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ORIGINAL ARTICLE

Impact of Antiinflammatory Treatment on the Onset of Uveitis in Juvenile Idiopathic Arthritis: Longitudinal Analysis From a Nationwide Pediatric Rheumatology Database

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Objective. **Based on a nationwide database, this study analyzed the influence of methotrexate (MTX), tumor necrosis factor (TNF) inhibitors, and a combination of the 2 medications on uveitis occurrence in juvenile idiopathic arthritis (JIA) patients.**
Methods. **Data from the National Paediatric Rheumatological Database in Germany were used in this study. Between 2002 and 2013, data from JIA patients were annually documented at the participating pediatric rheumatologic sites. Patients with a JIA disease duration of <12 months at initial documentation and ≥2 years of followup were included in this study. The impact of antiinflammatory treatment on the occurrence of uveitis was evaluated by discrete-time survival analysis.**
Results. **A total of 3,512 JIA patients (mean ± SD age 8.3 ± 4.8 years, 65.7% female, 53.2% antinuclear antibody positive, and mean ± SD age at arthritis onset 7.8 ± 4.8 years) fulfilled the inclusion criteria. Mean ± SD total followup time was 3.6 ± 2.4 years. Uveitis developed in a total of 180 patients (5.1%) within 1 year after arthritis onset. Uveitis onset after the first year was observed in another 251 patients (7.1%). Disease-modifying antirheumatic drug (DMARD) treatment in the year before uveitis onset significantly reduced the risk for uveitis as follows: MTX: hazard ratio (HR) 0.63, $P = 0.022$; TNF inhibitors: HR 0.56, $P < 0.001$; and a combination of the 2 medications: HR 0.10, $P < 0.001$. Patients treated with MTX within the first year of JIA had an even a lower uveitis risk (HR 0.29, $P < 0.001$).**
Conclusion. **The use of DMARDs in JIA patients significantly reduced the risk for uveitis onset. Early MTX use within the first year of disease and the combination of MTX with a TNF inhibitor had the highest protective effect.**

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic arthritides with onset before age 16 years (1–4). Uveitis occurs at a rate of approximately 9–13% in these patients (5–7) and may cause vision-threatening complications (8–12). The major known risk factors for the development of uveitis are JIA oligoarthritis, young age at arthritis onset, short duration of disease, and antinuclear antibody (ANA) positivity (13–16). Previous epidemiologic data suggest that the prevalence of uveitis in JIA varies among different geographic regions, with a higher rate in north-

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Significance & Innovations

- Based on a nationwide database in Germany, we analyzed the influence of methotrexate (MTX), tumor necrosis factor (TNF) inhibitors, and a combination of the two on uveitis occurrence in a total of 3,512 juvenile idiopathic arthritis (JIA) patients.
- Oligoarthritis patients age <3 years and with a high disease activity at baseline (clinical Juvenile Arthritis Disease Activity Score >10) had a very high risk for subsequent uveitis (33.9%).
- The use of disease-modifying antirheumatic drugs in JIA patients significantly reduced the risk of uveitis onset.
- Early MTX use within the first year of disease and the combination of MTX with a TNF inhibitor had the highest protective effect.

ern countries, such as the Scandinavian countries and Germany, and a lower frequency in eastern and southern Asia (6,7,15).

Systemic antiinflammatory treatment with synthetic and/or biologic disease-modifying antirheumatic drugs (DMARDs) is often required to achieve inactivity of arthritis (1,17–22). Based on data from 2 randomized controlled trials (20,23), methotrexate (MTX) is the first-choice treatment for active arthritis in JIA. On the other hand, biologic DMARDs, mainly tumor necrosis factor (TNF) inhibitors, offer a further option for treatment-refractory disease (18,22,24–28). Previous reports suggest that systemic antiinflammatory treatment in JIA may influence whether uveitis develops in patients with JIA (29,30).

Using a prospective nationwide pediatric rheumatologic database (NPRD), we performed a longitudinal analysis in a large cohort of JIA patients to evaluate the impact of DMARDs on the occurrence of uveitis.

PATIENTS AND METHODS

Data acquisition: rheumatologic and ophthalmologic documentation. The study was based on JIA patients who fulfilled the International League of Associations for Rheumatology (ILAR) criteria (31) and who were included in the NPRD between January 2002 and December 2013. The database design has been described in detail previously by our group (7,32). The following clinical parameters were reported at yearly intervals by the pediatric rheumatologists: the patient's age, sex, diagnosis (JIA category), age at onset of arthritis, systemic treatment, physicians' global assessment of disease activity, number of swollen or tender joints, number of joints with limited range of motion, and extraarticular manifestations, such as the presence of uveitis. Additionally, laboratory results such as the presence of ANA and rheumatoid factor (RF) were also reported. Patients (or their parents) judged their overall well-being on a numeric rating scale (range 0–10). In addition, they assessed their functional status by applying the Childhood Health Assessment Questionnaire (C-HAQ). The C-HAQ disability index may range from 0 to 3. A value of zero indicates no functional disability, and values between 0 and 1.0 represent mild to moderate disability (33). The Juvenile Arthritis Disease Activity Score (JADAS-10) and the clinical JADAS (cJADAS-10) were developed as composite tools for scoring disease activity in JIA. The JADAS-10 is calculated as the arithmetic sum of the scores of the following variables: physician global rating of disease activity; parent/child rating of well-being; active joint count, assessed in 10 joints; and erythrocyte sedimentation rate, normalized to a 0–10 scale. The cJADAS-10 is calculated as the sum of the first 3 variables. JADAS-10 and cJADAS-10 values >10 classify patients as being in a high active disease state, according to Consolaro et al (34,35).

Inclusion criteria and data analysis. To assess the impact of different treatments on the occurrence of uveitis, JIA patients with a JIA disease duration of <12 months at first documentation and ≥2 years of followup were included in this analysis.

Clinical and demographic characteristics, systemic antiinflammatory treatment, and onset of uveitis are reported by using standard descriptive statistics. Baseline sociodemographic and clinical characteristics of patients without uveitis, those who develop uveitis within the first year, and those with uveitis onset during followup years were compared by using multinomial logistic regression models. Multivariable logistic regression analysis was conducted to test the baseline risk factors of sex, age at JIA onset, disease duration, ILAR category, ANA positivity, and disease activity on the risk of uveitis in the total sample. The followup assessments were conducted annually. To examine the impact of disease activity, MTX, and TNF inhibitor therapy on uveitis onset, we used discrete-time survival analysis (36) adjusted for ANA positivity, ILAR category, age at JIA onset, disease duration, and systemic therapy with glucocorticoids. Using this method, the hazard of uveitis onset was estimated for each year during the followup period. Discrete-time survival analysis started with patients who had no history of uveitis at the first documentation; the 180 patients in whom uveitis developed in the first year were dropped for this analysis. Once uveitis occurred, the subsequent followup years were dropped for these patients. To test the hypotheses, treatment in the year before uveitis onset or in the year before the last documentation was used to assess whether uveitis developed after treatment with MTX and/or TNF inhibitors or disease activity was higher, respectively. The interaction terms of MTX × cJADAS-10 and TNF inhibitors × cJADAS-10 were entered into the regression analyses for modeling the higher disease activity of patients treated with DMARDs compared to those who were not. Other variables were entered as time-invariant and time-dependent predictors into the model. The discrete-time survival model was estimated by the complementary log-log function, as it provides consistent estimates of proportional hazards parameters, regardless of the interval length or the size of the failure rate (36,37). Meaningful thresholds for age at arthritis onset and cJADAS-10

Table 1. Impact of systemic antiinflammatory treatment on the onset of uveitis in patients with JIA. Demographic characteristics at baseline (first documentation) in the registry for patients with JIA (n = 3,512)*

	All patients, no. (%) or mean ± SD	Patients without uveitis, no. (%) or mean ± SD (reference)	Patients with uveitis onset within the first year		Patients with uveitis onset after first year	
			No. (%) or mean ± SD	OR (95% CI), *P*†	No. (%) or mean ± SD	OR (95% CI), *P*†
No. of patients	3,512	3,081	180	–	251	–
Female sex	2,307 (65.7)	2,006 (65.1)	123 (68.3)	0.86 (0.63–1.19), 0.377	178 (70.9)	0.77 (0.58–1.01), 0.063
Age, years	8.3 ± 4.8	8.6 ± 4.8	6.2 ± 3.9	0.89 (0.86–0.92), < 0.001	5.3 ± 4.0	0.84 (0.81–0.87), < 0.001
Age at arthritis onset, years	7.8 ± 4.8	8.1 ± 4.8	5.7 ± 3.9	0.89 (0.86–0.92), < 0.001	4.9 ± 4.0	0.84 (0.81–0.87), < 0.001
Age at uveitis onset, years	7.0 ± 4.2	–	5.9 ± 4.1	*P* < 0.001‡	7.9 ± 4.2	*P* < 0.001‡
JIA category						
RF-positive polyarthritis	103 (2.9)	97 (3.2)	2 (1.1)	1.15 (0.46–2.90), 0.763	4 (1.6)	0.63 (0.25–1.55), 0.310
RF-negative polyarthritis	578 (16.5)	515 (16.7)	22 (12.2)	1.79 (1.11–2.90), 0.017	41 (16.3)	1.21 (0.85–1.73), 0.283
Systemic JIA	227 (6.5)	222 (7.2)	0 (0.0)	0.13 (0.07–0.24), < 0.001	5 (2.0)	0.34 (0.15–0.76), 0.009
Persistent oligoarthritis	1,749 (49.8)	1,480 (48.0)	127 (70.6)	3.51 (2.42–5.07), < 0.001	142 (56.6)	1.46 (1.12–1.91), 0.005
Extended oligoarthritis	137 (3.9)	111 (3.6)	9 (5.0)	3.58 (1.93–6.66), < 0.001	17 (6.8)	2.34 (1.43–3.85), 0.001
Psoriatic arthritis	174 (5.0)	159 (5.2)	3 (1.7)	0.96 (0.42–2.20), 0.918	12 (4.8)	1.15 (0.66–2.01), 0.619
Enthesitis-related arthritis	398 (11.3)	367 (11.9)	11 (6.1)	1.30 (0.73–2.31), 0.370	20 (8.0)	0.83 (0.53–1.30), 0.419
Disease activity, physician global NRS 0–10	2.8 ± 2.2	2.8 ± 2.2	3.2 ± 2.4	1.09 (1.02–1.16), 0.013	3.2 ± 2.3	1.08 (1.02–1.15), 0.005
ESR, mm/hour	21.8 ± 20.6	21.3 ± 20.5	23.1 ± 19.0	1.00 (0.99–1.01), 0.277	27.7 ± 22.4	1.01 (1.005–1.02), < 0.001
ESR >35	445 (18.5)	373 (17.6)	23 (19.2)	1.11 (0.70–1.78), 0.652	49 (29.9)	2.00 (1.41–2.85), < 0.001
JADAS-10	9.7 ± 6.6	9.6 ± 6.5	9.6 ± 6.1	1.00 (0.97–1.03), 0.932	11.6 ± 7.1	1.04 (1.02–1.07), < 0.001
JADAS-10 score >10	763 (39.0)	652 (37.8)	41 (41.4)	1.16 (0.77–1.76), 0.932	70 (52.6)	1.83 (1.28–2.61), 0.001
cJADAS-10	7.8 ± 5.8	7.7 ± 5.8	8.0 ± 5.3	1.01 (0.98–1.03), 0.606	8.8 ± 6.1	1.03 (1.01–1.05), 0.010
cJADAS-10 score >10	787 (28.0)	668 (27.1)	41 (28.9)	1.09 (0.75–1.59), 0.640	78 (38.1)	1.65 (1.23–2.22), 0.001
ANA positive	1,549 (53.2)	1,265 (49.6)	129 (86.6)	6.55 (4.06–10.56), < 0.001	155 (73.1)	2.76 (2.02–3.78), < 0.001
C-HAQ total score	0.39 ± 0.54	0.38 ± 0.53	0.35 ± 0.49	0.89 (0.65–1.23), 0.486	0.53 ± 0.62	1.52 (1.20–1.92), < 0.001
Systemic antiinflammatory treatment in previous 12 months						
Synthetic DMARD	909 (36.8)	781 (36.0)	65 (50.8)	1.84 (1.29–2.63), 0.001	63 (36.4)	1.02 (0.74–1.41), 0.904
Methotrexate	777 (29.7)	663 (28.9)	58 (41.1)	1.72 (1.21–2.43), 0.002	56 (29.8)	1.04 (0.75–1.44), 0.803
Azathioprine	12 (0.5)	11 (0.5)	1 (0.7)	–	0 (0.0)	–
Cyclosporine A	8 (0.4)	7 (0.4)	1 (0.8)	–	0 (0.0)	–
Biologic DMARD	58 (2.1)	48 (2.0)	5 (3.4)	1.77 (0.69–4.50), 0.234	5 (2.5)	1.27 (0.50–3.23), 0.612
Etanercept	49 (2.1)	41 (2.0)	3 (2.3)	1.18 (0.36–3.88), 0.781	5 (2.9)	1.51 (0.59–3.86), 0.394
Adalimumab	4 (0.3)	2 (0.2)	2 (3.0)	18.53 (2.57–133.74), 0.004	0 (0.0)	–
Infliximab	0 (0)	0 (0)	0 (0)	–	0 (0)	–
Corticosteroids, systemic	470 (19.4)	418 (19.9)	17 (13.3)	0.62 (0.37–1.04), 0.071	35 (18.8)	0.94 (0.64–1.37), 0.735
Corticosteroids, ≤0.15 mg/kg	274 (10.0)	243 (10.2)	9 (6.3)	0.59 (0.30–1.18), 0.135	22 (10.7)	1.05 (0.66–1.67), 0.827
Corticosteroids, >0.15 mg/kg	263 (9.6)	232 (9.7)	11 (7.7)	0.77 (0.41–1.45), 0.426	20 (9.7)	1.00 (0.62–1.62), 0.996
Corticosteroids, intraarticular	127 (5.3)	113 (5.4)	5 (3.9)	0.72 (0.29–1.79), 0.473	9 (4.9)	0.90 (0.45–1.81), 0.767
NSAIDs	1,889 (68.4)	1,646 (68.2)	96 (67.1)	0.95 (0.66–1.36), 0.788	147 (71.4)	1.16 (0.85–1.59), 0.352

* JIA = juvenile idiopathic arthritis; OR = odds ratio; 95% CI = 95% confidence interval; RF = rheumatoid factor; NRS = numerical rating scale; ESR = erythrocyte sedimentation rate; JADAS = Juvenile Arthritis Disease Activity Score; cJADAS = clinical JADAS; ANA = antinuclear antibody; C-HAQ = Childhood Health Assessment Questionnaire; DMARD = disease-modifying antirheumatic drug; NSAIDs = nonsteroidal antiinflammatory drugs.
† OR estimated by univariate logistic regression analysis.
‡ Comparing patients with uveitis onset within and after the first 12 months of JIA.

Table 2. Overview of systemic treatment with synthetic and biologic DMARDs for patients without uveitis onset within the first year of disease (n = 3,332 JIA patients)*

Systemic antiinflammatory treatment during previous 12 months	Year 1 (n = 3,322)	Year 2 (n = 2,845)	Year 3 (n = 2,196)	Year 4 (n = 1,697)	Year 5 (n = 1,090)	Year 6 (n = 743)	Year 7 (n = 532)
Synthetic DMARD	735 (30.5)	1,301 (53.3)	1,128 (59.6)	821 (54.8)	479 (48.5)	294 (43.3)	210 (43.6)
Methotrexate	719 (29.0)	1,285 (52.3)	1,106 (57.9)	797 (52.8)	457 (46.8)	280 (41.2)	200 (41.6)
Azathioprine	11 (0.4	17 (0.7)	22 (1.2)	21 (1.4)	16 (1.6)	14 (2.1)	10 (2.1)
Cyclosporine A	7 (0.3)	4 (0.2)	5 (0.4)	3 (0.3)	2 (0.3)	0 (0.0)	0 (0.0)
Others	3 (0.1)	2 (0.1)	4 (0.3)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Biologic DMARD	53 (2.0)	168 (6.7)	245 (12.5)	229 (15.1)	151 (15.4)	114 (16.6)	92 (19.0)
Etanercept	46 (2.1)	149 (6.1)	199 (10.4)	184 (12.2)	121 (12.4)	94 (13.8)	74 (15.4)
Adalimumab	2 (0.2)	8 (0.5)	22 (1.6)	28 (2.2)	13 (1.5)	15 (2.2)	13 (2.7)
Infliximab	0 (0.0)	0 (0.0)	2 (0.2)	3 (0.2)	4 (0.5)	0 (0.0)	1 (0.2)
Others	5 (0.4)	12 (0.8)	24 (1.7)	15 (1.1)	13 (1.5)	7 (1.1)	6 (1.2)
Corticosteroids systemic	453 (19.8)	439 (19.4)	251 (14.7)	132 (9.9)	67 (8.3)	47 (8.5)	38 (9.3)
Corticosteroids, ≤0.15 mg/kg body weight/day	265 (10.2)	388 (15.4)	230 (12.3)	118 (7.9)	59 (6.3)	45 (7.0)	39 (8.3)
Corticosteroids, >0.15 mg/kg body weight/day	252 (9.7)	113 (4.5)	45 (2.4)	29 (2.0)	16 (1.7)	8 (1.3)	4 (0.9)
NSAIDs	1,793 (68.5)	2,044 (80.1)	1,192 (63.0)	700 (46.9)	410 (43.5)	251 (39.0)	195 (41.0)

* Values are the number of patients (percentage). DMARDs = disease-modifying antirheumatic drugs; JIA = juvenile idiopathic arthritis; NSAIDs = nonsteroidal antiinflammatory drugs.

for its use in the prediction models were calculated by considering the threshold associated with the maximum sum of sensitivity and specificity (38). A P value of less than 0.05 was considered significant. All statistical analyses were conducted using SAS software (version 9.3).

Regarding ethics approval, the NPRD was approved by the Ethics Committee of Charité in Berlin and, as appropriate, also by the local ethics committee. The study was performed according to the Declaration of Helsinki and conforms to the standards applied in Germany.

RESULTS

Baseline characteristics. A total of 3,512 JIA patients (65.7% female, 53.2% ANA positive) fulfilled the inclusion criteria. Patients were enrolled in 60 pediatric rheumatologic centers (2002: 27 centers with a mean of 101 patients per center; 2013: 60 centers with a mean of 88 patients per center). Demographic characteristics and ILAR category classifications are shown in Table 1. At first documentation, mean ± SD age was 8.3 ± 4.8 years and mean ± SD duration of JIA was 5.6 ± 3.4 months. Mean ± SD total followup time was 3.6 ± 2.4 years.

Onset of uveitis. A history of uveitis was recorded in a total of 431 patients: 180 patients (41.8%) developed uveitis already in the first year of documentation. Uveitis occurred in the second year in another 60 patients (13.9%), in the third year in 66 additional patients (15.3%), in the fourth year in another 53 patients (12.3%), and in an additional 72 patients (16.7%) later on.

Uveitis onset within 1 year after arthritis onset. In a multivariable logistic regression analysis, ANA positivity (86.6%; odds ratio [OR] 6.55, 95% confidence interval [95% CI] 4.06–10.56, $P < 0.001$) and a younger age at JIA onset (5.7 years; OR 1.12, 95% CI 1.09–1.16, $P < 0.001$), in addition to JIA category, were highly associated with the early onset of uveitis (n = 180 patients with uveitis in the first year of disease). Patients with uveitis were treated more often with synthetic DMARDs, in particular MTX (41.1% versus 28.9%), and biologic DMARDs, mainly adalimumab (3.0% versus 0.2%), in the first year of JIA. Due to the study design, it is not possible to show the temporal relationship of uveitis onset and treatment start, i.e., whether treatment was started as a consequence of uveitis onset or whether uveitis occurred after treatment was initiated. Most cases of early uveitis were recorded for the JIA category of oligoarthritis (n = 136, 75.6% of 180; OR 3.55, 95% CI 2.14–5.35, $P < 0.001$). Among them, almost all patients were ANA positive (92.4%; OR 7.1, 95% CI 3.54–14.04, $P < 0.001$), and an increased risk for early uveitis was found in oligoarthritis patients with a cJADAS-10 score >10 (11.9% versus 6.7%; OR 1.88, 95% CI 1.19–2.97, $P = 0.007$).

Uveitis manifestation after the first year of disease. Uveitis developed in another 251 patients 2 years (median; interquartile range: 1–3 years) after JIA onset. Results of the univariate regression analysis for potential uveitis risk factors are shown in Table 1. In a multivariate logistic regression model, demographic and clinical risk factors of uveitis were a younger age at JIA onset (OR 1.21, 95% CI 1.16–1.27, $P < 0.001$), enthesitis-related arthritis (OR 1.95, 95% CI 1.09–3.49, $P = 0.024$), ANA positivity (OR 1.85,

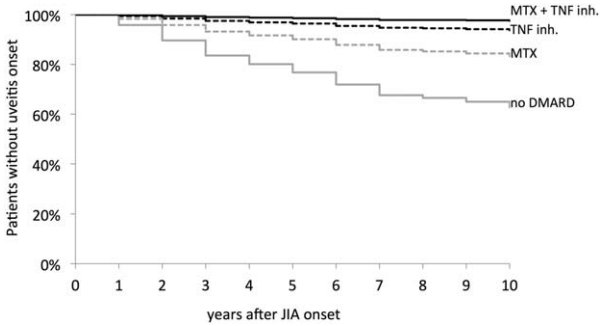

Figure 1. Predicted survival curves for the time of juvenile idiopathic arthritis (JIA) onset to occurrence of uveitis with respect to disease-modifying antirheumatic drug (DMARD) treatment in the last 12 months before uveitis onset. Survival curves show the estimated proportion of patients without uveitis onset for no DMARD, methotrexate (MTX) monotherapy (n = 953; HR 0.63, $P = 0.022$), tumor necrosis factor inhibitor (TNF inh.) monotherapy (n = 48; HR 0.56, $P = 0.001$), or a combination of the two (n = 436; HR 0.10, $P = 0.001$); n = 3,332 patients with JIA.

95% CI 1.25–2.74, $P = 0.001$), and a cJADAS-10 above a threshold of 10 (OR 1.76, 95% CI 1.23–2.51, $P = 0.002$), but duration of JIA disease (OR 0.98, 95% CI 0.93–1.03, $P = 0.418$) and female sex (OR 1.23, 95% CI 0.86–1.75, $P = 0.250$) did not change significantly the risk for uveitis. Whereas an erythrocyte sedimentation rate (ESR) >35 mm/hour (OR 2.00, 95% CI 1.41–2.85, $P < 0.001$) or a high C-HAQ total score at baseline (OR 1.52, 95% CI 1.20–1.92, $P < 0.001$) were significantly associated with uveitis onset in the univariate analysis (Table 1), these parameters were not revealed to be independent risk factors in the multivariate logistic regression model ($P > 0.05$ for both).

In the subsample of patients with oligoarthritis, patients with age <3 years at arthritis onset (17.9% versus 6.1%; OR 3.63, 95% CI 2.12–6.23, $P < 0.001$) and with a high active disease at baseline (cJADAS-10 >10, 16.5% versus 7.6%; OR 2.24, 95% CI 1.32–3.78, $P = 0.003$) had a higher risk for developing uveitis after the first year of JIA disease. Patients age <3 years and with a high disease activity had a very high risk for subsequent uveitis (33.9%; OR 9.29, 95% CI 5.13–16.81, $P < 0.001$) compared to patients who did not meet both conditions (5.2%) at baseline, whereas the risk for uveitis was doubled (11.3%; OR 2.31, 95% CI 1.60–3.35, $P < 0.001$) for patients who fulfilled only 1 of the 2 conditions.

Impact of systemic antiinflammatory treatment in JIA on uveitis onset. Systemic antiinflammatory treatment for all patients without uveitis onset within the first 12 months of JIA (n = 3,332) is shown in Table 2. In the particular year before uveitis onset, a total of 779 JIA patients did not receive DMARD treatment, while 1,801 patients were treated with MTX, 48 patients with TNF inhibitor monotherapy (n = 38 for etanercept, n = 5 for adalimumab, and n = 5 for other), and another 436 patients were treated with a combination of MTX and a TNF inhibitor (n = 65 for adalimumab, n = 9 for infliximab, and n = 362 for etanercept). The mean ± SD cJADAS-10 score in the year before uveitis onset was 3.4 ± 4.6 for patients who were treated with a DMARD compared to those who were not (mean ± SD 2.8 ± 3.7). Cumulative uveitis incidence for patients without systemic treatment and different immunosuppressive treatment groups is shown in Figure 1. The risk for uveitis was significantly decreased by MTX therapy (hazard ratio (HR) 0.63, 95% CI 0.42–0.94, $P = 0.022$), TNF inhibitors (HR 0.56, 95% CI 0.38–0.81, $P = 0.001$), and the combination of MTX and a TNF inhibitor (HR 0.10, 95% CI 0.05–0.23, $P = 0.001$) compared to no DMARD treatment in the year before uveitis onset after adjusting for ANA status, ILAR category, age at JIA onset, disease duration and cJADAS-10 (Table 3). The uveitis incidence was 5.9% (22 of 364 patients with uveitis onset) in JIA patients treated with a combination of MTX and etanercept, whereas it was 1.4% for children taking a combination of MTX and adalimumab (1 patient with uveitis onset of 64 patients).

Table 3. Multivariable regression analysis for the impact of DMARD treatment and cJADAS-10 on the onset of uveitis in JIA (n = 3,332)*

	JIA patients without uveitis	JIA patients with uveitis onset during followup	HR†	95% CI	*P*†
Use of MTX‡	1,669 (64.1)	132 (52.6)	0.63	0.42–0.94	0.022
Early use of MTX during first year after arthritis onset	818 (26.6)	41 (16.3)	0.29	0.19–0.45	< 0.001
Use of biologic DMARD‡	462 (15)	22 (8.8)	0.56	0.38–0.81	< 0.001
Early use of biologic DMARDs during first year after arthritis onset	134 (4.4)	5 (2.0)	0.51	0.18–1.47	0.214
MTX plus TNF-inhibitor‡	414 (17.1)	22 (10.2)	0.10	0.05–0.23	< 0.001
cJADAS-10	3.5 (3.9)	4.6 (4.2)	1.06	1.01–1.12	0.044

* Values are the number (percentage) unless indicated otherwise. DMARD = disease-modifying antirheumatic drug; cJADAS-10 = clinical Juvenile Arthritis Disease Activity Score; JIA = juvenile idiopathic arthritis; HR = hazard ratio; 95% CI = 95% confidence interval; MTX = methotrexate; TNF = tumor necrosis factor.
† Adjusted for antinuclear antibody positivity, International League of Associations for Rheumatology category, age at JIA onset, disease duration and cJADAS-10, therapy with glucocorticoids, MTX, and biologic DMARDs during followup.
‡ For patients with uveitis onset, treatment in the year before uveitis onset was evaluated, whereas for patients without uveitis, the year before the last documentation was analyzed.

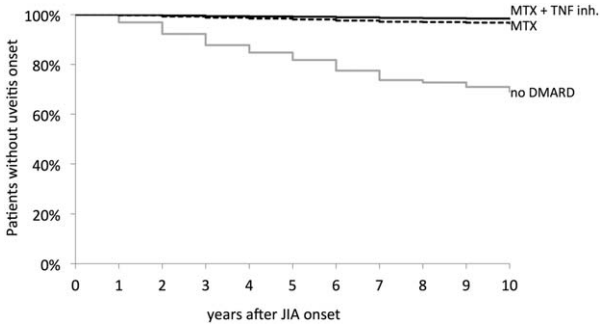

Figure 2. Predicted survival curves for the time of juvenile idiopathic arthritis (JIA) onset to occurrence of uveitis with respect to early disease-modifying antirheumatic drug (DMARD) treatment. Curves for patients without early DMARDs, early methotrexate (MTX) monotherapy (n = 41; HR 0.29, $P < 0.001$) and a combination of MTX and a tumor necrosis factor inhibitor (TNF inh.; n = 61; HR 0.15, $P = 0.002$) within the first year of JIA disease are shown. The y-axis shows the estimated cumulative proportion of patients without uveitis during followup; n = 3,332 patients with JIA.

Patients with early MTX treatment tended to have a higher disease activity (mean ± SD cJADAS-10 10.8 ± 6.4 versus 6.6 ± 5.1 without early MTX). The risk for developing uveitis during the subsequent followup was significantly lower for patients who were treated early with MTX, i.e., within the first year of JIA (early MTX: n = 41 [4.8%] versus no early MTX: n = 184 [8.5%]; HR 0.29, 95% CI 0.19–0.45, $P < 0.001$) (Figure 2), whereas uveitis occurred insignificantly less frequently in patients treated with TNF inhibitors during the first year (early use of biologic DMARD: n = 5 [3.6%] versus no early biologic DMARD: n = 225 [7.6%]; HR 0.51, 95% CI 0.18–1.47, $P = 0.51$) (Table 3).

The protective effect of DMARDs was slightly more pronounced in the category of patients at high risk for uveitis, namely oligoarthritis and RF-negative polyarthritis (use of MTX: HR 0.59, 95% CI 0.38–0.92, $P = 0.020$; early use of MTX during the first year after arthritis onset: HR 0.29, 95% CI 0.18–0.48, $P < 0.001$; use of biologic DMARD: HR 0.52, 95% CI 0.29–0.75, $P < 0.001$; early use of biologic DMARDs during the first year after arthritis onset: HR 0.69, 95% CI 0.16–3.07, $P = 0.628$; and MTX plus TNF inhibitor: HR 0.09, 95% CI 0.05–0.31, $P < 0.001$).

Disease activity, measured by using the cJADAS-10, significantly decreased during the followup period (mean ± SD 7.1 ± 5.8 for baseline and 3.6 ± 4.0 for last followup); however, an increased cJADAS-10 before uveitis onset was significantly associated with a higher risk for uveitis (mean ± SD 3.5 ± 4.0 for patients without uveitis, 4.6 ± 4.2 for patients with uveitis; HR 1.06, 95% CI 1.01–1.12, $P = 0.044$).

DISCUSSION

The introduction of MTX and, later on, TNF inhibitors constitute milestones in the treatment of JIA (39–41). Although we know from animal models using guinea pigs that MTX is able to prevent experimental uveitis (42), sufficient evidence about a similarly protective effect of DMARDs in humans is still lacking. Both MTX and TNF inhibitors have been reported to be efficacious in treating JIA and associated uveitis (21,22,28,43–45). However, only limited data are available for DMARDs regarding their potential impact on reducing the risk for uveitis onset in JIA. A previous retrospective study gave preliminary evidence for such an effect using MTX (29), with uveitis developing in 10.5% of 86 JIA patients with MTX monotherapy, compared to 20.2% of 168 patients without MTX (OR 0.46, $P = 0.049$; n = 254). In our prospective study of a large cohort of JIA patients, we analyzed the influence of synthetic DMARD and/or biologic DMARD treatment on the risk of uveitis onset in JIA.

Overall, uveitis was observed in 12.3% of 3,512 children diagnosed with JIA in our study. Apart from geographic variations, this uveitis prevalence is similar to data from other population-based studies (6,7,46–52). In Finland, Kotaniemi et al reported a median onset of uveitis 4 to 5 months after arthritis onset, with uveitis occurring in 49% of patients within the first 3 months after JIA onset and in 90% within the first 4 years (5). Grassi et al reported similar data (53). A few patients might develop uveitis even years after JIA onset (54). The findings in our study are comparable.

There are several known risk factors for uveitis in JIA, e.g., young age at arthritis onset, disease duration, ANA positivity, and JIA category (5,16). Extended oligoarthritis, followed by persistent oligoarthritis, RF-negative polyarthritis, and psoriatic arthritis were found to be the JIA categories at highest risk for uveitis (7,16,55). Interestingly, in Scandinavia the highest risk for uveitis was found in the polyarticular group (56,57). Although girls are at higher risk for JIA itself, sex has not been found to be an independent risk factor for uveitis (5,6,55). However, young girls with early onset of arthritis seem to be at higher risk than boys (16). In our study, we were able to confirm these risk factors, namely JIA category (oligoarthritis, persistent and extended, followed by RF-negative polyarthritis), age at disease onset, and ANA positivity. The risk for uveitis was slightly higher in the extended oligoarthritis group than in the persistent one. These data compare well with previous studies (5,7,16,58–62).

High disease activity has been reported to be associated with a higher risk of uveitis occurrence in JIA (53,63), but the subsequent clinical course of uveitis appears to be quite independent of arthritis activity (64). The C-HAQ score is a sensitive tool for evaluating functional outcomes in children with chronic arthritis (65). In our study, patients with a high C-HAQ score at initial documentation revealed a significantly higher risk for uveitis onset during further followup. Such a correlation was also found for the JADAS (also including the ESR as a parameter) and the cJADAS in our study. Indeed, the risk for uveitis occurrence during followup was nearly twice as high for patients with a cJADAS >10 at first documentation than for those with a lower JADAS (HR 1.64, $P = 0.047$).

Apart from demographic and clinical data, further biomarkers to predict uveitis risk for an individual patient are highly desirable. Interestingly, ESR has been shown to correlate well with the risk for uveitis (66–69). In our study, an ESR >35 mm/hour at first documentation was

associated with a significantly higher risk for uveitis onset during followup (OR 2.0, $P < 0.001$; univariate analysis) (Table 1). This is even more interesting considering that these children were treated more frequently with DMARDs (data not shown).

Although there are indications that DMARDs may reduce the risk for uveitis in JIA (29,49), such an effect was not clearly confirmed in other studies (70), which showed a nearly stable uveitis prevalence despite more frequent use of DMARDs. In our large cohort, we found a significantly lower risk for uveitis onset in patients with MTX as a monotherapy than in patients not taking any DMARDs. This effect was even stronger if MTX was initiated at an early stage of disease (Figure 2) or when combined with a TNF inhibitor (Figures 1 and 2), and even more pronounced in the subgroup analysis for patients at high risk for uveitis, namely RF-negative polyarthritis and oligoarthritis, persistent or extended.

Current JIA treatment guidelines of the American College of Rheumatology (ACR) recommendations (1) and the German Society for Paediatric Rheumatology (2) recommend starting MTX when nonsteroidal antiinflammatory drugs (NSAIDs) and intraarticular corticosteroids do not succeed. According to the ACR recommendations, MTX treatment is also advised in patients with oligoarthritis who have high disease activity and poor prognostic features (1). If the response to MTX is insufficient or also in high-risk disease, rapid escalation to include biologic DMARDs, namely a TNF inhibitor, is encouraged (1). Considering our study results, it is important to discuss whether a high uveitis risk should also be considered as an indication for early MTX therapy in terms of a risk-adapted strategy. As our data clearly show a reduced risk for uveitis under MTX, JIA patients at higher risk for uveitis (ANA positive, oligoarthritis, young age at JIA onset) might benefit from an immunosuppressive treatment, even if arthritis is stable under NSAIDs or corticosteroid treatment. Indeed, DMARD treatment in oligoarthritis patients age <3 years at arthritis onset (17.9% versus 6.1%; OR 3.63, $P < 0.001$) and with a high active disease at baseline (cJADAS-10 >10, 16.5% versus 7.6%; OR 2.24, $P = 0.003$) may significantly reduce the risk for uveitis, according to our data.

This study was performed using data from a prospective, nationwide database. The large patient cohort is representative for all JIA patients in Germany. As the majority of cases of uveitis present within the first 4 years (5,71), the followup time of our study should allow us to identify the majority of uveitis manifestations in the analyzed study cohort. A relevant limitation of the NPDR is the documentation interval of 1 year, with missing time-dependent data in between. Using this method, it is not possible to determine whether the particular DMARD treatment was instituted before or after uveitis onset during the first year after JIA onset and what the indication for therapy was (arthritis and/or uveitis). As no dosing information for DMARDs is collected in the case report forms of the NPDR, it cannot be excluded that uveitis manifestation despite DMARD treatment may be due to dosing in individual patients. Nevertheless, the high patient numbers of the largest JIA databases worldwide should balance potential biases between patient groups.

In conclusion, this prospective population-based study corroborates published data on the JIA-associated uveitis incidence in Central Europe. In addition to specific disease characteristics (e.g., disease onset after age 6 years, ANA negativity, and a disease category other than oligoarthritis), early treatment with MTX was associated with a lower risk of uveitis in JIA patients. This protective effect was highest for a combination of MTX with a TNF inhibitor (mainly etanercept was used in this study). Further studies are needed to show whether early treatment in JIA patients could improve the outcome by preventing uveitis onset with all the consequences for visual acuity, ocular complications and, last but not least, quality of life. Therefore, in addition to the severe course of arthritis, preventing uveitis may constitute another indication for DMARD treatment.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Tappeiner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Tappeiner, Schenck, Niewerth, Heiligenhaus, Minden, Klotsche.

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ROLE OF THE STUDY SPONSOR

Pfizer Pharma had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer Pharma.

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