Predictive factors and biomarkers for the 2-year outcome of uveitis in juvenile idiopathic arthritis: data from the Inception Cohort of Newly diagnosed patients with Juvenile Idiopathic Arthritis (ICON-JIA) study

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Abstract

Objective. To define predictors for the 2-year outcome in terms of achieving inactivity, subsequent uveitis reactivation and occurrence of uveitis-related complications of JIA-associated uveitis.

Methods. Demographic and clinical parameters and serum samples of JIA-associated uveitis patients enrolled in ICON at ≤1 year of JIA diagnosis were collected at study enrolment, every 3 months during the first year and subsequently every 6 months. Predictors for the 2-year outcome were evaluated by linear mixed models.

Results. Of 954 JIA patients included, uveitis occurred in 106 up to the first 2-year follow-up, with 98 of them having complete ophthalmological documentation. In 81.8% and 80.0% of patients, uveitis inactivity was achieved at the 1- and 2-year follow-up after uveitis onset, respectively. JIA onset after the age of 5 years, no use of topical corticosteroids, and adalimumab treatment were significantly associated with an inactive uveitis for at least 6 months (n = 57). Correlates for subsequent uveitis reactivation (n = 16, 30.2%) were age at uveitis onset ≤ 5 years and active disease (clinical Juvenile Arthritis Disease Activity Score > 4.5). Uveitis-related complications were present in 29.8% of patients at first uveitis documentation and in 30.7% and 32.8% at 1- and 2-year follow-up, respectively. Older age at JIA onset, short duration between JIA and uveitis onset, high anterior chamber (AC) cell grades, poor visual acuity, and topical steroid use at first uveitis documentation correlated with uveitis-related complications.

Conclusion. In addition to demographic risk factors, JIA disease and uveitis activity scores and adalimumab are significant predictors for the 2-year outcome of JIA-associated uveitis patients.

Key words: adalimumab, DMARDs, juvenile idiopathic arthritis, predictors, uveitis

Introduction

Uveitis is a significant cause of visual morbidity in children with JIA, which is one of the diseases most frequently associated with the condition [1]. According to the International League of Associations for Rheumatology criteria, JIA comprises a heterogeneous group of arthritis of yet unknown cause and with onset before 16 years of age, characterized by joint inflammation lasting ≥ 6 weeks [2]. As vision-threatening complications develop in more...
than half of the JIA-associated uveitis (JIAU) children, there is a high incidence of visual loss, and eye surgery is frequently required [3–5]. Currently, treatment of JIAU comprises topical and systemic corticosteroids, and conventional synthetic and/or biologic DMARDs for achieving inactivity in refractory disease [6, 7].

New developments in genetics and immunology and the analysis of environmental factors are instrumental for better defining, classifying and treating patients with JIA [8]. Indeed, genetic and environmental factors may influence the prevalence of JIA and associated uveitis, as it varies among different geographic regions [9]. Among the JIA categories, uveitis occurs in 10–13% of patients [3, 10], and even at higher percentages in particular subgroups. Known risk factors for uveitis incidence include young age at arthritis onset, oligoarthritis subtype and short disease duration [3, 11]. ANA [3, 12], elevated ESR [13] and carrying certain HLA-DRB1 alleles [14, 15] appeared as risk factors for uveitis occurrence in JIA. Recently, it was suggested that there is a correlation between elevated S100A8/9 and A12 serum levels and intraocular inflammation [16]. Indeed, systemic anti-inflammatory treatment instituted for arthritis may reduce the risk of uveitis onset in JIA patients [10, 17], particularly if given early during the disease course [18].

Biomarkers can be implemented in daily routine to identify JIA patients at particular risk for uveitis occurrence and a complicated disease course, e.g. for achieving disease inactivity or if the disease is subsequently reactivated or complications develop. Based on data from the prospective Inception Cohort of Newly diagnosed patients with JIA (ICON-JIA) study, clinical and laboratory predictors for the 2-year outcome of JIA-associated uveitis were defined in a large cohort of JIA patients.

Methods

Inception cohort of newly diagnosed patients with JIA (ICON)

ICON is an ongoing, multicentre, observational cohort study of patients in whom JIA was diagnosed within 12 months before enrolment and who are to be observed for at least 10 years [19]. JIA was defined according to the International League of Associations for Rheumatology criteria [2]. International League of Associations for Rheumatology diagnoses of all patients were subjected to a review process to validate the JIA category [19].

The study protocol was approved by the ethics committee of the Charité–Universitätsmedizin Berlin. All parents and patients (of 8 years and above) gave their informed consent at study inclusion according to the Declaration of Helsinki. The study reflects the currently applied standard of care in Germany.

Consecutive JIA patients from 11 paediatric rheumatology clinics in Germany were included, reaching 1/3 of the expected incident JIA cases nationwide during the recruitment period. Demographic and anamnestic clinical data, as well as family history and patient-reported outcomes, were recorded with standardized questionnaires completed by physicians and parents or patients, respectively. Clinical data, treatment and patient-reported data were collected at ICON enrolment, quarterly in the first year of observation and half-yearly thereafter [19], including rheumatological and ocular assessments.

The paediatric rheumatologists assessed the JIA patients at each visit. The clinical assessment included the JIA core set of criteria, such as the active joint count, physician’s global assessment of disease activity on a numeric rating scale (21-point numeric rating scale [NRS], 0–10), and whether the disease was clinically inactive according to the Wallace criteria [20]. In addition, the clinical Juvenile Arthritis Disease Activity Score (cJADAS-10) was calculated. The cJADAS-10 (range 0–30) includes physician’s global assessment, parent’s global assessment and the number of active joints (maximum 10). The cJADAS-10 thresholds proposed by Consolaro and Ravelli [21] for oligoarticular and polyarticular JIA were applied to define disease activity states. The patient or parent reported about overall well-being on a NRS, functional ability by the Childhood Health Assessment Questionnaire (CHAQ).

Laboratory parameters recorded at ICON enrolment included ANA, RF and HLA-B27, whereas ESR, CRP, and S100A12 [16] were determined at enrolment and follow-up visits.

A detailed and regular assessment by cooperating ophthalmologists was performed in all JIAU patients at each time point, including the clinical characterization of uveitis, visual acuity, slit-lamp examination, tonometry, ophthalmoscopy, uveitis-related complications and treatment (ongoing and newly started systemic and topical treatments). Patients were considered to be off treatment if they did not receive medication and did not start a new treatment (e.g. topical corticosteroids) at that visit.

JIAU patients were thoroughly evaluated according to the Standardization of Uveitis Nomenclature [22] with particular attention to disease activity (e.g. inactivity = no anterior chamber (AC) cells in field size 1 x 1 mm slit beam; grade 0), topical and systemic anti-inflammatory treatment and comprehensive documentation of complications (e.g. synechiae with number of involved quadrants, cataract, macular oedema). Accordingly, anterior uveitis was defined by the primary site of inflammation in the anterior chamber, including iritis and iridocyclitis. Onset of uveitis was described as sudden (typically pain, eye redness), or insidious (asymptomatic) during the attacks. Intraocular pressure >21 mmHg (ocular hypertension) and glaucoma (presence of glaucomatous optic disc damage, or typical visual field loss) were documented. Best-corrected visual acuity was described as logMAR = \(-\log_{10}\) visual acuity fraction.

The first ophthalmologic evaluation in ICON patients with uveitis was referred to as first uveitis documentation or uveitis baseline (U-BL), and the subsequent assessment as uveitis follow-up (U-FU). The most recent, regular ICON visit by the paediatric rheumatologist was designated for ophthalmological assessment with a maximum time gap of 4 weeks.
Outcome
The primary outcome of our study was to determine the rate of patients with inactive uveitis for ≥6 months within 2 years after first uveitis documentation, whether under topical anti-inflammatory medication and systemic DMARD treatment or not. The secondary outcomes of the study included subsequent uveitis reactivation and the presence of uveitis complications. Uveitis reactivation was analysed in patients who attained inactive uveitis for at least 6 months. The association of sociodemographic variables, JIA and uveitis characteristics and treatment with uveitis inactivity ≥6 months, reactivation and complications was determined.

Statistical analysis
Descriptive statistics were used to describe the distribution of categorical and continuously distributed variables. The primary and secondary outcomes of the study were analysed by generalized mixed linear models to account for the longitudinal data structure and the correlation between assessments within a patient. Furthermore, the grouping variable eye was introduced in the analyses on the eye level as an additional cluster variable. These models result in unbiased effect estimates in the presence of missing data in the follow-up because a patient is not excluded from analysis when an assessment is missing. Clinical and laboratory parameters at baseline (fixed variables) and treatment (time-varying variables) were assessed in terms of their predictive value for achieving the primary outcome.

The association of treatment and JIA disease characteristics with the outcomes was analysed on the patient level. In contrast, uveitis disease characteristics were analysed on the eye level. If uveitis activity, Tyndall, visual acuity and topical CS were reported on the patient level, the data were collapsed for the reporting within a patient by choosing the eye with worse AC cell score (Standardization of Uveitis Nomenclature) for the analysis, and the right eye if the score was similar in both eyes. A P-value of <0.05 is considered significant. Data analyses were performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA).

Results
Demographic factors and patient characteristics
A total of 954 JIA patients were included in this study (67.2% female, 54.2% ANA positive, mean age at JIA onset 7.1 (s.d. 4.6) years). Uveitis occurred in a total of 133 patients (13.9%) during the present observation period of the ICON study (mean follow-up of 45.2 (s.d. 22.1) months). In 106 of the patients, uveitis developed up to 2 years after enrolment in ICON. In fact, uveitis occurred before first JIA symptoms in four of the patients (0.4%), before enrolment in 52 patients (5.5%), in another 26 within the first year (2.7%), and in a further 24 within the second year (2.5%) after ICON enrolment. For this study, however, only those 98 (10.3%) patients were included, for whom the detailed uveitis characterization by the ophthalmologist was available (Supplementary Fig. 1, available at Rheumatology online). In these patients, observed for a mean period of 36 (s.d. 19.1) months, the uveitis disease course, including uveitis activity and secondary complications, among other uveitis characteristics, could be investigated. This is a representative sample of all 133 patients, as the 98 patients did not significantly differ with respect to sex (P = 0.168), JIA category (P = 0.653), ANA positivity (P = 0.692) and age at JIA onset (P = 0.358). Of the 98 patients, 76 were female (77.6%), 83 (84.7%) were ANA positive; the mean age at uveitis diagnosis was 5.1 (s.d. 3.0) years, and the mean age at JIA onset was 3.9 (s.d. 3.0) years. JIA categories in patients with and without uveitis are compared in Table 1.

Uveitis characteristics
The first ophthalmological assessment (U-BL) in patients with uveitis took place 3.2 (s.d. 5.3) months after uveitis diagnosis. Anterior uveitis (in 100% of 98 patients) was bilateral in 39.4% at this time point, in 62.7% at 2-year U-FU (P < 0.001). Insidious onset of uveitis was documented in 80.7% (n = 79) of patients at U-BL, correlating with oligoarthritis in 44 (65.7%) of them. Onset of uveitis was acute in another four patients (4.8%) and was unknown in the remaining 14.5%. Mean visual acuity (logMAR) was 0.21 (s.d. 0.30), 0.08 (s.d. 0.17), and 0.11 (s.d. 0.22) at U-BL, 1-year, and 2-year U-FU (P = 0.10), and logMAR < 0.1 was detected in 84.7% at U-BL, in 95.5% at 1-year U-FU and in 93.4% of patients at 2-year U-FU (P = 0.621).

Achievement of uveitis inactivity ≥6 months with anti-inflammatory treatment within 2 years after first uveitis documentation
In 81.8% and 80.0% of the JIAU patients, inactivity of uveitis was reported at the 1- and 2-year U-FU, respectively. Uveitis inactivity ≥6 months within the 2-year U-FU was reported in 57 (58.2%) of 98 JIAU patients, and this was achieved at a mean of 11.5 (s.d. 15.9) months after uveitis diagnosis.

57.5% of JIAU patients received methotrexate at U-BL (for a median of 5.4 months), 73.3% at the 1-year U-FU and 68.7% at the 2-year U-FU in (P < 0.001). In addition, adalimumab use increased significantly within the 2 years after U-BL (6.4%, 14.7%, 22.4% at U-BL, 1-year and 2-year U-FU, respectively, P < 0.001). At the U-BL, the patients had been treated with adalimumab for 3.1 months (median).

Topical and systemic corticosteroids were used at U-BL in more patients (74.5% and 11.4%, respectively) than at 1-year (48.0% and 10.3%, respectively) or at 2-year U-FU (38.8% and 6.3%, respectively) (P < 0.001 for topical steroids) (see Supplementary Tables 1 and 2, available at Rheumatology online).

Correlates for uveitis inactivity ≥6 months’ duration
JIA onset after the age of 4 years and uveitis onset after the age of 5 years were significantly associated with ≥6 months inactive uveitis during follow-up. Furthermore,
| Parameter                                      | Total sample (n%) | Patients with uveitis onset before enrolment in ICON (n%) | Patients with uveitis onset after enrolment and until 1-year in ICON (n%) | Patients with uveitis onset after 1-year and until 2-years in ICON (n%) | P-value |
|-----------------------------------------------|-------------------|----------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------|---------|
| Female, n (%)                                 | 641 (67.2)        | 40 (71.4%)                                               | 20 (76.9%)                                                               | 17 (70.8%)                                                            | 0.444   |
| Age at JIA onset, mean (S.D.), years          | 7.1 (4.6)         | 4.9 (3.5)                                                | 2.9 (2.0)                                                                | 3.3 (2.9)                                                             | **0.003**|
| JIA disease duration, median (IQR), months    | 6.0 (3.0–11.1)    | 7.0 (4.4–10.9)                                           | 2.8 (1.5–6.5)                                                            | 3.2 (2.3–8.9)                                                         | 0.142   |
| JIA category, n (%)                           |                   |                                                          |                                                                          |                                                                       |         |
| Systemic arthritis                            | 35 (3.8)          | 0 (0.0%)                                                 | 0 (0.0%)                                                                | 0 (0.0%)                                                             | 0.119   |
| Oligoarthritis persistent                     | 365 (38.3%)       | 30 (63.6%)                                               | 15 (57.7%)                                                               | 10 (41.7%)                                                           | 0.003   |
| Oligoarthritis extended                       | 79 (8.3%)         | 5 (8.9%)                                                 | 4 (15.4%)                                                               | 2 (8.3%)                                                             | 0.258   |
| Psoriatic arthritis                           | 45 (4.7)          | 1 (1.8%)                                                 | 0 (0.0%)                                                                | 1 (2.6%)                                                             |         |
| Enthesitis-related arthritis                  | 100 (10.5)        | 6 (10.7%)                                                | 1 (3.8%)                                                                | 0 (0.0%)                                                             | 0.001   |
| Polyarthritis RF positive                     | 15 (1.6)          | 0 (0.0%)                                                 | 0 (0.0%)                                                                | 0 (0.0%)                                                             |         |
| Polyarthritis RF negative                     | 252 (26.4)        | 10 (17.9%)                                               | 6 (23.1%)                                                               | 11 (45.8%)                                                           |         |
| Undifferentiated arthritis                    | 63 (6.6)          | 4 (7.1%)                                                 | 0 (0.0%)                                                                | 0 (0.0%)                                                             |         |
| ANA positive, n (% tested)                    | 517 (54.2)        | 48 (85.7%)                                               | 19 (74.4%)                                                               | 23 (95.8%)                                                           | 0.249   |
| RF positive, n (% tested)                     | 31 (3.3)          | 0 (0.0%)                                                 | 0 (0.0%)                                                                | 0 (0.0%)                                                             | —       |
| HLA-B27 positive, n (% tested)                | 146 (15.3)        | 7 (12.5%)                                                | 2 (7.7%)                                                                | 0 (0.0%)                                                             | 0.358   |
| Physician’s global assessment, NRS 0–10, mean (s.o.) | 3.8 (2.6)       | 3.2 (2.1)                                                | 4.0 (3.0)                                                                | 3.6 (2.8)                                                            | 0.258   |
| Active joint count, mean (s.o.)               | 41 (7.0)          | 3.8 (4.9)                                                | 4.3 (6.8)                                                                | 3.7 (6.2)                                                             | 0.933   |
| cJADAS-10, mean (s.o.)                        | 9.8 (6.2)         | 7.4 (5.1)                                                | 10.2 (4.2)                                                               | 9.2 (5.9)                                                             | 0.088   |
| ESR, mean (s.o.), mm/h                        | 22.8 (21.7)       | 23.7 (18.8)                                              | 34.1 (21.5)                                                              | 36.2 (26.3)                                                           | 0.092   |
| CRP, mean (s.o.), mg/l                        | 9.8 (18.5)        | 6.6 (11.8)                                               | 15.8 (21.5)                                                              | 17.5 (28.0)                                                           | 0.236   |
| S100A12, mean (s.o.), ng/ml                   | 337.5 (806.8)     | 235.4 (970.2)                                            | 594.1 (839.3)                                                            | 405.3 (462.4)                                                        | 0.137   |
| CHAQ, median (IQR)                            | 0.25 (0.08–0.88)  | 0 (0.0–0.75)                                             | 0.88 (0.1–1.63)                                                          | 0.63 (0.13–1.25)                                                     | **0.015**|
| Patient’s global, NRS 0–10, mean (s.o.)       | 3.0 (2.3)         | 2.6 (2.4)                                                | 3.1 (2.2)                                                                | 2.5 (1.9)                                                            | 0.607   |
| Pain, NRS 0–10, mean (s.o.)                   | 3.0 (2.8)         | 2.1 (2.4)                                                | 3.2 (2.3)                                                                | 2.1 (2.2)                                                            | 0.102   |
| Uveitis, n (%)                                | 133 (13.9%)       | 56 (100.0%)                                              | 26 (100.0%)                                                              | 24 (100.0%)                                                          |         |

Uveitis diagnosis either before enrolment or after enrolment and until 1 or 2 years in ICON. Data from 98 patients with detailed uveitis characterization by ophthalmologists. *P*-value of less than 0.05 are indicated in bold. CHAQ: Childhood Health Assessment Questionnaire; cJADAS: clinical juvenile arthritis disease activity score; IQR: interquartile range; NRS: numeric rating scale.
adalimumab treatment and no use of topical corticosteroids in the involved eyes during the 2-year observation period were also significantly associated with ≥6 months inactive uveitis during follow-up (Table 2). We could not find a significant association for the numerous other clinical, laboratory and disease activity parameters at first uveitis documentation or for other anti-inflammatory medications.

A decreasing JIA disease activity (cJADAS-10; OR 0.76; 95% CI: 0.63, 0.92; P = 0.035; physician’s global: OR 0.92; 95% CI: 0.85, 0.97; P = 0.046) during follow-up was significantly associated with sustaining uveitis inactivity.

**Correlates for uveitis reactivation**

In 16 patients (28% of 57) uveitis was subsequently reactivated after attaining inactive uveitis within 2 years after U-BL. Fifty-three of the 57 patients with uveitis inactivity for ≥6 months had sufficient follow-up for analysis of predictors (Tables 3 and 4). Subsequent uveitis reactivation (n = 16, 30.2%) was associated with age at uveitis onset <5 years. An active disease (cJADAS-10 >4.5) and the use of topical corticosteroids during U-FU were significantly associated with uveitis reactivation.

**Uveitis-related complications**

Uveitis-related complications were present in 28 patients (29.8% of 98) at U-BL and in 30.7% and 32.8% at 1-, and 2-year U-FU, respectively. During the follow-up period, a total of nine patients (12.9% of 70) without complications at first uveitis documentation developed new uveitis-related complications (Supplementary Table 3, available at Rheumatology online indicates changes in eye complications). Patients with eye complications at the first uveitis documentation were more likely to show complications at the 2-year U-FU compared with patients without (73.7% vs 13.5%, P < 0.001). The number of patients with ocular hypertension increased during the 2-year follow-up (from 0 at U-BL, to two at 2-year U-FU), possibly related also to the topical steroid use in these patients (Table 5). The number of patients with typical inflammation-related eye complications (e.g. optic disc or macular oedema) was slightly reduced during the observation period, which is probably related to the anti-inflammatory treatment. Meanwhile, the number of other eye complications increased only insignificantly, and only one patient required ocular surgery (EDTA chelation for band-keratopathy) during the observation period (Table 5).

**Correlates for uveitis complications**

Older age at JIA onset, short duration between JIA and uveitis onset, high AC cell grades ≥2+, the presence of complications and poor visual acuity (high logMAR rates) at first uveitis documentation were significantly associated with the occurrence of uveitis-related eye complications. Treatment with topical steroids was positively associated with the subsequent development of complications (Table 6).

However, no significant correlation was found between achievement of uveitis inactivity ≥6 months within 2 years after first uveitis documentation and occurrence of uveitis-related eye complications. Nor did the use of conventional synthetic or biologic DMARDs appear to significantly alter the rate of eye complications during the follow-up period. However, combined use of adalimumab and methotrexate showed a lower rate of eye complications in follow-up, but without reaching significance (P = 0.09).

**Discussion**

**Achievement of uveitis inactivity and subsequent reactivation**

In this ICON study, patient characteristics and demographic risk factors compare favourably with previously published studies [3, 4, 10, 12, 13, 23–25]. Our data show for the first time that patients in whom uveitis inactivity ≥6 months was achieved with anti-inflammatory medication were significantly older at onset of JIA and uveitis, and the chance to achieve inactivity was particularly high when uveitis had begun after age 5. Herein, gender did not appear as a predictive factor for response to DMARD treatment, or subsequent uveitis reactivation, or development of complications. Previously, male gender was related to good visual outcome [25]. Others found that males had an increased risk of developing complications and worse visual outcome [23, 24, 26, 27], probably related to the notion that, in boys, uveitis more often manifests earlier in the disease course or is more severe, or that there is less awareness of disease occurrence in boys [3, 28]. Others did not find differences in uveitis severity between males and females [29].

ANA positivity is a well-known predictor for uveitis occurrence in JIA patients [3, 11, 12, 18, 30]. In the present study it was not a significant predictor for the 2-year outcome of JIAU, which is in agreement with previous observations [3, 27]. Others found more complications in ANA-negative than in the ANA-positive patients [31, 32], probably related to inadequate uveitis screening of JIA patients.

Elevated ESR appeared as a valid baseline prognostic factor for uveitis occurrence in JIA patients [13, 27, 29, 33, 34]. According to our present data, it did not appear as a useful predictor of the further uveitis course, which is probably influenced by anti-inflammatory treatment instituted for JIA.

Previous data disclosed that S100 serum levels in JIAU patients were higher in patients with active uveitis and suggested that they may reflect eye disease [16]. High S100A12 levels in JIA patients were significantly associated with the risk for uveitis [34]. Our presented data show that S100A12 might not be a useful biomarker for monitoring uveitis activity during the course of JIA, probably influenced by the DMARDs being used to treat the underlying rheumatic disease [35].

Grading AC cells is an important measure of uveitis activity [22], accepted also in JIAU [36] primarily involving the iris and ciliary body [37, 38]. Herein, baseline AC cell grade was not a significant predictor for uveitis inactivity ≥6 months duration. High AC cell scores and the use of topical corticosteroids at the initial uveitis documentation
## Table 2: Association of initial clinical/laboratory parameters with ≥6 months uveitis inactivity

| Parameter                                           | Patients without achievement of uveitis inactivity ≥6 months until 2-year U-FU in ICON | Patients with achievement of uveitis inactivity ≥6 months until 2-year U-FU in ICON | OR; 95% CI; P value |
|-----------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------|
| Female, n (%)                                       | 31 (75.6%)                                                                             | 42 (73.7)                                                                             | 1.29; 0.61, 2.75; 0.502 |
| Age at JIA onset, mean (s.d.), years                | 3.5 (3.3)                                                                              | 4.3 (3.4)                                                                             | 1.10; 1.02, 1.18; 0.014 |
| Age at uveitis onset, mean (s.d.), years            | 4.6 (3.4)                                                                              | 4.7 (2.5)                                                                             | 1.09; 1.01, 1.19; 0.030 |
| Uveitis onset >5 years, n (%)                       | 10 (24.4%)                                                                             | 19 (33.3%)                                                                            | 1.84; 1.09, 3.10; 0.023 |
| Interval between JIA and uveitis onset, mean (s.d.), years | 1.0 (1.2)                                                                              | 0.5 (1.4)                                                                             | 0.84; 0.62, 1.12; 0.237 |
| JIA category, n (%)                                 |                                                                                        |                                                                                      |                     |
| Oligoarthritis persistent                           | 18 (45.0%)                                                                             | 33 (57.9%)                                                                            | (Reference)         |
| Oligoarthritis extended                             | 5 (12.5%)                                                                              | 6 (10.5%)                                                                             | 0.62; 0.20, 1.86; 0.375 |
| Psoriatic arthritis                                | 1 (2.5%)                                                                               | 1 (1.8%)                                                                              | 0.81; 0.09, 7.50; 0.852 |
| Enthesitis-related arthritis                        | 4 (10.0%)                                                                              | 3 (5.3%)                                                                              | 0.48; 0.10, 2.24; 0.347 |
| Polychaetosis RF negative                           | 9 (22.5%)                                                                              | 12 (21.1%)                                                                            | 0.90; 0.37, 2.21; 0.816 |
| Undifferentiated arthritis                          | 3 (7.5%)                                                                               | 2 (3.5%)                                                                              | 0.75; 0.14, 4.10; 0.738 |
| ANA positive, n (%)                                 | 33 (82.5%)                                                                             | 47 (82.5%)                                                                            | 0.38; 0.11, 1.37; 0.140 |
| HLA-B27 positive, n (%)                             | 4 (10.0%)                                                                              | 3 (5.3%)                                                                              |                     |
| Laboratory markers                                  |                                                                                        |                                                                                      |                     |
| ESR, mean (s.d.)                                    | 22.1 (16.9)                                                                             | 24.6 (17.6)                                                                            | 1.00; 0.98, 1.03; 0.744 |
| CRP, mean (s.d.)                                    | 4.1 (4.8)                                                                              | 6.3 (10.0)                                                                             | 1.03; 0.98, 1.07; 0.248 |
| S100A12, mean (s.d.)                                | 427.4 (679.7)                                                                           | 320.6 (438.8)                                                                          | 0.99; 0.99, 1.01; 0.321 |
| Disease activity                                    |                                                                                        |                                                                                      |                     |
| cJADAS-10, mean (s.d.)                              | 6.7 (5.0)                                                                               | 6.3 (4.0)                                                                              | 1.02; 0.93, 1.12; 0.675 |
| Physician’s global, NRS, mean (s.d.)                | 2.8 (2.6)                                                                               | 2.4 (2.2)                                                                             | 0.95; 0.80, 1.13; 0.554 |
| Number of active joints, mean (s.d.)                | 2.3 (2.2)                                                                               | 1.9 (2.1)                                                                             | 0.85; 0.73, 1.01; 0.060 |
| Parent’s global, mean (s.d.)                        | 1.7 (2.1)                                                                               | 1.2 (1.3)                                                                             | 0.92; 0.71, 1.18; 0.505 |
| Pain, NRS, mean (s.d.)                              | 2.4 (2.7)                                                                               | 1.9 (2.2)                                                                             | 0.98; 0.84, 1.14; 0.763 |
| CHAQ, mean (s.d.)                                   | 0.71 (0.88)                                                                             | 0.40 (0.59)                                                                            | 0.69; 0.39, 1.21; 0.191 |
| Uveitis activity, AC cell grade/involved eye, mean (s.d.) | 1.23 (0.94)                                                                             | 0.93 (0.72)                                                                            | 1.09; 0.66, 1.79; 0.756 |
| Tyndall/involved eye                                | 2.00 (1.24)                                                                             | 1.61 (1.32)                                                                            | 1.10; 0.81, 1.49; 0.546 |
| Visual acuity/involved eye, logMAR                  | 0.19 (0.23)                                                                             | 0.22 (0.38)                                                                            | 0.75; 0.24, 2.38; 0.626 |
| Any uveitis eye complications                       | 9 (24.3%)                                                                               | 19 (33.3%)                                                                            | 0.89; 0.57, 1.99; 0.848 |
| Anti-inflammatory treatment (time-varying)          |                                                                                        |                                                                                      |                     |
| NSAD                                                | 0.87; 0.41, 1.83; 0.714                                                                 |                                            |                     |
| Any DMARD                                           | 0.79; 0.40, 1.59; 0.516                                                                 |                                            |                     |
| MTX                                                 | 0.66; 0.34, 1.27; 0.209                                                                 |                                            |                     |
| Etanercept ± MTX                                    | 1.65; 0.25, 11.06; 0.608                                                                |                                            |                     |
| Adalimumab ± MTX                                    | 1.89; 1.15, 3.73; 0.014                                                                 |                                            |                     |
| CS, systemic                                        | 2.12; 0.86, 5.20; 0.101                                                                   |                                            |                     |
| CS, topical in involved eyes                        | 0.36; 0.20, 0.63; 0.001                                                                  |                                            |                     |

Association of clinical and laboratory parameters at first uveitis documentation and treatment during follow-up (time-varying) with uveitis inactivity for ≥6 months. P-value of less than 0.05 are indicated in bold. AC cell grade = anterior chamber cell grade; CHAQ: Childhood Health Assessment Questionnaire; CI: confidence interval; cJADAS: clinical juvenile arthritis disease activity score; CS: corticosteroids; NRS: numeric rating scale; OR: odds ratio; PedsQL: Pediatric Quality of Life Inventory; U-FU: uveitis follow-up.
### TABLE 3  Association of subsequent uveitis reactivation with time-independent clinical parameters

| Parameter                      | Patients without subsequent uveitis reactivation until 2-year U-FU | Patients with subsequent uveitis reactivation until 2-year U-FU | OR; 95% CI; P value |
|--------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|-------------------|
|                                | 37                                                           | 16                                                           |                   |
| Female, n (%)                  | 26 (70.3%)                                                   | 12 (75.0%)                                                   | 0.96; 0.32, 2.91; 0.947 |
| Age at JIA onset, mean (S.D.), years | 4.3 (2.5)                                                   | 3.2 (1.9)                                                   | 0.89; 0.71, 1.11; 0.289 |
| Age at uveitis onset, mean (S.D.), years | 4.1 (1.9)                                                   | 3.8 (1.7)                                                   | 0.91; 0.82, 0.98; 0.039 |
| Age at uveitis onset >5 years, n (%) | 15 (40.5%)                                                   | 3 (18.8%)                                                   | 0.67; 0.33, 0.92; 0.034 |
| Interval between JIA and uveitis onset | 0.5 (0.9)                                                   | 0.6 (0.6)                                                   | 1.60; 0.70, 3.63; 0.263 |
| JIA category, n (%)            |                                                              |                                                              |                   |
| Polyarthritis RF negative      | 6 (16.7%)                                                   | 4 (25.0%)                                                   |                   |
| Oligoarthritis persistent      | 24 (66.7%)                                                   | 9 (56.3%)                                                   |                   |
| Oligoarthritis extended        | 4 (11.1%)                                                   | 1 (6.3%)                                                   |                   |
| Psoriatic arthritis            | 0 (0.0%)                                                   | 1 (6.3%)                                                   |                   |
| Enthesitis-related arthritis   | 1 (2.8%)                                                   | 0 (0.0%)                                                   |                   |
| Undifferentiated arthritis     | 1 (2.8%)                                                   | 1 (6.3%)                                                   |                   |
| ANA positive, n (%)            | 32 (86.5%)                                                   | 12 (75.0%)                                                  | 1.70; 0.22; 13.17; 0.608 |
| HLA-B27 positive, n (%)        | 2 (5.4%)                                                   | 1 (6.3%)                                                   |                   |

Association of subsequent uveitis reactivation (n = 16; 28.1%) with time-independent clinical parameters. Fifty-three of 57 patients with uveitis inactivity for ≥6 months had sufficient follow-up for analysis. P-value of less than 0.05 are indicated in bold. Due to collinearity and small numbers, JIA subcategory and ANA could not be estimated. OR: odds ratio; U-FU: uveitis follow-up.

### TABLE 4  Association of treatment, change in laboratory markers, and disease activity during follow-up with subsequent uveitis reactivation

| Parameter                      | OR; 95% CI       | P value |
|--------------------------------|-----------------|---------|
| Laboratory marker              |                 |         |
| ESR                            | 1.02; 0.92, 1.13 | 0.738   |
| CRP                            | 0.89; 0.67, 1.19 | 0.433   |
| S100A12                        | 1.01; 0.98, 1.00 | 0.203   |
| Disease activity               |                 |         |
| cJADAS-10 >4.5                 | 1.84; 1.18, 7.02 | 0.017   |
| Physician’s global, NRS        | 0.80; 0.33, 1.96 | 0.626   |
| CHAQ                           | 0.04; 0.01, 33.51 | 0.341   |
| Parent’s global                | 1.05; 0.57, 1.93 | 0.878   |
| Pain, NRS                      | 1.15; 0.70, 1.89 | 0.58    |
| Uveitis activity, AC cell grade/involved eye | 2.04; 1.27, 3.26 | 0.003   |
| Tyndall/involved eye           | 5.65; 2.09, 15.26 | 0.001   |
| Visual acuity/involved eye, logMAR | 0.60; 0.07, 4.99 | 0.632   |
| Any uveitis eye complications  | 1.05; 0.65, 1.48 | 0.198   |
| Anti-inflammatory treatment    |                 |         |
| NSAID                          | 1.41; 0.40, 4.95 | 0.591   |
| Any DMARD                      |                 |         |
| MTX                            |                 |         |
| Etanercept ± MTX               |                 |         |
| Adalimumab ± MTX               | 1.03; 0.26, 4.05 | 0.966   |
| CS, systemic                   | 1.62; 0.27, 9.77 | 0.596   |
| CS, topical in involved eyes   | 3.47; 1.36, 8.86 | 0.01    |

Subsequent uveitis reactivation (n = 16; 30.2%) until 2 years of follow-up, after achieving uveitis inactivity ≥6 months. P-value of less than 0.05 are indicated in bold. AC: anterior cell; CHAQ: Childhood Health Assessment Questionnaire; cJADAS: clinical juvenile arthritis disease activity score; CS: corticosteroids; NRS: numeric rating scale; OR: odds ratio; PedQL: Pediatric Quality of Life Inventory.
were associated with subsequent uveitis reactivation. Accordingly, mild disease was an important predisposing factor for subsequent remission in a previous study [26], and a severe disease and worse visual outcome were previously observed in patients with severe disease at onset [23, 24, 26].

In previous studies, high Tyndall effect reflected a more severe uveitis course in terms of uveitis activity and tissue damage [39]. It is, therefore, conceivable that high Tyndall effect at initial documentation correlated with subsequent uveitis reactivation in the present study.

Previous retrospective results indicated that arthritis and uveitis activity are commonly independent of each other [40], and retrospective analysis did not find a significant relationship between the time point of clinical remission for arthritis and uveitis [41]. Our previous study showed that patients with high cJADAS-10 scores at baseline had a higher risk of uveitis occurrence [18]. Accordingly, our data now show that moderate or high JIA disease activity was a reliable predictor for subsequent uveitis reactivation.

Use of DMARDs is critical for achieving uveitis inactivity. The common use of methotrexate in this study is in agreement with previous publications [1, 42]. Methotrexate was associated with a reduced risk of visual loss in recent studies [10, 43], and also prevented uveitis onset when treatment was commenced early after JIA onset [17, 18]. According to the data presented herein, however, methotrexate was not a predictor for attaining uveitis inactivity.

Recent studies with adalimumab found that uveitis inactivity in methotrexate (combined with topical corticosteroids) non-responders is obtained in ≥3/4 of patients, improving the subsequent disease course particularly when given early during the JIA course [6, 7, 18, 44]. In our study, under DMARDs (including adalimumab use in up to 22.4% of included cases) uveitis inactivity was documented in 81.8% and 80.0% of the JIAU patients at 1- and 2-year U-FU, respectively, which is in agreement with previous publications. Indeed, our data now point to adalimumab use as an important predictor for achieving uveitis inactivity. Adalimumab has proven to be effective for JIAU [7] and recently received approval for this indication. Recent studies further suggested that treatment with adalimumab reduced the uveitis incidence in JIA patients [10, 18].

### Uveitis-related complications and their predictors

In this study, the incidence of uveitis and second eye involvement progressively increased during the first 2 years after JIA onset in up to 2/3 of patients, supporting previous observations [10, 12, 26, 30]. The numbers of uveitis-related complications in JIA given herein during the first 2-year course in ICON are in agreement with recent publications providing longer follow-up [3, 10], and the increasing complication rates during the long-term course commonly reported [3, 4, 12, 28, 31].

Herein, late JIA onset and short duration between JIA and uveitis onset were significant predictors for occurrence of uveitis-related eye complications. Accordingly, higher complication rates were previously also found in patients with late onset of arthritis, with uveitis presenting before JIA onset or with a shorter interval between arthritis and uveitis onset [3, 25, 26, 31, 45], probably related to the longer disease period of insidious onset uveitis without sufficient treatment.

Among the factors analysed herein, significant predictors for uveitis complications were high AC cell score, and presence of complications and poor visual acuity at first uveitis documentation. This is supported by a previous notion, as severity of uveitis at first uveitis documentation was the most significant, independent risk factor for subsequent development of complications [26]. In a previous study, increasing AC cell grade was associated with increased rates of visual loss, while DMARD use was associated with a reduced risk of visual loss [46]. Although high flare values (reflecting intraocular inflammation and also tissue damage) in JIAU patients were associated with poor vision and a higher prevalence of uveitis complications in previous studies [31, 39, 47-49], no

### Table 5: Uveitis-related eye complications at first uveitis documentation and at 1- and 2-year follow-up

| Eye complication               | First uveitis documentation (n = 98) | 1-year U-FU (n = 87) | 2-year U-FU (n = 75) | P-value |
|-------------------------------|-------------------------------------|----------------------|----------------------|---------|
| Any, n (%)                    | 28 (29.8%)                          | 23 (30.7%)           | 22 (32.8%)           | 0.845   |
| Band-keratopathy, n (%)        | 2 (2.1%)                            | 2 (2.3%)             | 1 (1.5%)             | 0.611   |
| Synchiae, n (%)                | 21 (22.3%)                          | 17 (22.7%)           | 16 (23.9%)           | 0.869   |
| Cataract, n (%)                | 7 (7.5%)                            | 7 (9.3%)             | 9 (13.4%)            | 0.377   |
| Optic disc oedema, n (%)       | 1 (1.1%)                            | 1 (1.3%)             | 0 (0.0%)             | 0.669   |
| Macular oedema, n (%)          | 1 (1.1%)                            | 0 (0.0%)             | 0 (0.0%)             | 0.484   |
| Ocular hypertension, n (%)     | 0 (0.0%)                            | 0 (0.0%)             | 4 (6.0%)             | 0.01    |
| Glaucoma, n (%)                | 0 (0.0%)                            | 1 (1.3%)             | 2 (3.0%)             | 0.228   |
| Iris ruberosis, n (%)          | 0 (0.0%)                            | 1 (1.3%)             | 0 (0.0%)             | 0.340   |
| Vitreous haze, n (%)           | 2 (2.1%)                            | 2 (2.7%)             | 1 (1.5%)             | 0.900   |
| Any eye surgery, n (%)         | 0 (0.0%)                            | 0 (0.0%)             | 1 (1.5%)             | 0.264   |

*Out of 98 patients, data from 87 patients were available at 1-year follow-up, and from 75 patients at 2-year follow-up. P-value of less than 0.05 are indicated in bold. U-FU: uveitis follow-up.
significant correlation was found for the Tyndall effect in the present study. In the present study, topical corticosteroid use was significantly associated with the subsequent development of uveitis-related eye complications, particularly cataract formation, which is in accordance with previous reports [5]. Others showed that significantly higher amounts of oral corticosteroids were used in patients with complications [50], while this was not obvious in our study. While the rate of uveitis-related complications was reduced under adalimumab treatment in previous publications [7, 18], our present data disclose only a tendency for a reduced risk for such complications, probably because most complications already existed at the initial study visit and DMARD therapy, or because this analysis was limited to 2 years, and the preferential use of adalimumab in patients with a severe JIAU course. Herein, no effect of conventional synthetic DMARDs on the development of eye complications could be demonstrated, supporting previous findings [26], while DMARDs reduced the risk of hypotony and other complications in a previous study [4].

Synechiae formation at initial presentation is often followed by the development of vision-threatening complications [4, 26, 46], and their presence, AC flare ≥1+

| Parameter | Patients without uveitis complications | Patients with uveitis complications | OR; 95% CI; P value |
|-----------|----------------------------------------|------------------------------------|-------------------|
| Female, n (%) | 53 (80.3%) | 26 (70.3%) | 2.30; 0.60, 8.76; 0.224 |
| Age at JIA onset, mean (s.d.), years | 3.67 (2.92) | 4.68 (3.55) | 1.15; 1.01, 1.32; 0.039 |
| Age at uveitis onset, mean (s.d.), years | 4.62 (2.94) | 4.92 (3.01) | 1.10; 0.95, 1.27; 0.192 |
| Uveitis onset >5 years, n (%) | 19 (28.8%) | 13 (35.1%) | 1.99; 0.81, 4.91; 0.135 |
| Interval between JIA and uveitis onset, mean (s.d.), years | 0.96 (1.05) | 0.25 (1.56) | 0.48; 0.23, 0.99; 0.046 |
| JIA category, n (%) | | | |
| Polyarthritis RF negative | 15 (22.7%) | 6 (17.1%) | (Reference) |
| Oligoarthritis persistent | 9 (13.6%) | 3 (8.6%) | 0.77; 0.08, 7.22; 0.822 |
| Oligoarthritis extended | 35 (53.0%) | 19 (54.3%) | 1.03; 0.21, 5.08; 0.968 |
| Psoriatic arthritis | 1 (1.5%) | 2 (5.7%) | 3.07; 0.07, 128.13; 0.554 |
| Enthesitis-related arthritis | 3 (4.6%) | 3 (8.6%) | 2.98; 0.17, 51.69; 0.452 |
| Undifferentiated arthritis | 3 (4.6%) | 2 (5.7%) | — |
| ANA positive, n (%) | 54 (81.8%) | 33 (89.2%) | 1.86; 0.22, 16.00; 0.572 |
| HLA-B27 positive, n (%) | 5 (7.6%) | 3 (8.1%) | — |
| Laboratory markers | | | |
| ESR, mean (s.d.) | 23.40 (16.37) | 24.27 (19.30) | 1.01; 0.97, 1.05; 0.678 |
| CRP, mean (s.d.) | 7.07 (11.13) | 4.04 (5.06) | 0.95; 0.86, 1.04; 0.275 |
| S100A12, mean (s.d.) | 398.29 (608.21) | 341.01 (452.86) | 0.99; 0.99, 1.01; 0.387 |
| Disease activity | | | |
| cJADAS-10, mean (s.d.) | 6.33 (4.29) | 7.67 (4.17) | 1.04; 0.90, 1.20; 0.627 |
| Physician’s global, NRS, mean (s.d.) | 2.46 (2.14) | 2.81 (2.82) | 0.95; 0.73, 1.23; 0.685 |
| Number of active joints, mean (s.d.) | 2.62 (2.21) | 3.42 (2.05) | 1.01; 0.89, 1.46; 0.891 |
| Parent’s global, mean (s.d.) | 1.25 (1.65) | 1.44 (1.65) | 1.20; 0.92, 1.57; 0.182 |
| Pain, NRS, mean (s.d.) | 2.19 (2.31) | 2.19 (2.59) | 1.05; 0.85, 1.31; 0.477 |
| CHAQ, mean (s.d.) | 0.51 (0.71) | 0.65 (0.81) | 1.54; 0.68, 3.53; 0.302 |
| Uveitis activity, AC cell grade/involved eye | 0.87 (0.70) | 1.23 (0.99) | 2.24; 1.16, 4.31; 0.016 |
| Visual acuity/involved eye, logMAR | 1.55 (1.33) | 1.96 (1.33) | 1.16; 0.77, 1.75; 0.469 |
| Anti-inflammatory treatment (time-varying) | | | |
| NSAID | 1.07; 0.36, 3.19 |
| Any DMARDs | 0.98; 0.60, 3.25 |
| MTX | 1.34; 0.42, 4.23 |
| Etanercept ± MTX | 0.94; 0.04, 24.68 |
| Adalimumab ± MTX | 0.64; 0.13, 1.09 |
| CS, systemic | 1.21; 0.22, 6.60 |
| CS, topical, applications/day in involved eyes | 4.06; 1.63, 10.13 |

Clinical and laboratory parameters at first uveitis documentation and treatment during follow-up (time-varying) with uveitis complications. P-value of less than 0.05 are indicated in bold. AC cell grade: anterior chamber cell grade; CHAQ: Childhood Health Assessment Questionnaire; cJADAS: clinical juvenile arthritis disease activity score; CS: corticosteroids; NRS: numeric rating scale; OR: odds ratio; PedsQL: Pediatric Quality of Life Inventory.
hypotheny were associated with vision loss or poor vision during follow-up [4, 26, 43]. Herein, the presence of uveitis-related complications was not a significant predictor for achieving uveitis inactivity under anti-inflammatory treatment or subsequent reactivation.

Our study has some limitations. (i) ICON is an observational study and the analysis of treatment is a challenge. The association between treatment and outcome is biased by the individual treatment decision of the pediatric rheumatologist or ophthalmologist. Patients on a more severe disease course were more likely to be intensively treated. Furthermore, treatment individually starts at different time points depending on the disease course of the patient and it is not possible to define a baseline for comparisons. (ii) We did not collect data about the indication to start treatment. DMARD treatment may be initiated to control the JIA disease activity or the uveitis activity. (iii) The first uveitis documentation does not necessarily reflect the assessment of uveitis activity at the uveitis onset. Treatment may already have started before the first documentation. However, during the recruitment period, an estimated one-third of all new cases with JIA in Germany were included in ICON and examined by pediatric rheumatologists and ophthalmologists in a standardized way, so that representative data on the uveitis outcome and its predictors could be obtained.

In summary, in addition to demographic risk factors, JIA disease and uveitis activity scores and treatment with adalimumab were significant predictors for the 2-year course of JIAU patients in this inception cohort study. Laboratory tests found to be significant biomarkers for uveitis occurrence (e.g. ANA, ESR, S100), however, may lose their respective predictive value for the disease course under the influence of anti-inflammatory treatment instituted early in the JIA course.

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Supplementary data

Supplementary data are available at Rheumatology online.

References

1 Sen ES, Dick AD, Ramanan AV. Uveitis associated with juvenile idiopathic arthritis. Nat Rev Rheumatol 2015;11:338–48.
2 Petty RE, Southwood TR, Manners P et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.
3 Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K; German Uveitis in Childhood Study Group. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology 2007;46:1015–9.
4 Thorne JE, Woreta F, Kedhar SR, Dunn JP, Jabs DA. Juvenile idiopathic arthritis-associated uveitis: incidence of ocular complications and visual acuity loss. Am J Ophthalmol 2007;143:840–6.
5 Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology 2010;117:1436–41.
6 Leman MA, Burnham JM, Chang PY et al. Response of pediatric uveitis to tumor necrosis factor-α inhibitors. J Rheumatol 2013;40:1394–403.
7 Ramanan AV, Dick AD, Jones AP et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. N Engl J Med 2017;376:1637–46.
8 Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet 2011;377:2138–49.
9 Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis: why does it vary so much? J Rheumatol 2002;29:1520–30.
10 Tappeiner C, Klotzsche J, Schenck S et al. Temporal change in prevalence and complications of uveitis associated with juvenile idiopathic arthritis: data from a cross-
sectional analysis of a prospective nationwide study. Clin Exp Rheumatol 2015;33:936–44.

11 Angeles-Han ST, Pelajo CF, Vogler LB et al. Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. J Rheumatol 2013;40:2088–96.

12 Kotaniemi K, Kautiainen H, Karma A, Aho K. Occurrence of uveitis in recently diagnosed juvenile chronic arthritis: a prospective study. Ophthalmology 2001;108:2071–5.

13 Haasnoot AJW, van Tent-Hoeve M, Wulffraat NM et al. Erythrocyte sedimentation rate as baseline predictor for the development of uveitis in children with juvenile idiopathic arthritis. Am J Ophthalmol 2015;159:372

14 Angeles-Han ST, McCracken C, Yeh S et al. HLA associations in a cohort of children with juvenile idiopathic arthritis with and without uveitis. Invest Ophthalmol Vis Sci 2015;56:6043–8.

15 Haasnoot AJW, Schilham MW, Kamphuis S, Hissink Muller PCE et al. An amino acid motif in HLA-DRβ1 distinguishes patients with uveitis in juvenile idiopathic arthritis. Arthritis Rheumatol 2018;70:1155–65.

16 Walscheid K, Heiligenhaus A, Holzinger D et al. Elevated S100A8/9 and S100A12 serum levels reflect intraocular in inflammation in juvenile idiopathic arthritis-associated uveitis: results from a pilot study. Invest Ophthalmol Vis Sci 2015;56:7653–60.

17 Papadopoulou C, Kostik M, Böh m M et al. Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. J Pediatr 2013;163:879–84.

18 Tappeiner C, Schenck S, Niewerth M et al. Impact of antiinflammatory treatment on the onset of uveitis in juvenile idiopathic arthritis: longitudinal analysis from a nationwide pediatric rheumatology database. Arthritis Care Res 2016;68:46–54.

19 Sengler C, Klotzsche J, Niewerth M et al. The majority of newly diagnosed patients with juvenile idiopathic arthritis reach an inactive disease state within the first year of specialised care: data from a German inception cohort. RMD Open 2015;1:e000074.

20 Wallace CA, Ruperto N, Giannini E; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology International Trials Organization Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for selected categories of juvenile idiopathic arthritis. J Rheumatol 2004;31:2290–4.

21 Consolaro A, Ravelli A. Defining criteria for disease activity states in juvenile idiopathic arthritis. Rheumatology 2016;55:595–6.

22 Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of the Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol 2005;140:509–16.

23 Chia A, Lee V, Graham EM, Edelsten C. Factors related to severe uveitis at diagnosis in children with juvenile idiopathic arthritis in a screening program. Am J Ophthalmol 2003;135:757–62.

24 Kalinina Ayuso V, Ten Cate HA, van der Does P, Rotherova A, de Boer JH. Male gender and poor visual outcome in uveitis associated with juvenile idiopathic arthritis. Am J Ophthalmol 2010;149:987–93.

25 Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. Ophthalmology 1997;104:236–44.

26 Edelsten C, Lee V, Bentley CR, Kanski JJ, Graham EM. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. Br J Ophthalmol 2002;86:51–6.

27 Zulian F, Martini G, Falcini F et al. Early predictors of severe course of uveitis in oligoarticular juvenile idiopathic arthritis. J Rheumatol 2002;29:2446–53.

28 Edelsten C, Reddy MA, Stanford MR, Graham EM. Visual loss associated with pediatric uveitis in English primary and referral centers. Am J Ophthalmol 2003;135:676–80.

29 Kotaniemi K, Kotaniemi A, Savolainen A. Uveitis as a marker of active arthritis in 372 patients with juvenile idiopathic seronegative oligoarthritis or polyarthritis. Clin Exp Rheumatol 2002;20:109–12.

30 Papadopoulou M, Zetterberg M, Oskarsdottir S, Andersson GM. Assessment of the outcome of ophthalmological screening for uveitis in a cohort of Swedish children with juvenile idiopathic arthritis. Acta Ophthalmol 2017;95:741–7.

31 Woreta F, Thorne JE, Jabs DA, Kedhar SR, Dunn JP. Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis. Am J Ophthalmol 2007;143:647–55.

32 Chalom EC, Goldsmith DP, Koehler MA et al. Prevalence and outcome of uveitis in a regional cohort of patients with juvenile rheumatoid arthritis. J Rheumatol 1997;24:2031–4.

33 Pelegrin L, Casaroli-Marano R, Anton J et al. Predictive value of selected biomarkers, polymorphisms, and classical features for oligoarticular juvenile idiopathic arthritis-associated uveitis. Ocul Immunol Inflamm 2014;22:208–15.

34 Tappeiner C, Klotsche J, Sengler C et al. Risk factors and biomarkers for the occurrence of uveitis in juvenile idiopathic arthritis: data from the Inception Cohort of Newly Diagnosed Patients with Juvenile Idiopathic Arthritis Study. Arthritis Rheumatol 2018;70:1685–94.

35 Foell D, Wulffraat N, Wedderburn LR et al. Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission: a randomized clinical trial. JAMA 2010;303:1266–73.

36 Heiligenhaus A, Foeldvari I, Edelsten C et al. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multinational interdisciplinary working group for uveitis in childhood. Arthritis Care Res 2012;64:1365–72.

37 Parkh JG, Tawansy KA, Rao NA. Immunohistochemical study of chronic nongranulomatous anterior uveitis in juvenile idiopathic arthritis. Ophthalmology 2008;115:1833–6.

38 Kalinina Ayuso V, van Dijk MR, de Boer JH. Infiltration of plasma cells in the iris of children with ANA-positive anterior uveitis. Invest Ophthalmol Vis Sci 2015;56:6770–8.
39 Tappeiner C, Heinz C, Roesel M, Heiligenhaus A. Elevated laser flare values correlate with complicated course of anterior uveitis in patients with juvenile idiopathic arthritis. Acta Ophthalmol 2011;89:e521–7.

40 Rosenberg AM, Oen KG. The relationship between ocular and articular disease activity in children with juvenile rheumatoid arthritis and associated uveitis. Arthritis Rheum 1986;29:797–800.

41 Reininga JK, Los LI, Wulffraat NM, Armbrust W. The evaluation of uveitis in juvenile idiopathic arthritis (JIA) patients: are current ophthalmologic screening guidelines adequate? Clin Exp Rheumatol 2008;26:367–72.

42 Heiligenhaus A, Michels H, Schumacher C et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Rheumatol Int 2012;32:1121–33.

43 Paroli MP, Abbouda A, Restivo L et al. Juvenile idiopathic arthritis-associated uveitis at an Italian tertiary referral center: clinical features and complications. Ocul Immunol Inflamm 2015;23:74–81.

44 Simonini G, Taddio A, Cattalini M et al. Superior efficacy of adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: adalimumab as starting anti-TNF-α therapy in childhood chronic uveitis. Pediatr Rheumatol Online J 2013;11:16.

45 Zannin ME, Buscain I, Vittadello F et al. Timing of uveitis onset in oligoarticular juvenile idiopathic arthritis (JIA) is the main predictor of severe course uveitis. Acta Ophthalmol 2012;90:91–5.

46 Gregory AC 2nd, Kempen JH, Daniel E et al. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the Systemic Immunosuppressive Therapy for Eye Diseases Study. Ophthalmology 2013;120:86–92.

47 Davis JL, Dacanay LM, Holland GN et al. Laser flare photometry and complications of chronic uveitis in children. Am J Ophthalmol 2005;135:763–71.

48 Holland GN. A reconsideration of anterior chamber flare and its clinical relevance for children with chronic anterior uveitis (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc 2007;105:344–64.

49 Böhm MR, Tappeiner C, Breitbach MA et al. Ocular hypotony in patients with juvenile idiopathic arthritis-associated uveitis. Am J Ophthalmol 2017;173:45.

50 Sabri K, Saurenmann RK, Silverman ED, Levin AV. Course, complications, and outcome of juvenile arthritis-related uveitis. J AAPOS 2008;12:539–45.