Adherence to ophthalmological screening recommendations and course of uveitis in children with juvenile idiopathic arthritis: data from the Inception Cohort of Newly diagnosed patients with JIA (ICON-JIA) study

K. Walscheid[1,2], J. Klotsche[3,4], C. Tappeiner[1,3,5], M. Niewerth[3], D. Foell[6], K. Minden[3,7], A. Heiligenhaus[1,8]

[1]Department of Ophthalmology at St. Franziskus Hospital, Münster, Germany; [2]Department of Ophthalmology, University Hospital Essen, Germany; [3]German Rheumatism Research Centre, Leibniz Institute, Berlin, Germany; [4]Charité - Universitätsmedizin Berlin, Institute for Social Medicine, Epidemiology and Health Economics, Berlin, Germany; [5]Department of Ophthalmology, Inselspital, University of Bern, Switzerland; [6]Department of Paediatric Rheumatology and Immunology, University Hospital Münster, Germany; [7]Charité - Universitätsmedizin Berlin, Department of Rheumatology and Clinical Immunology, Berlin, Germany; [8]University of Duisburg-Essen, Essen, Germany.

Abstract

Objective

As JIA-associated uveitis (JIAU) is asymptomatic in the majority of patients, ophthalmologic screening examinations are recommended, depending on the risk constellation for uveitis development. This study analyses disease characteristics in JIAU depending on adherence with the screening intervals.

Methods

953 patients were included in the ICON registry. In patients without uveitis, ophthalmologic screening was recommended in accordance with the standards currently applied in Germany. Dates and results of the screening examinations were noted for each patient.

Results

Until the 3-year-follow up, uveitis developed in 133 of 953 JIA patients. In 56 of them, uveitis was present before study inclusion, and those were excluded from the prospective analysis. For the remaining 897 JIA patients, screening results were available in 557, 46 of whom developed uveitis. In those patients, adherence with the suggested screening intervals until uveitis onset was assessed, and patients were classified accordingly: screenings as recommended (Sc+ group, n=356) vs. infrequent screening (Sc- group, n=201). Non-adherence with the screening schedule significantly correlated with younger age at study inclusion and JIA diagnosis, shorter JIA disease duration, JIA oligoarthritis subtype and positive antinuclear antibody status. The Sc+ group had a better visual acuity (VA) at initial uveitis diagnosis, however, at the 3-year-follow up, VA and uveitis complication rates did not differ significantly.

Conclusion

Especially high-risk patients often do not adhere to the initial frequently recommended screening intervals, resulting in a reduced visual acuity at initial uveitis diagnosis. A recommendation for changing the current screening intervals cannot be deduced from our data.

Key words

uveitis, juvenile idiopathic arthritis, screening, complications, outcome

Karoline Walscheid, MD
Jens Klotsche, PhD
Christoph Tappeiner, MD
Martina Niewerth
Dirk Foell, MD
Kirsten Minden, MD
Arnd Heiligenhaus, MD

Please address correspondence to:
Karoline Walscheid,
Department of Ophthalmology
at St. Franziskus-Hospital,
Hohenzollernring 74,
48147 Münster, Germany.
E-mail:
karoline.walscheid@uveitis-zentrum.de

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood (1). Articular disease is frequently accompanied by a potentially vision-threatening uveitis (JIA-associated uveitis, JIAU), occurring predominantly in children with oligoarticular subtype of JIA (1). Several risk factors for development of ocular inflammation have been described, including JIA-subtype, detection of antinuclear antibodies (ANA), and young age at arthritis onset (1, 2).

JIAU typically takes a chronic course, and disease is usually with insidious onset of flare (1, 2). Except for the subgroup of mostly HLA-B27-positive patients with enthesitis-related JIA, in whom uveitis onset is frequently acute, manifesting with redness, pain, and photophobia, no external signs of inflammation are apparent in the majority of JIAU patients (uveitis in a "white eye") (2). Nevertheless, complications like posterior synechiae, macular oedema, cataract or glaucoma can develop and remain unnoticed in the young patients (3). Therefore, early detection of uveitis onset and prompt initiation of therapy is of major importance to ensure a good visual prognosis. Given the asymptomatic nature of ocular disease, routine ophthalmological examinations are recommended for all JIA patients. Screening intervals are defined in dependence on the combination of risk factors for uveitis development (4). Presently, screening examinations are recommended between every 3 and 12 months according to current German and Spanish nationwide guidelines, and also according to the very recently published guideline of the American College of Rheumatology (4-6). In ANA-positive children with oligoarticular subtype, early onset of arthritis and short duration of disease, ophthalmological screening visits are recommended at a three-monthly interval, as those patients have the highest risk for ocular inflammation. However, even though this approach intends to limit duration of possibly undetected disease, a subset of patients present with uveitis complications already at initial uveitis diagnosis, suggesting a need for even shorter screening intervals in certain patients (3).

Patients and methods

Patient cohort

The current study is based on the German Inception Cohort of Newly diagnosed patients with JIA (ICON). The ICON registry was initiated in 2010 and provides detailed information on patient characteristics and clinical course in a large cohort of children with JIA. Detailed information on the structure of the ICON registry and the clinical items has previously been published (7-9). In short, patients diagnosed with JIA as defined by ILAR criteria (10) and a disease duration of less than 12 months were enrolled in the study. Detailed documentation of clinical data and laboratory parameters was performed initially at study enrolment and then every three months during the first year of follow-up and every six months afterwards.

Ophthalmological screening visits were recommended to every JIA patient who was included in ICON, in accordance with the current screening guidelines in Germany (4). At each study visit, parents were asked whether an examination had taken place in the meantime as suggested and the corresponding visit data documented, or whether a planned examination had been skipped. Children who had developed uveitis were assessed by a specialised ophthalmologist on a regular and standardised basis, depending on clinical necessity. Documentation of the ophthalmological findings in patients with uveitis was done by the treating ophthalmologist three-monthly (8). The uveitis outcome was analysed at the three-year follow-up after uveitis manifestation (8). Parents of JIA patients were asked to complete the Family Burden Questionnaire (FaBel (11)) 3 months after study enrolment (12). The summary score (range 0–4) is a measure for the burden of a chronic illness on the family.

Ophthalmological documentation

Uveitis was classified according to SUN criteria (13), and ophthalmological documentation included the following items: best-corrected visual acuity (BCVA), intraocular pressure (IOP),

presence of any uveitis-related complications (band keratopathy of the central cornea, cataract, iris rubeosis, posterior synechiae, optic disc oedema, vitreous opacities, epiretinal membrane, retinal detachment, macular oedema, amblyopia/strabismus, ocular hypertension, glaucoma, ocular hypotony, phthisis bulbi), current topical therapy, uveitis activity during the previous three months, ocular surgery performed during the previous three months, clinical course of uveitis (acute, relapsing, or chronic), current uveitis activity. If uveitis was active (anterior chamber cell grade ≥0.5+ (13)) at the time of documentation, additional questions were to be answered: uni-/bilaterality of disease, anatomical classification (anterior/ intermediate/ posterior/ panuveitis), onset of uveitis (acutely symptomatic *vs*. insidious onset of flare), anterior chamber cell grade (13), and Tyndall grading (13).

Ethical approval

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

Statistical analysis

For patients with uveitis manifestation after JIA onset, the theoretically recommended number of screening visits was calculated between the date of JIA diagnosis and of uveitis, or the last follow-up (whatever was first), depending on the JIA category, age at JIA onset and ANA positivity (4). The number of actually documented visits was compared to the number of theoretically calculated visits under the possibility of a tolerance of one and a half weeks. If the number of screening visits was lower than the number of theoretical visits, the patients was assigned to be non-adherent with the screening intervals ("screening-" group), otherwise as adherent ("screening+" group). Categorical parameters were compared by a Chi-square test between groups, and continuously distributed variables with a two-sample *t*-test. All statistical analyses were conducted in SAS 9.4.

Results

Patient data

A total of 953 JIA patients were enrolled in the ICON registry between May 2010 and December 2014 (Table I). Mean follow-up was 39.7 months (SD 14.2). The majority of patients (67.2%, n=640) were female and ANA positive (54.3%, n=517). Mean age at onset of arthritis was 7.1 years (SD 4.6). Uveitis occurred before onset of arthritis in 4 (0.4%) patients, during the first year of disease in 65 (6.8%) patients, and during the second year in 24 (2.5%). At the time of the three-year follow-up visit, a total of 133 patients (13.9%) had been diagnosed with uveitis. 56 patients had been diagnosed with uveitis before study enrolment and were not taken into account for the prospective analyses of screening intervals. A more detailed description of the clinical characteristics of the ICON cohort has been published previously (8, 9).

Adherence to screening recommendations

The results of the ophthalmological screening examinations for those children without previous ocular involvement were available for 557 children, of which 46 patients (8.3%) developed uveitis. Less than 2/3 of patients (n=356, 63.9%) followed the screening intervals as recommended ("screening+" group), whereas a total of 201 patients did not attend the screenings as regularly as they were supposed to ("screening-" group). For a further total of 340, no information on regularity of screenings was available, and those were excluded from the prospective analysis. In those patients, only presence or absence of uveitis was documented, with 27 patients developing uveitis. Baseline patient characteristics of those with *versus* without screening information available did not differ.

Adherence to screening recommendations did not correlate with the families' socio-economic stress as determined by the FaBel. However, we observed an association between adherence to screening recommendations and higher age at study inclusion, higher age at JIA diagnosis and longer disease duration. Patients in the "screening-" group were more often ANA positive and had oligoarthritis more frequently (Table I).

The patients in the "screening-" group missed 2 screening visits on average (SD 1.9, median 3, p25 2, p75 5). Mean difference between screening examinations was 154.9% (SD 280.3%) of the suggested time interval considering all patients on whom screening information was available (n=557). When analysing those patients with uveitis onset during the follow-up period (n=46), the mean difference between the screening visit at which uveitis was diagnosed initially and the previous one was higher (mean 213.1%, SD 391.8%) than between the last documented screening visit and the previous one in those patients without uveitis development (mean 149.7%, SD 267.9%). No differences were noted between screening delay in those patients with (n=2; mean difference 215.6%, SD 304.9%) or without (n=40; 226.5%, SD 431.3%) uveitis complications at initial uveitis diagnosis, however, this finding does not allow meaningful conclusions for patient management due to extremely different patient numbers in both groups. Discrepancies between recommended and realised screening visits are listed in Table III.

Clinical course of uveitis in patients with / without screening

Both screening groups did not differ in JIA disease characteristics at ICON enrolment such as cJADAS10 (mean 9.7, SD 6.2 in the "screening+" group *vs*. 9.8, SD 6.1 for the "screening-" group, p=0.722), the number of active joints (mean 4.7, SD 7.7 *vs*. mean 3.8, SD 6.3, p=0.158) or the CHAQ (mean 0.6, SD 0.7 *vs*. mean 0.7, SD 0.7, p=0.08), except for ANA positivity (43.3% *vs*. 82.1%, p<0.001) (Table I). The mean visual acuity (BCVA) at uveitis diagnosis was better in the "screening+" group (Table II). 57.7% of patients (n=15) undergoing regular screening had an initial BCVA of <0.1 LogMAR, whereas this was achieved in none of the patients with infrequent screening (p<0.001). Apart from this finding, ad-

Table I. Clinical data.

	ICON cohort	Patients with documented uveitis screening n=557		
	n=953	"Screening+" n=356	"Screening-" n=201	*p*-value*
Sex				
female	640 (67.2%)	238 (66.9%)	148 (73.6%)	0.0958
male	313 (32.8%)	118 (33.2%)	53 (26.4%)	
Age at ICON inclusion	953; 7.9 (4.8); 7.3	356; 8.7 (4.7); 9.0	201; 5.6 (3.9); 4.3	<0.001
Age at JIA diagnosis	950; 7.1 (4.6); 6.5	355; 7.8 (4.5); 7.9	201; 4.9 (3.7); 3.5	<0.001
JIA disease duration	951; 9.3 (12.4); 6.0	355; 10.3 (13.0); 7.3	201; 7.9 (8.4); 5.1	<0.001
JIA subtype				<0.001
sJIA	35 (3.7%)	13 (3.7%)	3 (1.5%)	
OA	441 (46.3%)	141 (39.6%)	125 (62.2%)	
PsA	40 (4.2%)	14 (3.9%)	9 (4.5%)	
ERA	100 (10.5%)	49 (13.8%)	5 (2.5%)	
PA +	16 (1.7%)	10 (2.8%)	0 (0.0%)	
PA -	250 (26.2%)	101 (28.4%)	47 (23.4%)	
other JIA	71 (7.5%)	28 (7.9%)	12 (6.0%)	
ANA status				
positive	517 (54.3%)	154 (43.3%)	165 (82.1%)	<0.001
cJADAS71	937; 9.8 (6.2); 9.0	351; 9.7 (6.2); 9.0	200; 9.8 (6.1); 9.0	0.7218
inactive	55 (6.2%)	21 (6.2%)	16 (8.0%)	0.3943
low activity	23 (2.6%)	10 (2.9%)	3 (1.5%)	
moderate activity	168 (18.8%)	70 (20.6%)	33 (16.6%)	
severe activity	649 (72.5%)	239 (70.3%)	147 (73.9%)	
Number of active joints	953; 4.2 (7.0); 2.0	356; 4.7 (7.7); 2.0	201; 3.8 (6.3); 2.0	0.1577
ESR	869; 9.8 (18.5); 2.5	332; 9.3 (17.8); 2.0	186; 9.6 (17.6); 3.0	0.6927
CRP	793; 22.8 (21.7); 15.0	298; 22.8 (23.7); 14.0	179; 23.7 (19.6); 16.0	0.8322
CHAQ	894; 0.6 (0.7); 0.3	338; 0.6 (0.7); 0.4	186; 0.7 (0.7); 0.5	0.0757
Family Burden Questionnaire (FaBel)				
social burden of parents	826; 1.6 (0.4); 1.5	326; 1.6 (0.4); 1.5	189; 1.6 (0.4); 1.5	0.7534
burden for patient's siblings	629; 1.4 (0.5); 1.2	256; 1.4 (0.5); 1.3	128; 1.5 (0.5); 1.3	0.57
financial burden	823; 1.6 (0.6); 1.5	325; 1.6 (0.6); 1.5	188; 1.7 (0.6); 1.5	0.0713
personal burden	825; 1.7 (0.6); 1.6	326; 1.7 (0.6); 1.6	189; 1.8 (0.6); 1.6	0.3067
problems of coping with burden	825; 1.9 (0.8); 2.0	326; 1.8 (0.7); 1.7	189; 1.9 (0.7); 1.7	0.859
total	826; 1.7 (0.4); 1.6	326; 1.7 (0.4); 1.6	189; 1.7 (0.4); 1.7	0.1901
Socioeconomic status				0.1975
low	421 (46.1%)	155 (45.6%)	75 (37.7%)	
medium	302 (33.0%)	114 (33.5%)	75 (37.7%)	
high	191 (20.9%)	71 (20.9%)	49 (24.6%)	
Uveitis	133 (13.9%)	35 (9.8%)	11 (5.5%)	
Therapy in patients with uveitis (n=133)				
DMARD		25 (75.8 %)	5 (55.6 %)	0.115
csDMARD		23 (69.7 %)	5 (55.6 %)	0.230
MTX		20 (60.6 %)	5 (55.6 %)	0.217
bDMARD		6 (18.2 %)	0 (0.0 %)	0.141
etanercept		4 (12.1 %)	0 (0.0 %)	0.241
adalimumab		2 (6.1 %)	0 (0.0 %)	0.418

Categorical values: n (%); continuously distributed values: n; mean (SD); median; *regardig the groups "Screening+" and "Screening-".

herence to screening recommendations did not appear to affect clinical presentation or course of uveitis: Neither was uveitis severity different at initial diagnosis, nor did the course of disease during the three-year-follow-up differ significantly (Table II).

A subset of patients from the "screening+" group intermittently underwent screening examinations more frequently than recommended (Table III). Initial presentation and clinical course of uveitis up to the three-year follow-up was not obviously different from those patients undergoing screening as recommended (data not shown); however, due to the varying intervals and small patient numbers of those developing uveitis, statistical comparison did not seem meaningful here.

Discussion

JIAU typically takes an asymptomatic course, initially often going unnoticed by patients and parents in a majority of cases. Therefore, an ophthalmological screening routine has been established

Table II. Uveitis characteristics at first documentation and three-year follow-up.

	First uveitis documentation				3-year follow-up			
	Screening intervals				Screening intervals			
	"Screening-" n=9	"Screening+" n=32	no screening information available n=27	uveitis onset prior to ICON documentation n=51	"Screening-" n=9	"Screening+" n=32	no screening information available n=29	uveitis onset prior to ICON documentation n=54
Active uveitis	5 (56%)	25 (78%)	19 (70%)	30 (59%)	0 (0.0%)	5 (31.3%)	6 (30.0%)	9 (28.1%)
Uveitis activity during the last 3 months	NA	NA	NA	NA	1 (25.0%)	5 (33.3%)	5 (40.0%)	8 (26.7%)
Tyndall (grade)*								
none (0)	1 (33.3%)	7 (25.0%)	4 (20.0%)	12 (30.0%)	-	1 (20.0%)	2 (33.3%)	4 (50.0%)
faint (1+)	1 (33.3%)	16 (57.1%)	10 (50.0%)	18 (45.0%)	-	3 (60.0%)	1 (16.7%)	4 (50.0%)
moderate (2+)	1 (33.3%)	4 (14.3%)	5 (25.0%)	8 (20.0%)	-	1 (20.0%)	3 (50.0%)	0 (0.0%)
marked (3+)	0 (0.0%)	1 (3.6%)	1 (5.0%)	2 (5.0%)	-	5 (0.0%)	0 (0.0%)	8 (0.0%)
intense (4+)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)
AC cells/1 mm² (grade)*								
< 1 (0)	1 (16.7%)	5 (16.7%)	2 (9.5%)	7 (18.9%)	-	1 (20.0%)	0 (0.0%)	0 (0.0%)
1-5 (0.5+)	1 (16.7%)	7 (23.3%)	4 (19.1%)	10 (27.0%)	-	0 (0.0%)	0 (0.0%)	4 (57.1%)
6-15 (1+)	3 (50.0%)	10 (33.3%)	4 (19.1%)	8 (21.6%)	-	3 (60.0%)	4 (66.7%)	3 (42.9%)
16-25 (2+)	1 (16.7%)	6 (20.0%)	9 (42.9%)	9 (24.3%)	-	1 (20.0%)	2 (33.3%)	0 (0.0%)
26-50 (3+)	0 (0.0%)	2 (6.7%)	2 (9.5%)	3 (8.1%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)
> 50 (4+)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)
BCVA (mean (SD); median)	0.17 (0.08); 0.15	0.13 (0.30); 0.00	0.11 (0.09); 0.1	0.32 (0.36); 0.20	0.08 (0.10); 0.05	0.09 (0.25); 0.00	0.04 (0.07); 0.00	0.20 (0.31); 0.00
BCVA LogMAR < 0.1	0 (0.0%)	15 (57.7%)**	9 (45.0%)	6 (15.4%)	2 (50.0%)	12 (75.0%)	17 (81.0%)	18 (54.6%)
Uveitis complications	1 (11.1%)	1 (3.1%)	5 (18.5%)	24 (47.1%)	4 (44.4%)	7 (21.9%)	10 (34.5%)	32 (59.3%)
band keratopathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.9%)	0 (0.0%)	0 (0.0%)	3 (10.3%)	8 (14.8%)
cataract	0 (0.0%)	1 (3.1%)	0 (0.0%)	8 (15.7%)	1 (11.1%)	3 (9.4%)	4 (13.8%)	20 (37.0%)
rubeosis iridis	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.5%)	3 (5.6%)
posterior synechiae	1 (11.1%)	0 (0.0%)	3 (11.1%)	20 (39.2%)	2 (22.2%)	4 (12.5%)	7 (24.1%)	25 (46.3%)
papilledema	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (7.4%)
vitreous opacities	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (5.9%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	8 (14.8%)
epiretinal membrane	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.5%)	1 (1.9%)
retinal detachment	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
macular edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (7.4%)
amblyopia / strabismus	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.9%)	0 (0.0%)	1 (3.1%)	1 (3.5%)	2 (3.7%)
ocular hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	2 (6.3%)	3 (10.3%)	6 (11.1%)
glaucoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (11.1%)
ocular hypotony	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
phthisis bulbi	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Percentages refer to the total number of patients in whom the respective information was provided. * in patients with uveitis activity, ** significant difference between "Screening+" and "Screening-". ($p<0.001$).

for patients with JIA, with screening intervals based on the potential risk for development of uveitis (4, 5). There is no international consent regarding the recommended frequency of screening examinations. The current British guidelines employ a screening protocol with 2-monthly visits for the first 6 months after JIA diagnosis and 3–4-monthly examinations afterwards (1), which is different from the clinical practice currently employed in Germany and the US, where patients are seen at a minimum interval of 3 months, and some even less frequently (4, 6). Chia and colleagues found that uveitis disease at initial diagnosis tends to be more severe in male patients, and therefore suggested a prolonged period of more frequent screenings for boys (2-monthly for the first 12 months in boys as opposed to the first 6 months in girls) (3).

Obviously, there is a need for well-defined and feasible screening intervals. However, any recommendation given can only ever be a compromise between the clinician's intention to detect disease onset as early as possible, aspects of costs for the health care system, and the young patients' quality of life, which might be reduced by (too) frequent unnecessary medical procedures. Indeed, we found that a relevant number of JIA patients, especially those from the "high-risk" group for uveitis development did not adhere to the suggested screening schedule. Obviously, the relatively frequent examinations suggested for this group, in addition to the other medical appointments necessary during early course of disease, are not always realisable for the young patients and their parents. Increased dropout rates from rheumatological care have been found especially for those JIA patients with low disease activity (14). Those patients and their families might regard frequent examinations as unnecessary, as their quality of life is not or only very slightly reduced by arthritis disease. The

Table III. Discrepancies between recommended and realised screening visits.

	Patients screened less frequently than recommended								Patients screened more frequently than recommended							
	Cumulative discrepancy (%) from recommended screening dates summed up for all visits				Discrepancy (%) between recommended screening date and last visit / uveitis diagnosis				Cumulative discrepancy (%) from recommended screening dates summed up for all visits				Discrepancy (%) between recommended screening date and last visit / uveitis diagnosis			
	n	Mean	SD	Median	n	Mean	SD	Median	n	Mean	SD	Median	n	Mean	SD	Median
Total	557	266.4	316.2	156.8	557	154.9	280.3	0.0	154	135.9	254.7	31.8	154	77.1	232.5	0.0
Uveitis diagnosis																
no	511	263.6	307.2	159.0	511	149.7	267.9	0.0	129	66.4	93.3	11.5	129	23.9	60.6	0.0
yes	46	297.7	405.3	68.6	46	213.1	391.8	3.3	25	247.2	227.6	208.5		175.9	240.5	52.2
Ocular complications at uveitis onset																
no	40	292.1	423.7	63.7	40	226.5	431.3	1.6	20	234.1	247.5	187.2		176.4	268.4	0.7
yes	2	421.3	585.5	421.3	2	215.6	304.9	215.6	1	417.8		417.8		215.6		215.6

Discrepancies are displayed as percentage of the recommended interval as suggested by the current nationwide guidelines (Heiligenhaus *et al*. 2007).

same might apply in case of ophthalmological screening for a disease not manifested yet: As these children have no ocular symptoms, attending the screening examinations as recommended might not have priority in some cases. One has to keep in mind that these findings are observed even under study conditions, where parents are reminded of the suggested screening intervals even more frequently than in "real life", so one might suspect that the adherence to screening schedules could be even lower than documented here.

In contrast to the clinician's intuitive assumption of "the more frequent the screening, the better", our data do neither prove a worse outcome or a more complicated situation at initial uveitis diagnosis for those children not adhering to the current recommendations, nor do we observe a beneficial effect of more frequent examinations than the minimum suggested on the future course of disease. Given the data from the most recent follow up-documentation, which was three years after inclusion in ICON, the outcome of those patients screened more frequently than currently recommended (which might have led to an earlier diagnosis and, therefore, treatment of ocular disease) is not better than that of those children examined in accordance with recommendations. We also do not observe differences regarding the clinical course of uveitis between boys and girls, as suggested previously (3).

So why is it that earlier detection of ocular inflammation obviously does not have an impact on prognosis in the cohort studied here? We believe that our findings are probably biased by the structure of the patient data we were able to analyse: though the overall frequency of uveitis complications in our cohort is as high as described previously in the literature, newly manifesting complications during ICON documentation are rare (8, 9). There is a striking difference between those patients with development of uveitis prior to as opposed to during ICON documentation regarding the number of complications, which is markedly higher in those diagnosed with uveitis prior to enrolment in ICON. As ICON study enrolment was possible for up to one year after diagnosis of JIA and the majority of uveitis cases in JIA patients manifest early in the course of arthritis disease (4, 8), which we also find confirmed by our data, ICON naturally misses a relevant number of early detailed documentation of uveitis cases, which were therefore not taken into account in our prospective analysis. Those children manifesting early might be those with a more severe course of disease, and, as a majority of new uveitis manifestations during ICON documentation took place in patients already treated with DMARD therapy, manifestation and especially severity of ocular inflammation is probably different in our documented cases from those occurring during early disease course in mostly systemically untreated patients.

The fact that the majority of uveitis cases manifests during the first year after JIA onset (9) argues for screening with shorter intervals during the first 12 months, similar to current British recommendations (1); however, resulting from the structure of our data we cannot prove this assumption. Based on current epidemiologic data (8, 9, 15), it is probably of importance to take into account other parameters which obviously influence the risk for uveitis occurrence, such as arthritis disease activity, inflammation or genetic markers (16), in order to better identify patients in need of more frequent screenings. A more detailed follow-up of patients stratified according to these risk factors is needed, ideally directly starting at onset of arthritis, in order to define a meaningful schedule for the screening intervals depending on such biomarkers.

Considering the similar outcome of those children screened regularly *versus* less frequently, one might suggest even an extension of screening intervals after the first year of JIA disease, arguing that, as there is a tendency towards the institution of DMARD treatment more frequently and earlier in the course of disease, the risk for uveitis development and severe ocular inflammation decreases as was shown previously (9). However, one has to keep in mind that those children receiving DMARD treatment at an early stage of disease are those showing high systemic inflammation, which we know is associated with an increased risk for uveitis development (8). It would be interesting to analyse uveitis outcomes depending on the screening intervals between

those patients receiving DMARDs prior to uveitis occurrence *versus* those without DMARD therapy given for their arthritis, in order to assess whether early DMARD therapy really reduces the need for early detection of uveitis. Unfortunately, this was not possible within the current study due to low numbers of newly manifesting uveitis patients not receiving DMARD therapy.

In conclusion, though screening for uveitis in JIA patients will still be mandatory in future, there is an ongoing need for review of the suggested intervals, as therapeutic options change and influence course of disease, and as a significant number of JIA patients already have severe uveitis-related ocular complications at the initial uveitis diagnosis. Recent findings about the risk factors for development of uveitis (8, 15) as well as new therapeutic strategies, especially regarding the early use of biological DMARDs, will need to be taken into account, ideally resulting in a more individualised schedule for each patient.

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