	5.94 ± 2.68	5.69 ± 3.66	0.83[c]
Type of JIA			0.37[a]
Pauciarticular	16 (94.11)	13 (100)	
Polyarticular	1(5.8)	0	
ANA status: positive	15 (88.23)	11(84.61)	0.77[a]
Family history of JIA: positive	1(5.8)	1(7.6)	0.84[a]
Age at which IMT started: median (range), y	7 (4-9)	13(8-15)	0.02[b]
Duration of uveitis before starting IMT: median (range), mo	12 (6-12)	72 (36-120)	0.002[b]
Total duration of IMT: median (range), mo	55 (38-60)	35(24-52)	0.16[b]
Duration of inactivity of uveitis before stopping IMT: median (range), mo	24 (12-33)	18(12-24)	0.56[b]

ANA, anti-neutrophil antibody; *IMT*, immunomodulatory therapy; *JIA*, juvenile idiopathic arthritis; *SD*, standard deviation.
[a]Chi-square test.
[b]Mann-Whitney test.
[c]Independent *t*-test.

Statistical analysis was performed using STATA 11.0 (StataCorp LP, College Station, TX) and Origin 7.0 (OriginLab Corporation, Wellesley, MA). All continuous variables were tested for normality of distribution using the Shapiro-Wilk test. Continuous normally distributed data were reported as mean ± standard deviation, whereas continuous not normally distributed data were reported as median along with interquartile range (IQR). Comparison of the 2 independent groups was performed using independent *t* test (for normally distributed data) and Mann-Whitney *U*-test (for not normally distributed data). For univariate analysis of categorical variables, a χ^2 test was used. Kaplan-Meier survival estimator was used to compute the probability of remission to a given time. Cox proportional hazards

Table 2. Type of immunomodulatory therapy used

ID	IMT 1	IMT 2	IMT 3	IMT 4	Reason for change in IMT	Total duration of IMT, mo
Remission group						
1	MTX					108
2	MTX	MTX + MMF	IFX		IMT 1 and 2: failed	31
3	MTX					48
4	MTX					60
5	MTX	AZA	CHLM		IMT 1: intolerance; IMT 2: failed	22
6	MTX	AZA	MMF		IMT 1 and 2: failed	59
7	MTX					60
8	MTX					48
9	MTX					84
10	MTX	MMF			IMT 1: intolerance	60
11	MTX					72
12	MTX					30
13	MTX	CSA + MMF	CHLM		IMT 1 and 2: failed	39
14	MTX	MMF	CHLM		IMT 1: failed	18
15	MTX	MMF			IMT 1: failed	55
16	MTX	MMF	MMF + CSA	CHLM	IMT 1, 2, and 3: failed	67
17	MTX	MMF + CSA	IFX	CHLM	IMT 1 and 2: failed; IMT 3: reaction to IFX	38
Relapse group						
1	MTX	CHLM			IMT 1: failed	35
2	MTX	AZA + CSA	CHLM		IMT 1 and 2: failed	52
3	MTX					84
4	MTX	AZA			IMT 1: failed	84
5	MTX					24
6	AZA					32
7	MTX					60
8	MTX					17
9	IFX	IFX + MMF	MMF + IFX + CSA	CHLM	IMT 1 and 2: failed; IMT 3: intolerance	36
10	MTX					48
11	MTX + CSA					20
12	MTX					24
13	MTX	CHLM			IMT 1: intolerance	24

AZA, azathioprine; *CHLM*, chlorambucil; *CSA*, cyclosporine; *IFX*, infliximab; *IMT*, immunomodulatory therapy; *MMF*, mycophenolate mofetil; *MTX*, methotrexate.

model was used taking age at initiation of IMT and time course in disease after which IMT was started as covariates. A P value <0.05 was considered statistically significant.

Results

A total of 30 patients were included; an additional 7 patients were lost to follow-up during treatment, and 4 were lost to follow-up after discontinuing IMT. Of the 30 patients, 17 (56.7%) remained in remission, whereas 13 (43.3%) relapsed. Demographics and baseline characteristics of patients from both groups are shown in Table 2. The 2 groups did not show any significant difference in sex, age at diagnosis of uveitis and age at diagnosis of arthritis, family history of JIA, type of arthritis, and ANA positivity. Anterior uveitis was present in 28 patients, panuveitis in 2 patients, and all patients had bilateral disease.

The patients in the remission group received IMT drugs at an earlier age (median, 7 years; IQR, 4-9 years) compared with those who relapsed (median, 13 years; IQR, 8-15 years; $P = 0.02$). The time interval between onset of uveitis and initiation of IMT was significantly less in patients in the remission group (median, 12 months; IQR, 6-12 months) compared with those in the relapse group (median, 72 months; IQR, 36-120 months; $P = 0.002$). Figure 1 shows the probability of remission over time in patients with JIA-associated uveitis after withdrawal of IMT and a quiescence of 1 year off IMT. The median remission period was 84 months. The time interval of uveitis before starting IMT had a significant effect on the probability of remission over time (hazard ratio, 1.03; $P = 0.03$; 95% CI, 1.003-1.049).

Methotrexate was the initial drug used in all except 2 patients in this study. Another immunomodulatory drug was added or substituted if the patient did not respond to initial treatment or experienced significant side effects. Methotrexate monotherapy was sufficient to induce remission in 13 of 30 patients. Others were treated with more than 1 IMT in the persistent effort to achieve remission. Other immunomodulatory drugs used included mycophenolate mofetil, azathioprine, etanercept, infliximab, and chlorambucil. Nine patients received chlorambucil therapy. Of the remaining 21 patients, 16 completed the target of 2 years of remission on IMT; 4 stopped treatment before 2 years of remission on IMT because of side effects (leukopenia, infection), problems with health insurance, and lack of regular follow-up. Nausea and fatigue were the most common side effects; however, these were mild and

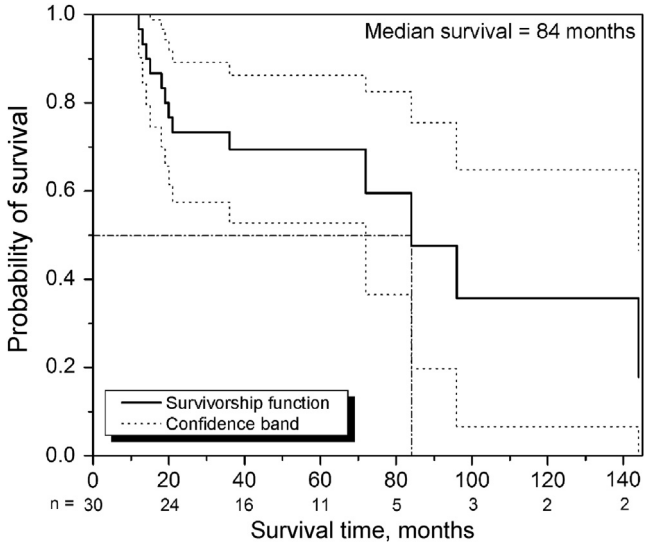

FIG 1. Survival plot of relapse of uveitis over time in patients with juvenile idiopathic arthritis–associated uveitis after withdrawal of immunomodulatory therapy (IMT) and a quiescence of 1 year off IMT. The median survival is 84 months: 50% of the patients are in remission up to 84 months after treatment with IMT and 1 year quiescence off IMT.

transient. Leukopenia was noted in 2 patients on methotrexate and in 9 patients on chlorambucil. One patient had an anaphylactic reaction to infliximab.

The median follow-up of patients was comparable in both groups with 72 months (IQR, 61-144 months) in the remission group and 96 months (IQR, 84-156 months) in the relapse group ($P = 0.2$). The duration of uveitis inactivity before withdrawal of the IMT was slightly greater (but not statistically different) in the remission group (median, 24 months; IQR, 12-33 months) than in the relapse group (median, 18 months; IQR, 12-24 months; $P = 0.56$). Total duration of IMT in the remission group (median, 55 months; range, 38-60 months) was comparable to that of the relapse group (median, 35 months; range, 24-52 months, $P = 0.16$). The median duration of follow-up after stopping IMT until relapse in the relapse group and until the date of last follow-up in the remission group was 20 months (IQR, 15-72 months) and 56 months (IQR, 36-67 months), respectively ($P = 0.06$). Again, this comparison is not statistically significantly different and in fact shows that the duration is larger in the remission group than in the relapse group.

Discussion

This study demonstrates that 43.3% of patients with JIA-associated uveitis had a relapse of uveitis after withdrawal of IMT and durable remission of 1 year. The data also show that patients who maintained remission had received treatment with IMT at a younger age and earlier after the diagnosis of uveitis.

IMT has been shown to be effective in treating chronic and recurrent JIA-associated uveitis, but the risk of relapse after withdrawal of IMT and the factors associated with relapse are unknown, and there is no consensus on how long to continue treatment with IMT once remission is achieved. Kalinina Ayuso and colleagues,[11] in a retrospective study, found that 69% of patients treated with methotrexate for JIA-associated uveitis relapsed after withdrawal of IMT, of which 46% had a relapse within 1 year of IMT withdrawal. Foeldvari and Wierk[6] reported that of 6 patients treated with methotrexate, 2 had a relapse of uveitis within 8 months of withdrawal of IMT. In the present study, 43.3% of patients relapsed after withdrawal of IMT; however, it is important to note that patients who relapsed within 1 year of treatment withdrawal as per our definition of durable remission were excluded.

Kalinina Ayuso and colleagues[11] also found that a relapse-freeintervalafter withdrawal of IMT was greater in patients who received treatment with methotrexate for more than 3 years and who had inactivity of more than 2 years before treatment withdrawal. In the present study, the total duration of IMT administration in the remission group (median, 55 months) was comparable to that of the relapse group (median, 35 months); thus, we are unable to confirm their findings. However, the remission group experienced a median treatment time approximately 2 years longer than the relapse group. Additionally, the remission group had a slightly longer median duration of inactivity of inflammation before withdrawal of IMT (median, 24) as compared with the relapse group (18 months). Neither of these differences achieved statistical significance. The small sample size may have contributed to the lack of statistical significance; nevertheless, we strongly believe that treatment with IMT should be continued for at least 2 years once inactivity of uveitis off all corticosteroids is achieved.

Interestingly, we noted that patients who continued to be in remission were treated with IMT at an earlier age (median age, 7 years) compared with those who relapsed (median, 13 years), despite the comparable age at onset of both uveitis and arthritis in JIA. Patients in remission also received IMT earlier after the onset of uveitis (median, 12 months) compared with those who relapsed (median, 72 months). The remission group received IMT earlier in the disease course and at an early age compared with the relapse group. The Cox proportional hazards model shows that the covariate "earlier initiation of IMT" has less probability of relapse (hazard ratio, 1.03; $P < 0.05$). As noted previously, therapy is rarely, if ever, delayed when patients present directly to our clinic. However, our site is a tertiary care center, and although this study (and others[12-14]) indicates favorable outcomes with early therapy initiation, we cannot control how long therapy is delayed by other caregivers. Delayed referral principally accounts for this time discrepancy in patients. This study clearly indicates the need for larger sample sizes deriving from multicenter trials. Given this result, however, we believe that early detection and earlier treatment is prudent. Ophthalmologists, rheumatologists,

and primary care physicians of children should not delay such care in patients with JIA-associated uveitis.

JIA is an autoimmune disease, and is thought to occur when patients develop T or B cell responses against self-tissues. Animal models of autoimmune disease suggest that the initial targets of immune response in these diseases can be extended to include other epitopes on the same protein or other proteins, a process known as epitope spreading.[15] For example, animal models of multiple sclerosis have shown that tissue destruction during acute disease leads to epitope spreading, which has a significant role in disease relapse.[16] Deeg and colleagues[17,18] has described intramolecular and intermolecular epitope spreading during the course of multiple induced recurrences of uveitis in horses. On the basis of our findings, we hypothesize that treatment with prolonged IMT soon after the onset of uveitis may lead to decreased tissue damage and decreased epitope spreading, resulting in a decreased chance of relapse once durable remission is achieved.

Limitations of this study include its retrospective design: consequently, comprehensive laboratory testing for all patients was not available. The small sample size also limits the results. Additionally, the study design choice of 12 months postachievement of durable remission, although assuring investigators that patients were en route to a lasting durable remission, may have excluded from the patient population those who had achieved a durable remission for less than 1 year. Finally, given our status as a tertiary referral center, the cohort of patients examined may not be representative of all uveitic JIA patients.

In conclusion, our data suggest that achieving sustainable durable remission in chronic or recurrent JIA-associated uveitis patients early in the course of the disease with IMT off all corticosteroid therapy is associated with favorable outcomes in patients, particularly in regard to maintenance of remission after IMT is discontinued.

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