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Course of uveitis in children with juvenile idiopathic arthritis (JIA): Five years follow-up data from a prospective multicenter Inception Cohort of Newly diagnosed patients with JIA (ICON-JIA) study

Karoline Baquet-Walscheid[1,2], Kirsten Minden[3,4], Martina Niewerth[3], Frank Dressler[5], Ivan Foeldvari[6], Dirk Foell[7], Johannes-Peter Haas[8], Gerd Horneff[9,10], Anton Hospach[11], Tilmann Kallinich[12,13], Jasmin Kümmerle-Deschner[14], Kirsten Mönkemöller[15], Christoph Tappeiner[2,16,17], Daniel Windschall[18,19], Jens Klotsche[3†] and Arnd Heiligenhaus[1,2*†]

Abstract

Background Juvenile idiopathic arthritis-associated uveitis (JIAU) typically takes a chronic course, frequently leading to ocular complications and often requiring long-term treatment. The present study assesses the 5-years outcome of JIAU by analyzing data from a prospective study initiated in 2010.

Methods Data from 75 patients with onset of uveitis after study enrollment, and with a documentation at 5-years follow-up (5yFU) were available for analysis of uveitis characteristics, frequency and predictors of „inactivity on medication " (defined as inactive uveitis for ≥ 6 months) and „inactivity off medication " (defined as inactive uveitis for ≥ 6 months off medication).

Results At the 5yFU, visual acuity remained good in the majority of eyes (LogMAR < 0.1 in 65.5%; mean LogMAR 0.11 ± 0.31), ocular surgery was required in only 5% of patients, although complications occurred in 46.7% of patients until the 5yFU. Uveitis was inactive in 85.3% of patients, with 77.3% still receiving disease-modifying antirheumatic drugs (DMARDs). Until 5yFU, 82.7% of patients experienced ≥ one episode of „inactivity on medication " (30.7% once, 37.3% twice, 14.7% three or more times), and 17.3% ≥ one episode of „inactivity off medication ", respectively. Both „inactivity on medication " as well as „inactivity off medication " were associated with lower JIA disease activity (cJADAS10; ESR), and with an increased quality of life.

Conclusions Despite intensified DMARD treatment, almost half of the children experience JIAU-related ocular complications after 5 years of disease; however, visual acuity mostly remains good. Uveitis inactivity can be achieved frequently, but is often limited in duration. Lower JIA activity appears to correlate with uveitis inactivity on and off medication.

† Jens Klotsche and Arnd Heiligenhaus shared last authorship.

*Correspondence:
Arnd Heiligenhaus
arnd.heiligenhaus@uveitis-zentrum.de
Full list of author information is available at the end of the article

Keywords Uveitis, Juvenile idiopathic arthritis, Prognosis, Biological therapy

Background

Juvenile idiopathic arthritis (JIA) is the most frequent chronic systemic disease associated with childhood uveitis. According to recent data, about 11–22% of children diagnosed with JIA will develop ocular involvement, manifesting as (mostly bilateral and chronic) anterior uveitis (JIAU) [1–4].

In the past, visual outcome of JIAU was often poor [5], due to both the asymptomatic onset of flare (uveitis in a "white eye") leading to a delay in diagnosis, as well as limited treatment options. During the last two decades, children with JIAU benefited from major improvements regarding earlier detection of disease (as ophthalmological screening schedules were implemented in various national guidelines [6–10]), and additional therapeutic options after approval of several biologics for treatment of JIA. Especially the approval of adalimumab for treatment of anterior uveitis in children in 2017 can be considered a milestone in managing JIAU [11]. Furthermore, it was recognized during the last years that management of pediatric uveitis patients requires close interdisciplinary collaboration between pediatric rheumatologists and ophthalmologists specialized in uveitis care of children, which is now explicitly stated in several guidelines [9, 12]. Various national and international expert committees were initiated, working on recommendations and scientific initiatives addressing the important topic of childhood uveitis, and especially JIAU [12–14].

The real-life effects of these efforts to improve disease management and (visual) prognosis in children diagnosed with JIAU are unclear. We therefore aimed to analyze the follow-up during the first five years after JIAU diagnosis in a large cohort of prospectively documented children with JIA, the so-called ICON cohort (Inception Cohort of Newly diagnosed patients with JIA). The focus of our analyses was the questions most relevant for patients and the treating clinicians: visual prognosis, uveitis complications, necessity of ocular surgery, and the chance to reach a period of inflammatory „inactivity on medication ", or even lasting disease inactivity after withdrawing disease-modifying antirheumatic drugs (DMARDs) during the first five years of disease.

Methods

Patient cohort and clinical documentation

The ICON study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Charité, Universitätsmedizin Berlin (EA1/056/10). Parents and patients ≥ 8 years of age provided written informed consent for participation.

The ICON documentation was initiated in 2010 with 11 pediatric rheumatology centers in Germany, initially enrolling a total of almost one thousand children within one year after JIA disease onset, aiming at a ten years follow-up. More detailed information on the ICON cohort was provided by Sengler et al. [15]. Briefly, JIA was categorized according to ILAR criteria [16]. The study documentation involved several physician- as well as patient-/parents-based questionnaires, which were filled in in regular intervals throughout study duration (at baseline, three-monthly during the first year of study documentation, and six-monthly afterwards). In addition, several laboratory parameters (e.g., ESR, CRP, S100A12) were determined at baseline and at the following visits, depending on the necessity to take blood samples for clinical assessment.

All children underwent regular ophthalmological assessment in accordance with the current screening recommendations in Germany [6]. Uveitis was classified according to SUN criteria [17]. The treating ophthalmologist was asked to complete an additional questionnaire (so-called "uveitis module"), documenting the following items: best-corrected visual acuity (BCVA; in LogMAR; for conversion to Snellen V, etc., see suppl. Table 1), intraocular pressure (IOP), uveitis complications, previous ocular surgery, current topical treatment, clinical course of uveitis (acute, relapsing, or chronic), uveitis activity at time of documentation and during the previous three months. In children with active uveitis (anterior chamber [AC] cell grade ≥ 0.5 + according to SUN criteria [17]), uni-/bilaterality of disease, anatomical classification (anterior/ intermediate/ posterior/ panuveitis), AC cell grade, flare, and uveitis symptoms (asymptomatic or symptomatic onset of flare) were documented for both eyes separately. Anti-inflammatory medication was documented at each visit, including topical corticosteroids (CS), systemic CS and DMARDs. In the majority of patients, the initial ophthalmological study documentation ("initial uveitis visit") took place at the time of uveitis onset. However, in a few patients, the initial uveitis documentation by the ophthalmologist was done some time after uveitis diagnosis (maximum of 3 months delay), which is why we documented systemic therapy separately for both timepoints ("uveitis onset" / "initial uveitis visit"). "Ocular hypertension" was defined as IOP > 21 mmHg without structural damage of the optic disc or visual field defects, whereas "glaucoma" was defined as IOP > 21 mmHg with either optic disc alterations, visual field defects, or both.

We defined the main outcomes as follows: "Inactive uveitis" was defined as no cells in the AC. Inactive uveitis for at least 6 months on anti-inflammatory medication was termed „inactivity on medication ". Inactive uveitis

for at least 6 months without both topical corticosteroids and systemic anti-inflammatory medication (corticosteroids and/or DMARD) was termed „inactivity off medication ".

Statistical analysis

The regular ophthalmological assessments of patients with uveitis were the base for this analysis. The JIA disease characteristics (physician- as well as patient-/parents-based questionnaire) were assigned to an ophthalmological assessment if the duration between the two visit dates was within 30 days. Standard descriptive statistics were used in order to report the distribution of parameters of interest. Kaplan–Meier analyses were performed to analyze the time until first uveitis „inactivity on medication " and first uveitis „inactivity off medication " during follow-up. The likelihood of achieving any phase of uveitis „inactivity on medication " or uveitis „inactivity off medication " during follow-up was analyzed by generalized linear mixed models with a binomial distribution and logit link function. The associations of JIA and uveitis disease characteristics with the two outcomes were determined by generalized linear mixed model. Statistical analyses were performed with SAS 9.4.

Results

Patient data

A total of 953 JIA patients were enrolled in the ICON registry between May 2010 and December 2014. Of those, 133 children (13.9%) developed uveitis in the course of disease. A detailed ophthalmological documentation at the time of initial uveitis onset was available for 128 of the children. Of these, 105 patients had uveitis onset after JIA disease onset. Seventy-five patients were included into analysis with uveitis onset after study enrollment and with detailed documentation of all ocular findings at (or close to) uveitis onset, and with a detailed documentation of ocular findings after a uveitis duration of five years (±6 months). Excluded were 3 patients with uveitis onset before JIA, another 20 patients without ≥12 months of follow-up, and 7 patients with insufficient documentation during the 5 years of follow-up (see Table 1). Mean follow-up was 5.4 years (SD 2.0) for all 133 uveitis patients, and 5.3 years (SD 0.3) for those with a 5-year follow-up. We did not find significant differences in uveitis characteristics at first uveitis documentation (uveitis activity, BCVA, rate of complications and surgeries) between all uveitis patients and those patients with data available at the 5-years follow-up (data not shown). Regarding those patients with at least five years of follow-up (Table 1), the majority were female (74.7%) and ANA positive (85.3%). Mean age at onset of arthritis was 3.0 years (SD 2.0), with mean ages of 3.2 (SD 1.9) years for female, and 4.6 (SD 2.3) years for male patients. Uveitis developed at a mean age of 4.2 years, and with a mean interval of 14.4 months (SD 13.3) after JIA onset. Most uveitis patients were diagnosed with extended or persistent oligoarthritis. A detailed description of the clinical characteristics of the complete ICON cohort has been published previously [18].

Visual course and occurrence of uveitis complications

Visual acuity remained satisfactory in the majority of patients. After five years, >90% of eyes revealed a BCVA of <0.4 LogMAR, and 65.5% even of <0.1 LogMAR (Table 2A). Respective data document visual improvement in 53% compared to baseline documentation, and worsening in only 11% of patients. Visual acuity significantly improved during follow-up (baseline: 0.21 (0.32); 5-year FU: 0.11 (0.31); p = 0.019). The number of eyes with a LogMAR lower than 0.1 significantly increased from baseline (37%) to 5-year FU (66%, $p < 0.001$).

At first uveitis documentation, 24% of patients already had at least one uveitis-related eye complication, and the respective percentage increased to almost half of the study population until the 5-year FU (Table 2B). Cataract and posterior synechiae were the most frequent uveitis-related complications observed. However, ocular surgery was rarely required (Table 2C).

Anti-inflammatory and glaucoma therapy

Almost 50% of patients already received conventional synthetic (cs)DMARDs at uveitis onset (mostly methotrexate [MTX]), and nearly 70% at 5-year FU (Table 3). While biological DMARDs were initially given less often, their use increased to almost 50% of 75 patients at 5-years FU (cumulative use over 5 years in 60% of patients). Notably, a large proportion (42.7%) of patients were (still or again) on topical CS at 5-year FU visit. However, the dosing regimen remains unclear, as the number of drops per day was not documented within the questionnaires. Six Patients (8%) received topical glaucoma medication at the 5-year FU visit (cumulative number of patients until then: $n = 9$ [12%]).

Uveitis course and achievement of „inactivity on medication " or „inactivity off medication "

„Uveitis inactivity on medication ": more than 80% of patients achieved this during the first five years of disease (Table 4). When comparing to the patients with a follow-up of at least one year, data were similar suggesting that this could often be achieved relatively early in the course of disease (see Table 4 and Fig. 1). The duration of these phases varied enormously between individual patients.

„Uveitis inactivity off medication " was achieved by 17% of patients during the five years follow-up. Children

Table 1 Patient data at study enrollment and after 5 years of uveitis disease

	Study enrollment	Initial uveitis visit	5-year uveitis FU visit
	n = 75	*n* = 63[a] (of 75)	*n* = 57[a] (of 75)
Female, n (%)	56 (74.7%)		
Age [y], mean (SD)	3.5 (2.1)		
Age [y] at JIA onset, mean (SD)	3.0 (2.0)		
Age [y] at uveitis onset, mean (SD)	4.2 (2.0)		
Disease duration [months], mean (SD)	6.6 (5.1)		
Interval JIA and uveitis onset [months], mean (SD)	14.4 (13.3)		
Oligoarthritis, extended, n (%)	10 (13.3%)		
Oligoarthritis, persistent, n (%)	42 (56.0%)		
Psoriatic arthritis, n (%)	1 (1.3%)		
Enthesitis-related arthritis, n (%)	1 (1.3%)		
RF-negative polyarthritis, n (%)	18 (24.0%)		
Other arthritis, n (%)	3 (4.0%)		
ANA positive, n (%)	64 (85.3%)		
HLA-B27 positive, n (%)	5 (6.7%)		
ESR [mm/h], mean (SD)	29.2 (24.5)	20.4 (15.8)	11.1 (8.1)
CRP [mg/dl], mean (SD)	11.2 (16.8)	5.2 (7.9)	1.2 (2.1)
S100 A12 [ng/ml], mean (SD)	362.5 (547.5)	246.9 (348.5)	362.5 (547.5)
Physician's global assessment, mean (SD)	3.6 (2.5)	2.5 (2.2)	0.9 (1.3)
Number of joints with active arthritis, mean (SD)	2.3 (2.5)	1.3 (1.8)	0.2 (0.8)
cJADAS-10, mean (SD)	8.8 (5.2)	6.7 (4.2)	2.4 (2.8)
Patient's global, mean (SD)	2.8 (2.3)	3.0 (2.4)	1.2 (1.6)
C-HAQ, mean (SD)	0.5 (0.6)	0.5 (0.7)	0.1 (0.3)
PedsQL, total, mean (SD)	72.1 (18.6)	76.9 (19.2)	88.7 (9.6)
PedsQL, physical, mean (SD)	66.2 (25.3)	74.1 (24.9)	92.1 (9.3)
PedsQL, psychosocial, mean (SD)	75.7 (16.8)	78.7 (18.1)	86.8 (12.2)

JIA Juvenile idiopathic arthritis, *RF* Rheumatoid factor, *ANA* Antinuclear antibody, *ESR* Erythrocyte sedimentation rate, *CRP* C-reactive protein, *cJADAS-10* Clinical Juvenile Arthritis Disease Activity Score, *C-HAQ* Childhood Health Assessment Questionaire, *PedsQL* Pediatric Quality of Life; [a]Number of patients for whom the respective data were available: During the course of disease, the timepoint of arthritis and uveitis documentation might not always match. Data from the arthritis questionnaire were considered if they were documented within 30 days prior to or after the respective uveitis questionnaire

achieving it during the first two years of uveitis documentation were without prior DMARD treatment (see also Suppl. Table 2). Regarding patients achieving it with DMARDs, prior treatment duration was 3.6 years (mean; SD 2.4; median 3.1 [IQR 1.6–5.2]) in case of 13 patients at the 5y FU visit, and 3.4 years (mean; SD 3.4; median 2.8 [IQR 1.6–4.9]) for those with a follow-up of at least 12 months, respectively.—Subsequently, uveitis frequently relapsed during a follow-up ≥ 12 months (relapse in 9/18 patients, Suppl. Table 2).

Characteristics of joint disease activity in those patients achieving uveitis „inactivity off medication " (laboratory and clinical parameters) over time are depicted in Suppl. Table 3. During the time of uveitis „inactivity off medication ", arthritis was also inactive for ≥ 6 months in all patients. However, in 6/13 patients the arthritis relapsed whilst uveitis was still quiescent. In 4/6 patients, arthritis reactivated shortly before uveitis relapse.

Correlates for uveitis „inactivity on medication " and „inactivity off medication "

When analyzing correlates of uveitis „inactivity on medication " during the first five years (Table 5), we found that the OR for achieving it did not correlate with any known risk factor for development of uveitis as such, or uveitis characteristics at initial visit. However, it correlated with lower inflammatory parameters over time (ESR, CRP), and decreased arthritis activity (cJADAS10, physician's and patient 's global assessment, C-HAQ; for OR see Table 5, all $p < 0.001$). It also correlated with higher quality of life over time (PedsQL total, physical, psychosocial; all $p < 0.001$).

Achieving uveitis „inactivity off medication " also correlated with laboratory and clinical signs of decreased disease or arthritis activity (ESR, cJADAS10, physician global assessment; for OR see Table 5, all $p < 0.05$), and importantly, a shorter duration between uveitis onset and

Table 2 Visual acuity, uveitis complications, and ocular surgery at initial uveitis visit, and at the 5-year uveitis follow-up visit

	Initial uveitis visit	**5-year uveitis FU visit**		
	108 eyes (of *n* = 75 patients)	Total cohort 115 eyes (of *n* = 75 patients)	Chronic uveitis 103 eyes (of *n* = 64 patients)	Acute / recurrent uveitis 12 eyes (of *n* = 11 patients)
BCVA, LogMAR[a],mean (SD)	0.21 (0.32)	0.11 (0.31)	0.10 (0.27)	0.18 (0.55)
< 0.1, n (%)	31 (36.9%)	74 (65.5%)	65 (64.4%)	9 (75.0%)
< 0.4, n (%)	67 (79.8%)	106 (93.8%)	95 (94.1%)	11 (91.7%)
AC cell grade[a]				
0, n (%)	19 (21.4%)	97 (87.4%)	87 (87.9%)	10 (83.3%)
0.5 +, n (%)	18 20.2%)	5 (4.5%)	3 (3.0%)	2 (16.7%)
1 +, n (%)	24 (27.0%)	4 (3.6%)	4 (4.0%)	0 (0.0%)
2 +, n (%)	23 (25.8%)	5 (4.5%)	5 (5.1%)	0 (0.0%)
3 +, n (%)	5 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4 +, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AC flare[a]				
0, n (%)	19 (21.6%)	96 (86.5%)	86 (87.8%)	10 (76.9%)
1 +, n (%)	53 (60.2%)	8 (7.2%)	6 (6.1%)	2 (15.4%)
2 +, n (%)	14 (15.9%)	7 (6.3%)	6 (6.1%)	1 (7.7%)
3 +, n (%)	2 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4 +, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Initial uveitis visit	**Cumulative until 5-year uveitis FU visit**		
	n = 75 patients	Total cohort *n* = 75 patients	Chronic uveitis *n* = 64 patients	Acute / recurrent uveitis *n* = 11 patients
Any complication, n (%)	18 (24.0%)	35 (46.7%)	29 (45.3%)	6 (54.6%)
Band keratopathy, n (%)	1 (1.3%)	8 (10.7%)	6 (9.4%)	2 (18.2%)
Posterior synechiae, n (%)	13 (17.3%)	23 (30.7%)	19 (29.7%)	4 (36.4%)
Cataract, n (%)	5 (6.7%)	20 (26.7%)	17 (26.6%)	3 (27.3%)
Iris rubeosis, n (%)	0 (0.0%)	2 (2.7%)	2 (3.1%)	0 (0.0%)
Vitreous opacities, n (%)	2 (2.7%)	8 (10.7%)	7 (10.9%)	1 (9.1%)
Optic disc swelling, n (%)	1 (1.3%)	3 (4.0%)	2 (3.1%)	1 (9.1%)
Macular edema, n (%)	0 (0.0%)	4 (5.3%)	3 (4.7%)	1 (9.1%)
Epiretinal membrane, n (%)	0 (0.0%)	2 (2.7%)	2 (3.1%)	0 (0.0%)
Retinal detachment, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Amblyopia / strabismus, n (%)	1 (1.3%)	2 (2.7%)	2 (3.1%)	0 (0.0%)
Ocular hypertension, n (%)	0 (0.0%)	9 (12.0%)	8 (12.5%)	1 (9.1%)
Glaucoma, n (%)	0 (0.0%)	6 (8.0%)	5 (7.8%)	1 (9.1%)
Ocular hypotension, n (%)	0 (0.0%)	1 (1.3%)	1 (1.6%)	0 (0.0%)
Phthisis bulbi, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Drug-associated complications[b], n (%)	0 (0.0%)	2 (2.7%)	2 (3.1%)	0 (0.0%)
	Initial uveitis visit	**Cumulative until 5-year uveitis FU visit**		
	n = 75 patients	Total cohort *n* = 75 patients	Chronic uveitis *n* = 64 patients	Acute / recurrent uveitis *n* = 11 patients
Cataract surgery, n (%)	0 (0.0%)	4 (5.3%)	3 (4.7%)	1 (9.1%)
Glaucoma surgery, n (%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	1 (9.1%)
EDTA chelation, n (%)	0 (0.0%)	2 (2.7%)	1 (1.6%)	1 (9.1%)
Vitrectomy, n (%)	0 (0.0%)	2 (2.7%)	2 (3.1%)	0 (0.0%)
Surgery for retinal detachment, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retinal cryotherapy, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Others #, n (%)	0 (0.0%)	4 (5.3%)	3 (4.7%)	1 (9.1%)

BCVA Best-corrected visual acuity, *LogMAR* Logarithm of the minimum angle of resolution, *AC* Anterior chamber, *FU* Follow-up; [a]in accordance with SUN classification (Jabs et al. 2005); [b]steroid-induced ocular hypertension / glaucoma or steroid-induced cataract; # iridectomies, iridotomies, secondary surgical procedures (such as

Table 2 (continued)

secondary IOL-implantation), surgical synechiolysis, intravitreal injections, YAG IOL polishing

Table 3 Systemic and topical anti-inflammatory therapy

	Initial diagnosis of uveitis	Initial uveitis documentation	5-year uveitis FU documentation	Cumulative until 5-year uveitis FU visit
	n = 75	*n* = 75	*n* = 75	*n* = 75
DMARD (any), n (%)	35 (46.7%)	45 (60.0%)	58 (77.3%)	69 (92.0%)
Combination of csDMARD and bDMARD, n (%)	1 (1.3%)	3 (4.0%)	26 (34.7%)	-
Number of DMARDs, mean (SD)	0.5 (0.4)	0.7 (0.7)	1.2 (0.9)	-
csDMARD (any), n (%)	34 (45.3%)	44 (58.7%)	52 (69.3%)	69 (92.0%)
Methotrexate	33 (44.0%)	43 (57.3%)	49 (65.3%)	69 (92.0%)
Cyclosporine	0 (0.0%)	1 (1.3%)	3 (4.0%)	6 (8.0%)
Leflunomide	1 (1.3%)	1 (1.3%)	0 (0.0%)	1 (1.3%)
Azathioprine	0 (0.0%)	0 (0.0%)	1 (1.3%)	2 (2.7%)
bDMARD (any), n (%)	3 (4.0%)	7 (9.3%)	36 (48.0%)	45 (60.0%)
Adalimumab	1 (1.3%)	5 (6.7%)	32 (42.7%)	45 (60.0%)
Infliximab	0 (0.0%)	0 (0.0%)	1 (1.3%)	4 (5.3%)
Tocilizumab	0 (0.0%)	0 (0.0%)	1 (1.3%)	4 (5.3%)
Systemic corticosteroids, n (%)	17 (22.7%)	14 (18.7%)	4 (5.3%)	18 (24.0%)
Topical corticosteroids, n (%)	-	56 (74.7%)	32 (42.7%)	71 (94.7%)

DMARD Disease-modifying antirheumatic drug, *csDMARD* Conventional-synthetic DMARD, *bDMARD* biologic DMARD, *FU* Follow-up

initiation of DMARD treatment. Only a minor effect on quality of life (PedQL physical) was noted.

Discussion

Within the present study, the 5-years outcome of JIAU with onset of uveitis after study enrollment was analyzed in a prospective nationwide JIA inception cohort. Our study population displayed characteristics described as typical for JIAU [1, 6, 19, 20]: the majority of uveitis patients were diagnosed with oligoarticular JIA, female, ANA-positive, young at JIA onset, and with a short interval between arthritis and uveitis onset.

The rate of ocular complications increased to almost 50% of patients after 5 years of disease duration, which is in accordance with the literature [19, 20]. In contrast to these previous data [20], vision remained good in the majority of patients in our cohort, despite comparable high rates of ocular complications. Similar to our data, Kotaniemi et al. found that all patients from their JIAU cohort enrolled between 2000 and 2003 had BCVA of LogMAR $\leq$ 0.3 after a mean follow-up of 5.9 years [19]. Visual outcomes from another cohort examined between 1985 and 2003 were a lot worse, with 28% of patients having BCVA of logMAR $\geq$ 1 after a mean uveitis duration of 5.01 years [21]. Of note, mean time to referral to a uveitis specialist was 3.37 years for these patients, which is markedly shorter in our ICON cohort. It is highly likely that this contributes to a better outcome. Similar results were found for children treated between 1982 and 2002, where the authors saw that patients diagnosed early after onset of uveitis by ophthalmological screening and followed up closely by uveitis specialists from the onset of disease had a markedly reduced risk for moderate to severe visual impairment [22]. The authors of both studies concluded (and we believe this to still be true) that close follow-up by physicians specialized in childhood uveitis / JIA and intensified treatment early in the course of disease is probably crucial in order to improve (visual) prognosis of the disease. With improved management of JIAU (e.g., screening, DMARD use), reduced rates of ocular surgery and improved visual outcomes are documented in recent studies [20], and also in ours. Nevertheless, the frequent occurrence of uveitis complications is accordance with recent notes [19, 23].

The frequency of DMARD use throughout the first 5 years of uveitis disease was high in our patients: more than 90% of JIAU patients received csDMARDs, and 60% biologics. This is in line with current recommendations for management of JIAU patients which advocate DMARD use in the course of disease, if uveitis relapses despite the use of low-dose topical corticosteroids [8, 9, 12].

Table 4 Course of disease regarding uveitis inactivity

	Patients with uveitis documentation for ≥ 1 year	Patients with uveitis documentation at 5-year FU
	n = 105	*n* = 75
Inactive uveitis at 5y-FU, n (%)	-	64 (85.3%)
Inactive on medication ≥ 6 months at 5y-FU, n (%)	-	41 (54.7%)
Inactive off medication ≥ 6 months at 5y-FU, n (%)	-	10 (13.3%)
Inactivity on medication ≥ 6 months, n (%)	85 (80.1%)	62 (82.7%)
Number phases of inactivity on medication ≥ 6 months during follow-up		
1, n (%)	42 (40.0%)	23 (30.7%)
2, n (%)	31 (29.5%)	28 (37.3%)
3, n (%)	10 (9.5%)	9 (12.0%)
4, n (%)	2 (1.9%)	2 (2.7%)
Duration of inactivity on medication [months], mean (SD)		
1st phase	24.4 (18.9)	26.1 (20.9)
2nd phase	20.8 (14.4)	21.6 (14.8)
3rd phase	24.4 (16.2)	25.0 (16.8)
Inactivity off medication ≥ 6 months, n (%)	18 (17.1%)	13 (17.3%)
Number phases of inactivity off medication during follow-up		
1, n (%)	15 (14.3%)	10 (13.3%)
2, n (%)	3 (2.9%)	3 (4.0%)
Duration of inactivity off medication [months], mean (SD)		
1st phase	26.5 (22.1)	29.5 (24.7)
2nd phase	35.9 (12.3)	35.9 (12.3)

Documentation of uveitis activity during five years of follow-up; inactive uveitis on medication for at least 6 months; inactive uveitis for at least 6 months off topical corticosteroids and systemic anti-inflammatory medication. 5y-FU: five years follow-up

The data herein document that topical corticosteroids were still employed in about half of patients at 5yFU, although uveitis was documented as inactive in the majority of patients at that time. We assume that patients in this study were on low daily applications according to current treatment guidelines, as topical drug dosages have not been documented in the questionnaires, [7–9].

We were especially interested in the rate of children achieving uveitis „inactivity on medication ", herein defined as a 6-months (or longer) interval of inactive uveitis. Although we found that > 80% of JIAU patients eventually reached such a state during the first 5 years of disease, it would be highly desirable to achieve this in all patients, especially given the multitude of effective systemic therapeutic options for JIAU [25, 26]. However, we need to consider that many of the drugs with documented benefit in uveitis, such as tocilizumab [27, 28] or Janus kinase inhibitors [29] so far lack approval for treatment of ocular disease. This fact considerably limits the potential therapeutic success in our patients, even if we assume that management of disease is optimized according to experts' recommendations. Indeed, we observed a high number of relapses after achieving „inactivity on medication ", and the duration of quiescent episodes varied immensely, suggesting that therapeutic management should be improved by novel treatment options.

Many experts and guidelines recommend continuation of systemic treatment for ≥ 2 years of continuous disease inactivity, before tapering medication [30, 31]. The duration of inactivity on medication herein (Table 4) documents conformity with this notion. Indeed, the high relapse rate of uveitis after achieving „inactivity off medication " observed in this study is in line with previous publications [19, 30, 31]. Kotaniemi et al. found an „inactivity off medication " rate of 42% after a mean follow-up of 5.9 years in a cohort of JIAU patients. However, „inactivity off medication " was defined as medication-free inactive uveitis at the most recent follow-up without any minimal duration of this state, and no information on uveitis relapses was given [19]. Saboo et al. found that uveitis relapsed in 13/30 JIAU patients (43.3%) who had been on medication-free „inactivity off medication " for one year [31]. Recently the SYCAMORE study showed that inactivity in JIAU mostly did not persist when adalimumab was withdrawn [32]. High relapse rates have also been found for articular disease in JIA: Garcia-Fernandez

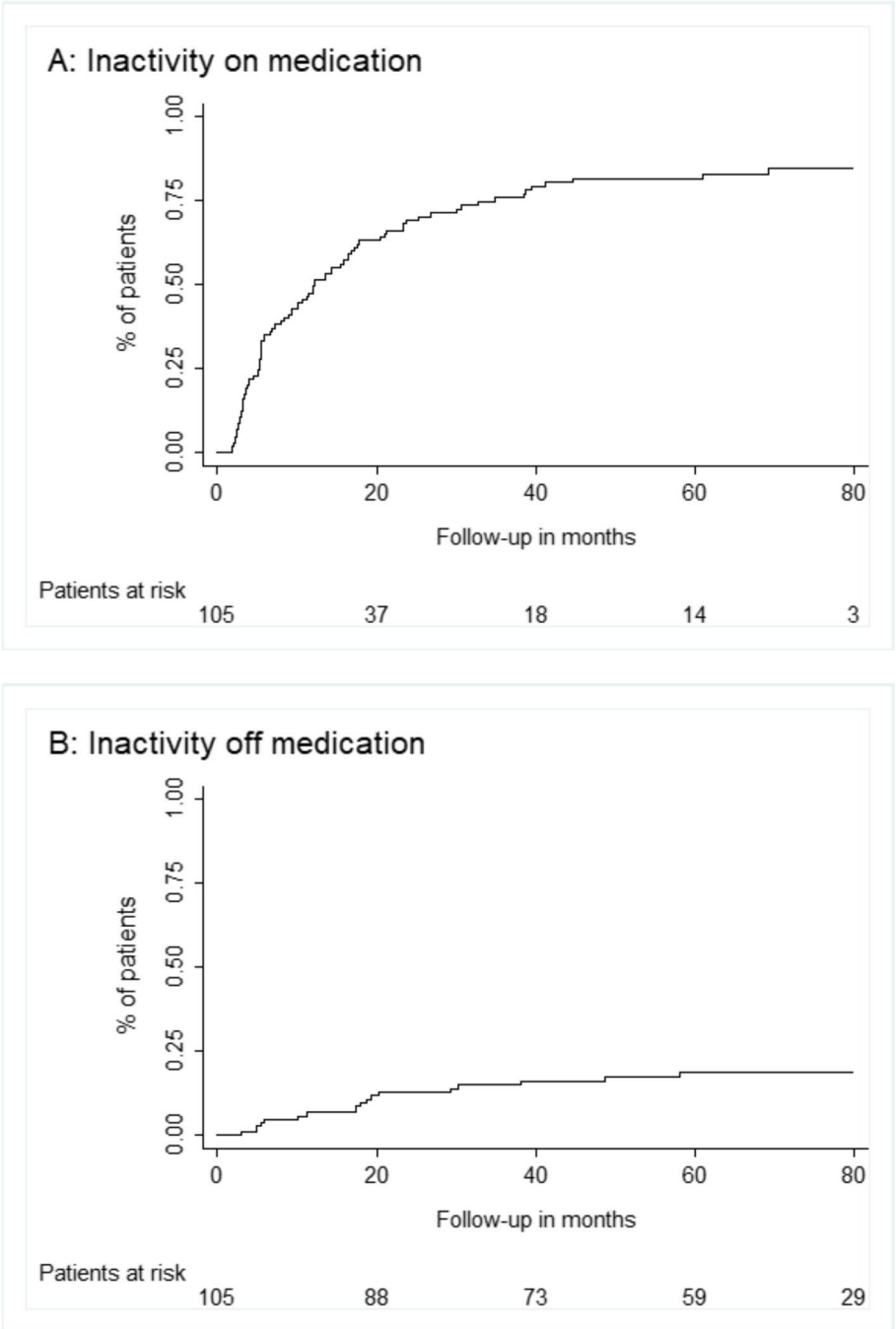

Fig. 1 Kaplan Meier curve of uveitis „inactivity on medication " and uveitis „inactivity off medication " during follow-up. „Inactivity on medication " was defined as inactive uveitis for at least 6 months; „inactivity off medication " was defined as inactive uveitis for at least 6 months without topical corticosteroids and systemic anti-inflammatory medication (corticosteroids, DMARD)

et al. described relapse rates of 52.1% 6 months after withdrawal of DMARD therapy, and 67.6% after 12 months, respectively [33].

The number of patients in our cohort was too low to analyze the effect of uveitis characteristics or previous therapy on persistent „inactivity off medication " or to verify the assumption that prolonged DMARD treatment prior to withdrawal increases the chance of permanent remission, which was suggested previously [30, 31]. However, our findings suggest that early initiation of DMARD

Table 5 Correlates of uveitis inactivity on—or off medication for ≥ 6 months

	Uveitis inactivity on medication ≥ 6 months			Uveitis inactivity off medication ≥ 6 months		
	OR	***p* value**	**95%CI**	**OR**	***p* value**	**95%CI**
Male sex	1.42	0.201	0.83; 2.44	1.23	0.723	0.39; 3.95
HLA-B27 positivity	0.55	0.216	0.21; 1.42	-	-	-
ANA positivity	1.01	0.978	0.53; 1.91	1.13	0.869	0.26; 5.02
Oligoarthritis, extended	1.56	0.504	0.42; 5.76	-	-	-
Oligoarthritis, persistent	2.61	0.103	0.82; 8.26	-	-	-
Psoriatic arthritis	3.04	0.261	0.44; 21.15	-	-	-
Enthesitis-related arthritis	0.48	0.464	0.07; 3.39	-	-	-
RF-negative polyarthritis	0.10	0.466	0.00; 45.33	-	-	-
Age at JIA onset	1.10	0.072	0.99; 1.22	1.17	0.083	0.98; 1.40
Age at uveitis onset	1.10	0.059	1.00; 1.21	1.09	0.386	0.90; 1.31
Duration JIA onset / uveitis onset [months]	1.00	0.776	0.99; 1.02	0.98	0.193	0.94; 1.01
Duration JIA onset / first DMARD [months]	1.01	0.171	0.99; 1.03	1.03	0.177	0.99; 1.07
Duration uveitis onset / first DMARD [months]	1.00	0.725	0.99; 1.01	**0.96**	**0.029**	**0.93; 1.00**
Duration uveitis onset / first bDMARD [months]	1.00	0.977	0.99; 1.01	1.00	0.601	0.98; 1.04
ESR at study enrollment	1.00	0.998	0.99; 1.01	0.98	0.287	0.95; 1.02
S100A12 at study enrollment	1.00	0.935	1.00; 1.00	1.00	0.228	1.00; 1.00
Any uveitis complication at initial uveitis visit	1.00	0.991	0.58; 1.72	0.37	0.239	0.07; 1.93
AC cell[a] grade at initial uveitis visit	0.98	0.809	0.80; 1.19	0.77	0.284	0.47; 1.24
BCVA [LogMAR] at initial uveitis visit	1.22	0.622	0.55; 2.71	0.1	0.119	0.01; 2.74
cJADAS-10	**0.78**	**< 0.001**	**0.73; 0.83**	**0.86**	**0.022**	**0.76; 0.98**
Physicians global assessment	**0.65**	**< 0.001**	**0.57; 0.74**	**0.68**	**0.014**	**0.50; 0.93**
Number of joints with arthritis	**0.60**	**< 0.001**	**0.48; 0.75**	0.75	0.173	0.49; 1.14
Patient's global	**0.68**	**< 0.001**	**0.61; 0.77**	0.81	0.057	0.65; 1.01
C-HAQ	**0.38**	**< 0.001**	**0.23; 0.64**	0.16	0.056	0.02; 1.05
PedsQL, total	**1.04**	**< 0.001**	**1.02; 1.06**	1.02	0.134	0.99; 1.05
PedsQL, physical	**1.03**	**< 0.001**	**1.02; 1.04**	**1.04**	**0.030**	**1.00; 1.07**
PedsQL, psychosocial	**1.03**	**< 0.001**	**1.01; 1.04**	1.01	0.433	0.98; 1.04
ESR	**0.96**	**< 0.001**	**0.94; 0.98**	**0.84**	**0.025**	**0.73; 0.98**
CRP	**0.95**	**0.026**	**0.90; 0.99**	0.98	0.699	0.86; 1.11
S100A12	1.00	0.119	0.99; 1.00	0.99	0.186	0.98; 1.00

ANA Antinuclear antibodies, *RF* Rheumatoid factor, *JIA* Juvenile idiopathic arthritis, *DMARD* Disease-modifying antirheumatic drug, *ESR* Erythrocyte sedimentation rate, *CRP* C-reactive protein, *AC* Anterior chamber, *BCVA* Best-corrected visual acuity, *LogMAR* Logarithm of the minimum angle of resolution, *cJADAS-10* Clinical Juvenile Arthritis Disease Activity Score, *C-HAQ* Childhood Health Assessment Questionnaire, *PedsQL* Pediatric Quality of Life, *OR* Odds ratio, *CI* Confidential interval; [a] in accordance with SUN classification (Jabs et al. 2005)

inactive uveitis for at least 6 months; inactive uveitis for at least 6 months without topical corticosteroids or systemic anti-inflammatory medication (corticosteroids or DMARDs). Scores for arthritis activity and quality of life as well as ESR, CRP and S100A12 were assessed as mean over time

treatment might have a beneficial effect on the probability of „inactivity off medication ", as was previously proposed [31]. Well known risk factors for development of uveitis (e.g., ANA positivity, oligoarthritis, young age at JIA onset) did not have an effect on the probability of inactivity on or off medication, nor did the initial severity of uveitis.

Interestingly, lower JIA disease activity (as documented via laboratory and clinical parameters) increased the OR of both „inactivity on and off medication " of uveitis. Regarding the state of „inactivity off medication ", this was to be expected, as no or minimal arthritis disease activity would almost always be the prerequisite for discontinuation of systemic therapy in JIAU interdisciplinary management. Our findings support the notion that there might be a temporal relationship between JIA disease activity and uveitis activity, in line with recent data [34].

Limitations of our study certainly result from the fact that we were not able to analyze effectiveness of treatments, due to the observational study design of the registry. Treatment comparisons are subject of selection bias

of patients with particular treatments in observational studies. Statistical methods exist to balance these group differences, e.g. propensity score modelling, but group sizes in our study were too small. It would have been desirable to have more information on the individual course of disease in order to identify reasons for use of topical steroids, initiation of DMARD treatment, reasons for tapering or discontinuation of systemic treatment. Long-term data from our cohort (such as a ten-years follow-up) will probably be even more interesting in order to assess outcomes such as visual prognosis or „inactivity off medication " in this chronic disease.

Nevertheless, we believe that this study adds valuable information on the course of disease and medium-term prognosis of children with JIAU, who are managed in accordance with up-to-date treatment recommendations. Patients and their families still have to expect a prolonged course of (systemic) treatment and need to be aware of the high risk for relapses after discontinuation of systemic therapy. However, the visual prognosis of JIAU nowadays is markedly improved compared to previous decades.

Conclusions

Despite intensified DMARD treatment, almost half of the children experience JIAU-related ocular complications after 5 years of disease; however, visual acuity mostly remains good. Uveitis inactivity can be achieved frequently, but is often limited in duration. Lower JIA activity appears to correlate with uveitis inactivity on and off medication.

Abbreviations

AC	Anterior chamber
ANA	Antinuclear antibodies
BCVA	Best-corrected visual acuity
cJADAS	Clinical Juvenile arthritis disease activity score
ESR	Erythrocyte sedimentation rate
DMARD	Disease-modifying anti-rheumatic drugs
FU	Follow-up
ICON-JIA	Inception Cohort of Newly diagnosed patients with JIA study
ILAR	International League of Associations for Rheumatology
IOP	Intraocular pressure
JIAU	Juvenile idiopathic arthritis-associated uveitis
LogMar	Logarithm of the minimum angle of resolution
PedQL	Pediatric quality of life inventory
RF	Rheumatoid factor
SUN	Standardization of uveitis nomenclature

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Authors' Contribution

KBW, AH, KM, and JK contributed to conception and designed the work. KBW, KM, MN, FD, IF, DF, JPH, GH, AHo, TK, JKD, KMö, CT, DW, JK and AH were involved in the data acquisition. KBW, JK, AH and KM analysed the data. KBW, AH, JK, and KM were involved in interpretation to data. KBW, AH, JK, and KM drafted the work, all authors proved the work and substantively revised it. All authors read and approved the final manuscript, agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Statement of ethics and consent: The ICON study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Charité, Universitätsmedizin Berlin (EA1/056/10). Parents and patients ≥ 8 years of age provided written informed consent for participation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Ophthalmology at St. Franziskus Hospital, Muenster, Germany. [2]University of Duisburg-Essen, Essen, Germany. [3]Deutsches Rheumaforschungszentrum Berlin, Berlin, Germany. [4]Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité - Universitätsmedizin Berlin, Corporate Member of, FreieUniversität Berlin and Humboldt-UniversitätZu Berlinaq, Berlin, Germany. [5]Department of Pediatrics, Hannover Medical School, Hannover, Germany. [6]Hamburg Centre for Paediatric and Adolescent Rheumatology, Schön Klinik Hamburg Eilbek, Hamburg, Germany. [7]Department of Pediatric Rheumatology and Immunology, University Hospital Muenster, Muenster, Germany. [8]German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany. [9]Centre for Paediatric Rheumatology, Department of Paediatrics, Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany. [10]Department of Paediatric and Adolescents Medicine, University Hospital Cologne, Cologne, Germany. [11]Centre of Paediatric Rheumatology, Olga Hospital, Stuttgart, Germany. [12]Department of Paediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. [13]Deutsches Rheuma-Forschungszentrum Berlin, Berlin, Germany. [14]Autoinflammation Reference Center Tübingen (Arct), Division of Paediatric Rheumatology, Department of Paediatrics, University Hospital Tübingen, Tübingen, Germany. [15]Department of Pediatric and Adolescent Medicine, Kliniken Der Stadt Köln gGmbH, Cologne, Germany. [16]Department of Ophthalmology, Pallas Klinik, Olten, Switzerland. [17]Medical Faculty, University of Bern, Bern, Switzerland. [18]Pediatric Rheumatology, St. Josef-Stift, Sendenhorst, Germany. [19]Faculty of Medicine, Martin Luther University of Halle Wittenberg, Halle, Germany.

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