



Uveitis in Juvenile Idiopathic Arthritis

18-Year Outcome in the Population-based Nordic Cohort Study

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Purpose: To assess the long-term outcome of uveitis in juvenile idiopathic arthritis (JIA).

Design: Population-based, multicenter, prospective JIA cohort, with a cross-sectional assessment of JIA-associated uveitis (JIA-U) 18 years after the onset of JIA.

Participants: A total of 434 patients with JIA, of whom 96 had uveitis, from defined geographic areas of Denmark, Finland, Norway, and Sweden.

Methods: Patients with onset of JIA between January 1997 and June 2000 were prospectively followed for 18 years. Pediatric rheumatologists and ophthalmologists collected clinical and laboratory data.

Main Outcome Measures: Cumulative incidence of uveitis and clinical characteristics, JIA and uveitis disease activity, ocular complications, visual outcome, and risk factors associated with the development of uveitis-related complications.

Results: Uveitis developed in 96 (22.1%) of 434 patients with JIA. In 12 patients (2.8%), uveitis was diagnosed between 8 and 18 years of follow-up. Systemic immunosuppressive medication was more common among patients with uveitis (47/96 [49.0%]) compared with patients without uveitis (78/338 [23.1%]). Active uveitis was present in 19 of 78 patients (24.4%) at the 18-year visit. Ocular complications occurred in 31 of 80 patients (38.8%). Short duration between the onset of JIA and the diagnosis of uveitis was a risk factor for developing ocular complications (odds ratio [OR], 1.4; 95% confidence interval [CI], 1.1–1.8). Patients with a diagnosis of uveitis before the onset of JIA all developed cataract and had an OR for development of glaucoma of 31.5 (95% CI, 3.6–274). Presence of antinuclear antibodies (ANAs) was also a risk factor for developing 1 or more ocular complications (OR, 3.0; 95% CI, 1.2–7.7). Decreased visual acuity (VA) <6/12 was found in 12 of 135 eyes (8.9%) with uveitis, and 4 of 80 patients (5.0%) with JIA-U had binocular decreased VA <6/12.

Conclusions: Our results suggest that uveitis screening should start immediately when the diagnosis of JIA is suspected or confirmed and be continued for more than 8 years after the diagnosis of JIA. Timely systemic immunosuppressive treatment in patients with a high risk of developing ocular complications must be considered early in the disease course to gain rapid control of ocular inflammation. *Ophthalmology* 2020;■:1–11 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).



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Juvenile idiopathic arthritis (JIA) is a chronic rheumatic disease of unknown etiology that develops in children and adolescents before the age of 16 years. Uveitis, inflammation of the uvea, is the most common extra-articular manifestation in JIA.^{1,2} The reported occurrence of uveitis in JIA varies considerably between different studies.^{3–5} Point prevalence is commonly reported between 10% and 15%.^{3,5,6} In a Finnish JIA cohort, the cumulative incidence was 24% during the first 7 years of JIA,⁴ and in a Canadian

cohort, 13% developed uveitis during a mean follow-up time of 6.9 years.⁵ Both lower and higher occurrences of uveitis in JIA are reported in other studies.^{7,8} Chronic anterior uveitis is the most frequent type of uveitis associated with JIA. Because of the asymptomatic nature of JIA-associated uveitis (JIA-U), all children with JIA should be routinely screened by an ophthalmologist.⁹ Early identification and timely treatment of uveitis are crucial to prevent complications that may lead to visual impairment

and, in some cases, blindness.^{10,11} Recently, evidence has emerged for a treatment strategy for JIA-U, where early introduction of immunomodulating treatment and rapid control of the uveal inflammation aim to reduce the risk of developing ocular complications and visual loss.^{12,13}

There are few long-term prospective studies on uveitis in JIA.^{4,14,15} Studies have shown that the majority of patients with JIA-U develop uveitis within the first 4 years after the onset of JIA^{5,16,17} and that high-grade uveitis and active uveal inflammation are associated with higher complication rates.^{11,13,18,19} At diagnosis, ocular complications are seen in up to 21% to 76% of eyes with JIA-U,^{11,13} and further complications are reported to occur during the course with a complication rate of 0.33 per eye per year.¹⁸ However, our knowledge is limited regarding long-term complications and complications in patients who develop uveitis late in the course of JIA.^{14,16}

Previous studies have reported that female gender, young age at onset of JIA, oligoarticular JIA, and the presence of antinuclear antibodies (ANAs) and human leukocyte antigen (HLA)-B27 are risk factors for the development of uveitis in JIA.^{3,5,20} Reported risk factors for ocular complications in established uveitis are male gender, the onset of uveitis before arthritis, short interval between the onsets of JIA and uveitis, and the presence of ocular complications early in the disease course.^{6,21} However, there are inconsistencies between studies concerning risk factors of ocular complications in JIA-U.

Our study describes the long-term clinical outcome in JIA-U in terms of cumulative incidence, the use of immunosuppressive treatment, visual outcome, ocular complications, and risk factors associated with the development of ocular complications.

Methods

Study Design

The Nordic JIA cohort is a prospective multicenter population-based study with 12 participating centers from specific geographic areas of Denmark, Finland, Norway, and Sweden. We included 510 consecutive patients with onset of JIA between January 1, 1997, and June 30, 2000. Onset of JIA was defined as the first episode of arthritis. Juvenile idiopathic arthritis was classified according to the International League of Associations for Rheumatology criteria.²² To reflect a population-based sample, the study included all referred children from defined catchment areas in each country. During the inclusion period, letters were repeatedly sent to primary healthcare providers, child health centers, and orthopedic, pediatric, and rheumatology specialists in the catchment areas to ensure the referral of all eligible patients.²³ The healthcare systems in the Nordic countries are mostly free of charge for children aged less than 16 years, making it feasible to conduct a population-based study. The baseline study visit took place at a median of 7 months (interquartile range [IQR], 6–8 months) after the onset of JIA. Thereafter, at a median of 98 months, the 8-year follow-up study took place, with 440 participants at this follow-up. All patients with a baseline visit were invited to the 18-year follow-up. Among the 510 patients with a baseline inclusion, 434 were followed for 18 years and 329 (75.8%) attended a study visit at a department of pediatrics; of these, 273 (62.9%) attended a study visit at a department of ophthalmology. The remaining 105 patients

(24.2%) participated in the 18-year follow-up study through a standardized telephone interview where we used the same questionnaires as for the patients who attended the visit in person (Fig 1). During the observation period, the patients were screened for uveitis. For the first 2 years, the interval between the ophthalmologic examinations was scheduled every 2 to 3 months; thereafter, the intervals were longer depending on the time since onset of JIA and JIA category. The screening followed local programs based on international recommendations.^{9,10,24}

Data Collection

Demographics, JIA and uveitis disease characteristics, and blood samples were collected. Laboratory tests analyzed in this study included HLA-B27, rheumatoid factor (RF), and immunofluorescence ANAs. Because no universal screening dilutions have been established, ANA was considered positive according to the cutoff value developed at the local laboratory related to the specific ANA kits used. The cutoff value was $\geq 1/320$ in Finland; $\geq 1/160$ in Copenhagen, Aarhus, and some parts of Sweden; and $\geq 1/80$ in Tromsø, Trondheim, and other parts of Sweden. Laboratory values from disease onset were used but supplemented from the 18-year visit in case of missing values.

For assessment of clinical remission in JIA, we applied Wallace et al's^{25,26} provisional criteria for inactive disease, requiring no active arthritis, absence of systemic features due to JIA, normal erythrocyte sedimentation rate or C-reactive protein, normal global assessment on a visual analog scale from 0 to 10, absence of active uveitis, and morning stiffness lasting ≤ 15 minutes. The criterion for remission on medication is inactive disease on medication for 6 successive months, and the criterion for remission off medication is inactive disease for at least 12 months without treatment for JIA.

Characteristics of uveitis were recorded following the Standardization of Uveitis Nomenclature (SUN) Working Group criteria.²⁷ The uveitis was recorded as an anterior, intermediate,

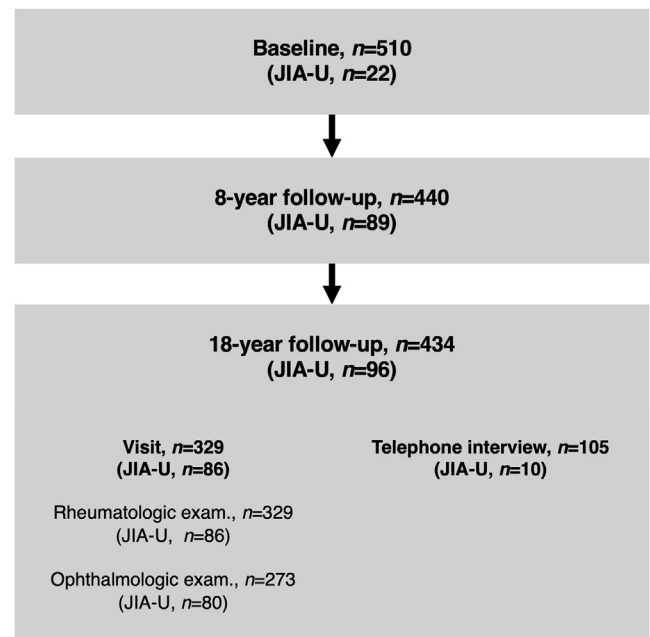


Figure 1. Flowchart of the study population throughout the observation period of 18 years. Total number of patients with juvenile idiopathic arthritis (JIA) and JIA-associated uveitis (JIA-U) at baseline, 8-year, and 18-year follow-up visits.

posterior, or pan uveitis, and as symptomatic or asymptomatic disease. The course of uveitis was defined as acute, recurrent, or chronic, as limited or persistent in duration, and as having a sudden or insidious onset.²⁷ The activity of uveitis in SUN grades and intraocular complications were recorded at the 18-year follow-up visit. Systemic medication was registered as previous if used in the period up to the 18-year follow-up and present if used at the 18-year visit. Systemic medication included synthetic disease-modifying antirheumatic drugs (sDMARDs) and biologic disease-modifying antirheumatic drugs (bDMARDs).

Ophthalmologic Assessment

The 18-year ophthalmologic examination included measurement of best-corrected visual acuities (BCVAs) monocular and binocular in Snellen fraction with a Snellen chart or a letter or number chart. We used the definition of visual impairment defined by the World Health Organization:²⁸ mild visual impairment as visual acuity (VA) <6/12, moderate visual impairment as VA <6/18, severe visual impairment as VA <6/60, and blindness as VA <3/60. Slit-lamp examination was performed for assessment of uveitis activity, which was defined as the presence of cells/mm² field in the anterior chamber, following the criteria of the SUN Working Group.²⁷ We defined uveitis course as acute if there was less than 3 months with uveitis activity and treatment, recurrent if there were recurrent episodes and at least 3 months without uveitis activity and treatment, and chronic if there was less than 3 months without uveitis activity and treatment. Information on ocular complications and ocular surgery was collected. We defined glaucoma as pathologic cupping of the optic disc or visual field defects in the presence of intraocular pressure >21 mmHg or history of glaucoma surgery. In the case of missing information in any variable, we excluded the patient from that particular assessment.

Statistical Analysis

We used medians and IQRs to describe demographics and clinical characteristics, and univariate logistic regression analysis with odds ratios (ORs) to assess baseline variables as risk factors of ocular complications in JIA-associated uveitis. Differences between groups were analyzed using Pearson's chi-square test and 2-proportion *z*-test for dichotomized variables, and continuous variables were analyzed using the Mann–Whitney *U* test. $P < 0.05$ was considered as significant. We performed a Kaplan–Meier analysis for the time interval between the onset of JIA and the diagnosis of uveitis, where the dates of uveitis diagnoses were obtained from the local screening programs. Separate Kaplan–Meier curves were constructed for patients who had uveitis-associated ocular complications at 18 years and patients without ocular complications at 18 years.

We constructed 2 heat maps. In the first, clinical characteristics were plotted in rows and eyes in columns. By using hierarchical clustering, rows and columns were ordered so that similar variables appeared next to each other, and afterward the heat map was annotated in the lower panel with ocular complications. In the second heat map, complications were plotted in rows and patients in columns. After applying hierarchical clustering, the map was annotated with previously reported risk factors for ocular complications (Fig S1).^{6,21}

We did not perform imputation for missing data, and we included only patients with information on the assessed variable. Statistical analyses were performed with Stata/MP version 15 (StataCorp LP, College Station, TX) and Wolfram (Champaign, IL) Mathematica version 11.1.1.0.

Ethical Approval and Consent to Participate

Written informed consent was obtained from all patients. The medical research ethics committees and data protection authorities in the respective participating countries approved the study. The study was conducted according to the guidelines of the Declaration of Helsinki.

Results

At the 18-year follow-up, 96 (22.1%) of the 434 patients with JIA had uveitis. The cumulative incidence of JIA-U was 44 of 143 (30.8%) in Finland, 22 of 111 (19.8%) in Denmark, 19 of 103 (18.4%) in Norway, and 11 of 77 (14.3%) in Sweden. Finland had significantly more patients with JIA-U compared with the other countries in the cohort ($P = 0.002$, Pearson's chi-square).

Uveitis was detected in 89 of 440 patients (20.2%) during the first 8 years of follow-up. Additionally, 12 patients (2.8%) were diagnosed with uveitis between the 8-year²⁰ and 18-year follow-ups. Five patients with uveitis were lost to follow-up during this period. Of the 96 patients with uveitis at the 18-year follow-up, 80 attended the ophthalmology visit (83.3%) (Fig 1). All patients who were diagnosed with uveitis before JIA and 9 of the 12 patients diagnosed with uveitis between the 8-year and 18-year follow-ups were among the 80 patients with JIA-U examined by the ophthalmologist.

The median age at the diagnosis of uveitis was 5.8 years (IQR, 3.8–11.7 years). The age at onset of JIA was lower for patients with uveitis compared with those without uveitis ($P = 0.006$, Mann–Whitney *U* test). For patients developing uveitis, the median time from the onset of JIA to the diagnosis of uveitis was 1.6 years (IQR, 0.4–5.0 years). The maximum time from the onset of JIA to the diagnosis of uveitis was 17.6 years. Uveitis was diagnosed before arthritis in 8 of 96 patients (8.3%). These 8 were diagnosed with uveitis at a median of 0.3 years (IQR, 0.2–1.8 years) before the onset of JIA. The majority of patients with uveitis, 59 of 96 (61.5%), were female (Table 1).

The distribution of uveitis in the different categories of JIA was as follows: enthesitis-related arthritis in 14 of 45 patients (31.1%), RF-negative polyarthritis in 21 of 71 patients (29.6%), psoriatic arthritis in 8 of 28 patients (28.6%), extended oligoarthritis in 19 of 85 patients (22.4%), undifferentiated arthritis in 13 of 66 patients (19.7%), and persistent oligoarthritis in 21 of 119 patients (17.6%). We did not detect uveitis in any of the patients with RF-positive polyarthritis or systemic-onset JIA.

We did not find any significant differences in gender or ANA positivity among the patients with or without uveitis at the 18-year visit. Human leukocyte antigen B27 was significantly more common in patients with uveitis than without ($P = 0.005$, Pearson's chi-square) (Table 1). There was no significant difference in ANA or HLA-B27 among the patients from Finland compared with the other Nordic countries.

Clinical Presentation of Uveitis and Disease Activity

Among the 80 patients with JIA-U who attended the 18-year ophthalmology visit, 58 of 77 (75.3%) had bilateral uveitis, and 19 of 77 (24.7%) had unilateral uveitis. A total of 135 eyes in 77 patients were affected by uveitis. In 3 of the 80 examined patients, the information regarding whether the uveitis was unilateral or bilateral was missing. Anterior uveitis was found in 68 of 71 patients (95.8%). One patient had intermediate uveitis, and 2 patients had panuveitis. Thirty-eight of 75 patients (50.7%) had a chronic

Table 1. Characteristics of the Total Juvenile Idiopathic Arthritis Cohort and Patients with or without Uveitis at the 18-Year Follow-up Study

Characteristics	Total JIA Cohort n = 434	JIA without Uveitis n = 338	JIA-Associated Uveitis n = 96	P Value
Female, n (%)	297/434 (68.4)	238/338 (70.4)	59/96 (61.5)	0.096
Age at JIA onset, yrs	5.7 (2.6–9.8)	6.2 (2.9–10.1)	4.5 (1.9–8.7)	0.006
Age at uveitis diagnosis, yrs	—	—	5.8 (3.8–11.7)*	
Age at 18-yr visit, yrs	23.4 (20.8–27.1)	23.5 (20.4–27.4)	21.6 (19.1–26.1)	0.003
Follow-up time, yrs	17.6 (16.7–18.4)	17.7 (16.8–18.6)	17.4 (16.5–18.2)	0.029
ANA positive, n (%)	142/384 (37.0)	101/291 (35.0)	41/93 (44.1)	0.103
HLA-B27 positive, n (%)	93/433 (21.5)	63/337 (18.7)	30/96 (31.3)	0.005
Cumulative joint count	7.0 (3.0–13.0)	6.5 (2.0–13.0)	8.5 (4.0–14.0)	0.027
Patient PA	0.5 (0.0–3.0) [†]	1.0 (0.0–3.5) [‡]	1.0 (0.0–4.0)*	0.057
Patient GA	0.5 (0.0–2.5) [†]	0.5 (0.0–2.0) [‡]	1.0 (0.0–3.0)*	0.013
JADAS27	1.0 (0.0–4.0) [†]	0.5 (0.0–3.5) [‡]	2.0 (0.0–6.0)*	0.001
JIA categories, n (%)				
Systemic JIA	14 (3.2)	14 (3.2)	0	—
Persistent oligoarthritis	119 (27.4)	98 (29.0)	21 (21.8)	0.087
Extended oligoarthritis	85 (19.6)	66 (19.5)	19 (19.9)	0.049
RF-negative polyarthritis	71 (16.4)	50 (14.8)	21 (21.9)	0.019
RF-positive polyarthritis	6 (1.4)	6 (1.4)	0	—
Psoriatic arthritis	28 (6.5)	20 (5.9)	8 (8.3)	0.026
Enthesitis-related arthritis	45 (10.4)	31 (9.2)	14 (14.6)	0.017
Undifferentiated arthritis	66 (15.2)	54 (15.7)	13 (13.5)	0.070

ANA = antinuclear antibody; GA = global assessment; HLA = human leukocyte antigen; JADAS27 = juvenile arthritis disease activity score based on evaluation of 27 joints; JIA = juvenile idiopathic arthritis; PA = pain assessment; RF = rheumatoid factor.

Values are median interquartile range (IQR) if not otherwise specified. P value for comparison of JIA with and without uveitis, by Pearson's chi-square for categorical variables, and Mann–Whitney U test for continuous variables. Numbers assessed: *n = 89, †n = 403, and ‡n = 315.

Self-reported pain on a visual analogue scale (range 0–10). Self-reported global assessment of well-being on a visual analogue scale (range 0–10).

course of uveitis, and 28 of 75 patients (37.3%) had a recurrent course. Nine of 75 patients (12.0%) had an acute course with sudden onset and limited duration (<3 months) of the episode of uveitis activity and treatment (Table 2). Six of the 9 patients with acute course uveitis were HLA-B27 positive, and 5 patients had a HLA-B27 positive enthesitis-related arthritis.

At the 18-year follow-up visit, there were no detectable cells in the anterior chamber (SUN 0) in 59 of 78 (75.6%) of the assessed patients with uveitis. Standardization of Uveitis Nomenclature 0.5+ to 1+ was found in 18 of 78 (23.1%) and SUN 2+ in 1 of 78 (1.3%) of the examined patients with JIA-U. None of the patients had >SUN 2+. Among the 19 patients with anterior chamber cells at the visit, 13 (68.4%) had at least 1 ocular complication. A faint flare (1+) was found in 14 of 78 (17.9%), and a moderate flare (2+) was found in 4 of 78 (5.1%) of the examined patients with uveitis (Table 2).

The proportion with active JIA disease according to the provisional criteria reported by Wallace et al^{25,26} for inactive disease was significantly higher in patients with JIA-U (45/86 [52.3%]) compared with those without uveitis (86/243 [35.4%]) ($P = 0.005$, Pearson's chi-square). The rate of remission without medication was lower among patients with uveitis (16/86 [18.6%]) compared with patients without uveitis (100/243 [41.2%]) ($P = 0.005$, Pearson's chi-square). The rate of remission on medication (inactive disease, including the absence of active uveitis for at least 6 continuous months, while the patient is on medication) was higher among patients with JIA-U, 14 of 86 (16.3%) compared with 23 of 243 (9.4%) for patients without uveitis, but this was not a significant difference ($P = 0.09$, Pearson's chi-square). Inactive disease but not yet fulfilling remission criteria was found in 11 of 86 (12.8%) patients with JIA-U and in 34 of 243 (14.0%) of the patients with JIA without uveitis.

Medication

At the baseline visit (median 7 months after onset of JIA), 25 of 96 (26.0%) of the patients with JIA-U were treated with synthetic disease-modifying antirheumatic drugs (sDMARDs). sDMARDs were used in 51 of 96 patients (53.1%) up to the 1-year visit (median 13 months after onset of JIA) and in 72 of 96 patients (75.0%) in the period up to the 8-year visit (median 98 months after onset of JIA). None of the patients with JIA-U were taking bDMARDs (infliximab or adalimumab) at baseline. Eight were treated with bDMARDs (infliximab, $n = 7$, adalimumab, $n = 1$) between the baseline and the 1-year visit, and 21 patients used bDMARDs (infliximab, $n = 16$, adalimumab, $n = 5$) within 8 years after onset of JIA.

Three of 8 patients with uveitis and ocular complications treated with bDMARDs within the 1-year visit were diagnosed with uveitis prior to JIA. Twelve of 21 patients treated with bDMARDs within the 8-year visit were diagnosed with uveitis during the first year after onset of JIA.

During the 18-year observation period, a total of 76 of 96 patients with uveitis (79.2%, 95% confidence interval [CI], 71.0–87.0) were treated with any sDMARDs compared with 223 of 378 patients without uveitis (59.0%, 95% CI, 54.0–64.0) ($P < 0.001$, 2-proportion z-test). Any bDMARDs were given to 52 of 96 patients with uveitis (54.2%, 95% CI, 44.0–64.0) and 76 of 335 patients without uveitis (22.7%, 95% CI, 18.0–27.0) ($P < 0.001$, 2-proportion z-test). Table S1 (available at www.aaojournal.org) shows detailed information on the different sDMARDs and bDMARDs. Among the 19 patients with active uveitis at the 18-year visit, 17 (89.5%) had been treated with sDMARDs or bDMARDs at some point during the 18-year observation period. Of the 59 patients with inactive uveitis (SUN 0) at the 18-year visit,

Table 2. Clinical Presentation of Juvenile Idiopathic Arthritis–Associated Uveitis According to the Standardization of Uveitis Nomenclature

Clinical presentation	Patients, n (%)
Uveitis localization, n = 71	
Anterior uveitis	68 (95.8)
Intermediate uveitis	1 (1.4)
Posterior uveitis	0
Pan uveitis	2 (2.8)
Uveitis symptoms, n = 76	
Mostly symptomatic	21 (27.6)
Mostly nonsymptomatic	55 (72.4)
Best judgment of onset of uveitis episodes, n = 72	
Sudden onset	14 (19.4)
Insidious onset	58 (80.6)
Best judgment of the duration of uveitis episodes, n = 71	
Limited duration (<3 months)	27 (38.0)
Persistent duration (≥3 months)	44 (62.0)
Uveitis course, n = 75	
Acute course (<3 mos with uveitis activity and treatment)	9 (12.0)
Recurrent course (≥3 mos without uveitis activity and treatment)	28 (37.3)
Chronic course (<3 mos without uveitis activity and treatment)	38 (50.7)
Anterior chamber cells at the 18-yr follow-up, n = 78	
SUN 0 (<1 cell in field)	59 (75.6)
SUN 0.5+ to 1+ (1–15 cells in field)*	18 (23.1)
SUN 2+ (16–25 cells in field)	1 (1.3)
Anterior chamber flare at the 18-yr follow-up, n = 78†	
SUN 0 (none flare)	59 (75.6)
SUN 1+ (faint flare)	14 (17.9)
SUN 2+ (moderate flare)	4 (5.1)

SUN = Standardization of Uveitis Nomenclature.

*Anterior chamber cells SUN 0.5+ to 1+ were grouped together in the study database; thus, it is not possible to divide into 2 separate groups (0.5+ and 1+).

†None of the patients had anterior chamber cells or flare SUN 3+ or SUN 4+.

50 (84.7%) had been treated with sDMARDs or bDMARDs during the observation period.

At the 18-year visit, 32 of 96 patients (33.3%) with uveitis were treated with sDMARDs compared with 55 of 338 patients (16.3%) without uveitis ($P < 0.001$, Pearson's chi-square). Biologic disease-modifying antirheumatic drugs were given to 34 of 96 (35.4%) of the patients with uveitis at the time of the visit and 50 of 338 (14.8%) of the patients without uveitis ($P < 0.001$, Pearson's chi-square). The use of any disease-modifying antirheumatic drugs (DMARDs) was significantly more common among patients with uveitis (47/96, 49.0%) at the 18-year visit compared with patients without uveitis (78/338, 23.1%) ($P < 0.001$, Pearson's chi-square) (Table S1). In 33.7% of the patients with JIA-U uveitis was reported to be the main reason for ongoing systemic immunomodulating treatment. Local treatment with any eyedrops were used by 29 of 92 (31.5%) of patients with JIA-U at the visit. Among the 19 patients with active uveitis at the visit, 14 (73.7%) were using sDMARDs or bDMARDs. Of the 59 patients with uveitis without active uveitis (SUN 0) at the 18-year visit, 29 (49.2%) had ongoing treatment with sDMARDs or bDMARDs.

Among the patients who had registered ocular complications at the 18-year visit, 6 of 31 (19.4%) used bDMARDs within 1 year of follow-up compared with 1 of 59 (1.7%) of the patients with uveitis who did not develop complications. This number was 13 of 31 (41.9%) and 5 of 59 (8.5%), respectively, within 8 years of follow-up. Of the patients who had ocular complications at the 18-year visit, 25 of 31 (80.6%) had used bDMARDs at some point during the 18-year observation period compared with 27 of 59 (45.8%) of the patients with uveitis who did not develop complications.

Ocular Complications and Visual Acuity

We found 1 or more ocular complications in 31 of 80 patients (38.8%) with uveitis attending the 18-year ophthalmology visit. Forty-two of 135 (31.1%) uveitis eyes were affected by at least 1 complication (Table 3). The most frequent ocular complications were cataract and glaucoma. Cataract was found in 25 of 80 (31.3%), of whom 21 of 25 (84.0%) had undergone cataract surgery. Among the patients who had cataract surgery, 16 patients also had glaucoma, 10 had synechiae, 8 had macular edema, 6 had band keratopathy, and 3 had epiretinal membrane, hypotony, and phthisis. Glaucoma occurred in 22 of 80 patients (27.5%), of whom 18 of 22 (82.0%) had undergone glaucoma surgery. Fifteen patients underwent surgery for both cataract and glaucoma. Four patients presented with an ocular complication at the baseline visit, 20 patients developed at least 1 complication during the first 8 years of follow-up, and 7 of the previously unaffected patients developed a uveitis-related complication between the 8-year and 18-year follow-up visits.

Eight patients were diagnosed with uveitis before JIA. All of them developed a cataract, and 7 were also diagnosed with glaucoma. In contrast, all patients with uveitis without ocular complications had their uveitis diagnosed after the onset of JIA. The timepoint for uveitis diagnosis for patients without complications was spread throughout the observation period, as presented in the Kaplan–Meier plots (Fig 2). An association was found between ocular complications and the starting point of uveitis with a median time of 0.4 years (IQR, 0.1–1.1 years) between the onset of JIA and the diagnosis of uveitis for the patients who developed ocular complications and 1.9 years (IQR, 0.5–4.1 years) for the patients who did not develop uveitis-related complications ($P < 0.001$, Mann–Whitney U test). Complications were most frequent among patients with anterior uveitis (28/68; 41.2%), asymptomatic uveitis (24/55; 43.6%), and a chronic course (23/38; 60.5%) or insidious onset of uveitis (27/58; 46.6%) (Fig 3).

In our cohort, 87.5% had been diagnosed with uveitis within 8 years after the onset of JIA (Fig 2). Among the 12 patients with onset of uveitis between the 8-year and 18-year follow-ups, only 1 patient developed uveitis-related complications. The age at uveitis diagnosis was available for 6 of the 12 patients (median age 22.9 years; IQR, 17.4–26.7 years). Four patients had persistent oligoarthritis, 2 patients had extended oligoarthritis, 1 patient had RF-negative polyarthritis, 1 patient had psoriatic arthritis, 1 patient had enthesitis-related arthritis, and 3 patients had undifferentiated arthritis. Nine patients were male, and 5 patients were HLA-B27 positive. Information on the clinical presentation of the uveitis was available for 9 of the 12 patients. Four patients had acute uveitis, 3 patients had recurrent uveitis, and 2 patients had chronic uveitis. Five had symptomatic uveitis.

We found worst-eye visual impairment with monocular BCVA <6/12 in 8 of 80 patients (10.0%) with uveitis examined by the ophthalmologist at the 18-year follow-up visit. Four of these 8 patients had BCVA >6/12 when tested with both eyes open, and thus binocular BCVA <6/12 in 4 of 80 patients (5.0%). Two patients had no light perception in both eyes, and 3 patients had no

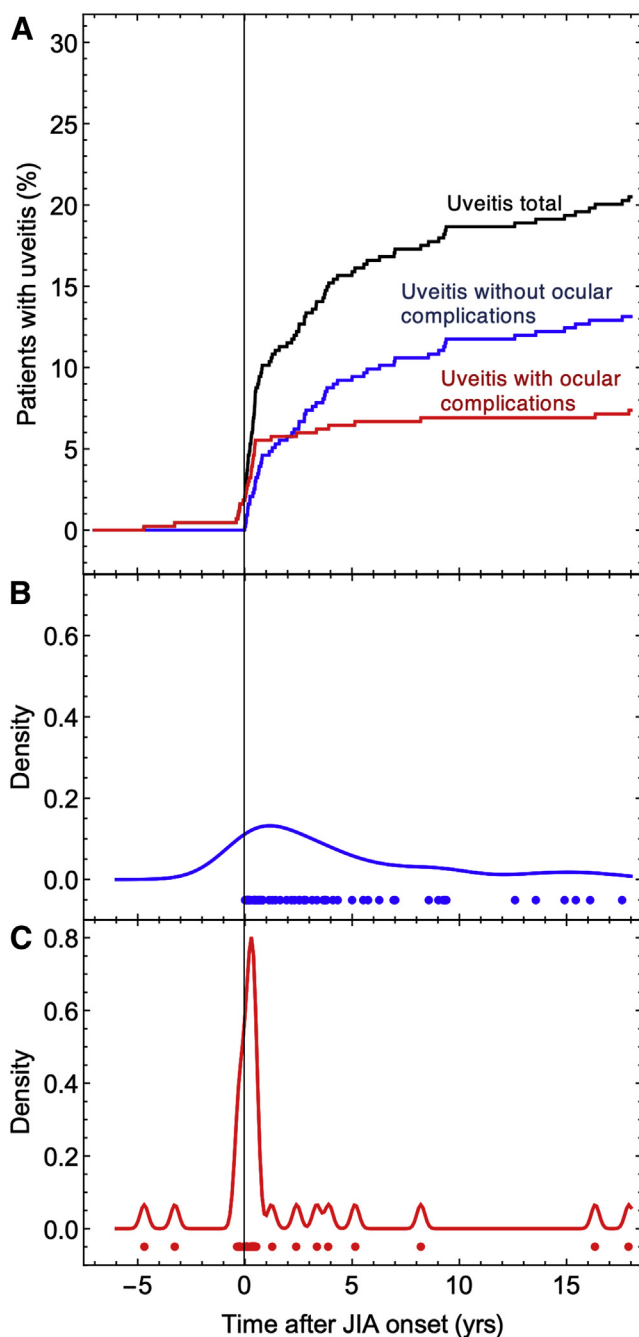


Figure 2. Time for diagnosis of uveitis during the 18-year observation period in the Nordic juvenile idiopathic arthritis (JIA) cohort for the patients who developed and did not develop ocular complications. **A**, Kaplan–Meier curve for the time points for diagnosis of uveitis in the total JIA cohort (black curve), patients with uveitis who did not develop ocular complications (blue curve), and patients with uveitis who developed ocular complications were assessed at the 18-year follow-up, and time points for diagnosis of uveitis were collected from ophthalmological screening. **B**, Density histogram for the onset time points of uveitis among the patients who remain complication free, with each blue dot representing 1 uveitis case. **C**, Density histogram for the onset time points of uveitis with ocular complications, with each red dot representing 1 uveitis case.

light perception in 1 eye (Table 3). Binocular BCVA $<6/12$ was found in 4 of the 21 patients who had undergone cataract surgery, and 2 of the patients who were blind at the 18-year visit had both undergone cataract surgery.

Risk Factors Associated with Ocular Complications

A short time interval between the onset of JIA and diagnosis of uveitis, including both positive and negative values, was a significant risk factor for at least 1 complication related to uveitis in univariate logistic regression (OR, 1.4; 95% CI, 1.1–1.8). Another significant risk factor for ocular complications was ANA positivity (OR, 3.0; 95% CI, 1.2–7.7). All 8 patients with a diagnosis of uveitis before the onset of JIA developed cataract, and the risk of glaucoma was high when uveitis was diagnosed before JIA (OR, 31.5; 95% CI, 3.6–274). We did not find any significant predictors of ocular complications in analyses of gender, age at diagnosis of uveitis, age at onset of JIA, different JIA categories, or uveitis development 8 to 18 years after onset of JIA. The distribution of ocular complications relative to these assessed variables is presented in the heat map in Fig S1 (available at www.aaojournal.org).

Discussion

In our Nordic JIA cohort, enrolled from pediatric rheumatology practices, the cumulative incidence of uveitis was 22.1% during the 18 years of 434 prospectively followed patients with JIA. Uveitis-related complications occurred in 38.8%, and decreased VA $<6/12$ occurred in 12 of 135 eyes (8.9%) with JIA-U.

The reported prevalence of uveitis in JIA varies considerably between different studies and populations.^{4,6,9,14,15,29-35} Several studies presenting uveitis prevalence are retrospective or registry-based, with a broad range of follow-up times, making it difficult to compare results. Other reasons for the variability in reported uveitis prevalence are differences in what is actually reported, such as point prevalence or period prevalence, study design, cohort compositions such as referral cohorts from which the patients are recruited, and genetic differences between populations. Some of the highest prevalence is reported from the Nordic countries,^{3,4,20} and it has been suggested that children with European descent, especially with Nordic descent, have a higher risk of uveitis in JIA.^{3,36} In other population-based studies from Spain, Czech Republic, Germany, and Estonia, the cumulative incidence of uveitis varied between 4.0% and 12.0%, but the follow-up period in these studies were shorter than in our study.³¹⁻³⁵

The overall recently reported prevalence of uveitis appears to be decreasing compared with the 1990s and 2000s.^{37,38} Kotaniemi et al³⁸ reported a decrease in the cumulative incidence of uveitis in JIA from 25.0% to 18.0% in 2 separate cohorts collected in 1990 to 1993 and 2000 to 2003. Likewise, Tappeiner et al³⁷ reported a decrease in uveitis from 33.6% to 23.9% between 2002 and 2013. In their study, the use of DMARDs was more common in the more recent cohort. In a later publication, they reported that methotrexate treatment started during

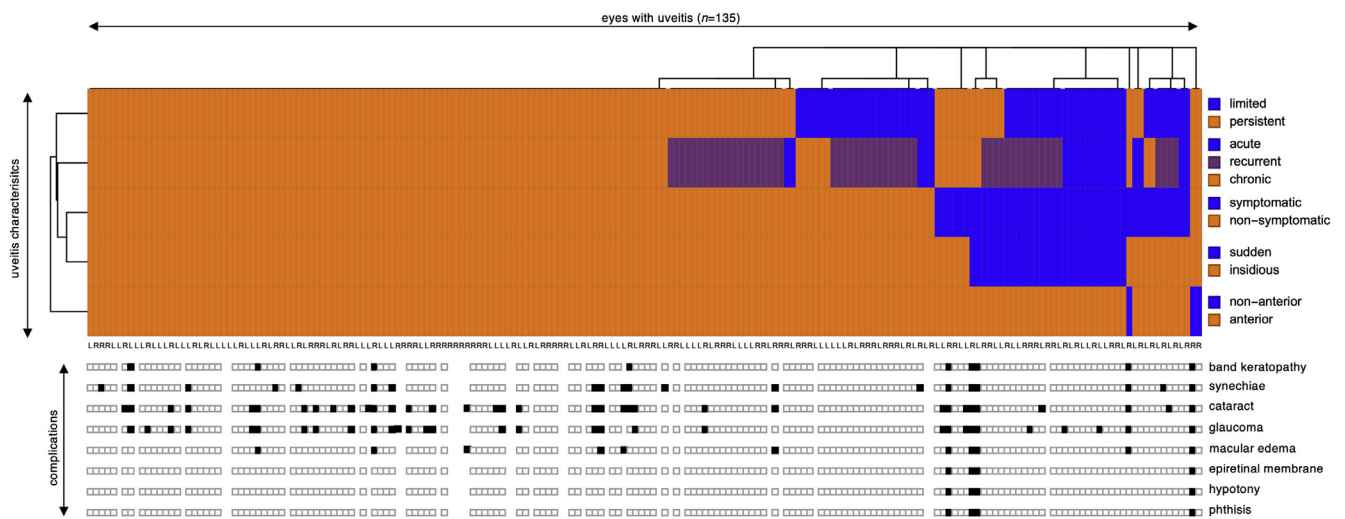


Figure 3. Heat map visualization of uveitis clinical characteristics per eye according to ocular complications. Uveitis clinical characteristics (rows) of each eye (columns) are ordered so that similar variables appear next to each other. The heat map is annotated (lower panel) with ocular complications. Uveitis characteristics; there is a cluster in orange to the left in the heat map consisting of eyes with persistent, chronic, nonsymptomatic, insidious, and anterior uveitis. Most complications occur for eyes that belong to this group. The blue color consists of limited, acute, symptomatic, sudden, and nonanterior (intermediate or pan) localization of the uveitis. The purple color is eyes with recurrent uveitis course. Ocular complications; **black square** represents each 1 eye with an ocular complication. L = left eye; R = right eye.

the first year after the onset of JIA was associated with a lowered risk of uveitis and that a combination treatment of methotrexate and anti-tumor necrosis factor was associated with an even lower risk of JIA-U.³⁹ In our study, the occurrence of uveitis remains high. This might partly be explained by the slightly less common sDMARD treatment in our study at the last study visit compared with the study by Tappeiner et al³⁷ and by the fact that our patients had onset of JIA in 1997–2000 when treatment with biologics was less common. Synthetic

disease-modifying antirheumatic drug treatment was ongoing at 18 years of follow-up in our study in 25.7% of patients with JIA with or without uveitis, compared with 47.2% in the study by Tappeiner et al.³⁷ Treatment with bDMARDs was ongoing at the 18-year visit in our study in 24.9% of patients, compared with 21.8% of patients in the study by Tappeiner et al.³⁷ The difference in the rate of sDMARD treatment may be explained by the longer follow-up time in our study. Remission of uveitis (in terms of no detectable cells in the anterior chamber and no

Table 3. Ocular Complications in Juvenile Idiopathic Arthritis–Associated Uveitis among Patients Examined by an Ophthalmologist at the 18-Year Follow-up Visit

	Patients, n (%) n = 80	Uveitis Eyes, n (%) n = 135
Ocular complications		
At least 1 ocular complication	31 (38.8)	42 (31.1)
Cataract	25 (31.3)	32 (23.7)
Glaucoma	22 (27.5)	30 (22.2)
Synechiae	14 (17.5)	19 (14.1)
Macular edema	8 (10.0)	9 (6.7)
Band keratopathy	7 (8.8)	9 (6.7)
Epiretinal membrane	3 (3.8)	4 (3.0)
Hypotony	3 (3.8)	4 (3.0)
Phthisis	3 (3.8)	4 (3.0)
BCVA, binocular and monocular worst eye		
Mild visual impairment 6/18 ≤ BCVA <6/12	1 (1.3),* 2 (2.5) [†]	3 (2.2)
Moderate visual impairment 6/60 ≤ BCVA <6/18	1 (1.3),* 2 (2.5) [†]	3 (2.2)
Severe visual impairment 3/60 ≤ BCVA <6/60	0,* 1 (1.3) [†]	1 (0.7)
Blindness <3/60 [‡]	2 (2.5),* 3 (3.8) [†]	5 (3.7)

BCVA = best-corrected visual acuity.

*Binocular.

[†]Monocular worst eye.

[‡]One patient with blindness had trauma to the eye.

flare) at the 18-year visit was more common among our patients (75.6%) compared with 42.0% in the study by Kotaniemi et al³⁸ and 65.3% by Tappeiner et al.³⁷

In our study, the median time from the onset of JIA to the diagnosis of uveitis was 1.6 years, whereas some previous studies report a mean time of 1.1 to 1.8 years and a median time of 5.5 months.^{4,5,9} Moreover, among study participants diagnosed with uveitis, 8.3% developed uveitis before JIA, and 80.0% had uveitis within 4 years after the onset of JIA. Uveitis reportedly develops before JIA in 3% to 7%^{3,30} and during the first 4 years after onset of JIA in up to 91%.^{4,5,9} These discrepancies with other studies may be explained by different definitions of the onset date of JIA. In our study, this was not the date of the physician's diagnosis of arthritis, but the date of the first evident clinical sign of arthritis, such as an obvious swelling or limp, even if reported the first time by the patients/parents and only later confirmed by a physician.

In contrast to most recent studies suggesting that uveitis rarely develops more than 7 years after the onset of JIA,^{4,5,9} 12.5% of the patients with JIA-U in our cohort had onset of uveitis after the 8-year follow-up. Our results are in line with those of Zak et al,¹⁴ who reported an increase in uveitis occurrence and complications from 1979 to 1980 to 1996 to 1997. Our study suggests that continuing the uveitis screening in patients with JIA after 7 to 8 years of diagnosis might be beneficial because approximately half of the late uveitis cases were asymptomatic. A lack of previous long-term prospective cohort studies may have led to an underestimation of the number of late uveitis cases and the overall cumulative incidence of uveitis.^{5,13} Other prospective, long-term follow-up studies are needed to better assess the risk of late onset of uveitis in JIA.

In our study, 38.8% of the patients with JIA-U developed at least 1 ocular complication during the 18 years of observation. The rate of complications is lower than in previous reports 2 or more decades ago.^{15,16,40} However, complications are more prevalent in our study compared with other recent studies from Europe.³⁷⁻³⁹ Kotaniemi et al³⁸ presented an overall ocular complication rate of 21.0% in 2000–2003. The German prospective study by Tappeiner et al³⁷ found a decrease in ocular complications from 33.6% to 23.9% in the period between 2002 and 2013. Our high prevalence of complications might be explained mainly by the long follow-up because 7 of 31 (22.6%) of the ocular complications occurred in the period between 8 and 18 years of follow-up.^{15,16,37,38,40} Earlier studies have shown that both treatment with synthetic and biologic DMARDs, and low uveitis activity are associated with lower occurrence of poor vision and ocular complications.^{11,18,19,39} The comparatively high complication prevalence in our study may be explained partly by the recruitment period in the era before the early start of bDMARDs was an established treatment strategy. In our study, complications are more common in the group of patients who are diagnosed with uveitis before or shortly after onset of JIA. For patients who develop complications, the use of bDMARDs increased from 16% to 77% from 1 year to 18 years after the onset of JIA. However, most of our patients (75.6%) had quiescence of

uveitis with no detectable cells in the anterior chamber at the 18-year visit.

In general, comparisons of studies on uveitis-related complications are challenging because of selection bias. Studies with shorter follow-up time may underreport the rate of complications, whereas studies from retrospective tertiary centers may report a higher rate of complications because they include the more severe uveitis cases. Cohorts selected from tertiary ophthalmology clinics may have more ocular complications than those collected from pediatric rheumatology centers. On the other hand, in many Nordic countries, tertiary pediatric rheumatology centers and tertiary ophthalmology clinics are often located at the same hospital, meaning that the selection of patients will not differ. In short, early introduction of DMARDs as a strategy for treatment of arthritis seems to reduce both the risk of uveitis and its complications.³⁹ Well-established ophthalmologic screening programs^{9,10} may also contribute to the reduced ocular complications, presumably by earlier diagnosis before complications have occurred and timely treatment of the ocular inflammation. We did not find a significant association between the development of ocular complications and male gender or young age at the onset of uveitis.^{21,41} However, we confirmed that developing uveitis before JIA, having a short duration between onset of JIA and diagnosis of uveitis, and having ANA positivity are risk factors for developing ocular complications. Notably, all patients who developed uveitis before JIA had ocular complications.

Long-term poor visual outcome has been associated with a diagnosis of uveitis before JIA, short interval between the diagnosis of arthritis and uveitis, high-grade uveal inflammation, and the presence of ocular complications early in the disease course and history of intraocular surgery.^{6,11,13,21} Despite a relatively high rate of complications, the proportion of patients with unfavorable visual outcome in our study was lower or in line with previous reports.^{2,4,17,40} Haasnoot et al¹⁷ found in their study from 2016 that 4% had a visual impairment or were legally blind ($\leq 20/200$) at the age of 18 years and that 33% had at least 1 eye with VA $\leq 20/50$. In our study, 2.5% of the patients with JIA-U were blind in both eyes and 3.8% were blind in the worst eye, and 5.0% in our study had a binocular VA $< 6/12$. Kotaniemi et al⁴ found that 3 of 104 children (2.9%) with JIA-U had a VA $\leq 20/60$ after a mean follow-up time of 4.5 years, whereas we found a BCVA $< 6/18$ for both eyes in 3 patients (3.8%) and in the worst eye for 6 patients (7.5%) after a median follow-up time of 17.6 years.

Study Strengths and Limitations

There are several strengths of this study. To our knowledge, this is one of few long-term prospective population-based studies on JIA-associated uveitis. This means that our results are generalizable to patients in the population with JIA, not just the patients with more severe JIA-U who are usually managed at tertiary ophthalmology centers. Despite the long observation period of 18 years, the proportion of patients lost to follow-up is relatively small, and we have

reliable ophthalmologic data for 83% of the patients with uveitis 18 years after JIA onset. The study is conducted according to the International League of Association for Rheumatology classification, the American College of Rheumatology disease activity criteria, and the SUN Working Group criteria, enabling comparison with other studies in the field. A limitation of the study is that we do not have information on the precise timepoints when patients started topical corticosteroids, the treatment starting point, or the indication (arthritis or uveitis) for treatment with systemic corticosteroids or DMARDs. Also, the inclusion period of the study was at the beginning of the biologic era. Thus, it may not reflect the effect of early implementation of immunomodulating treatment on uveitis outcomes. At the 18-year visit, 15% were lost to follow-up, and because patients with more severe disease are likely to attend follow-ups, this may lead to biases and an over-estimation of the cumulative uveitis incidence. For instance, the cumulative incidence of uveitis may be 96 of 510 (18.8%) rather than 96 of 434 (22.1%) if all uveitis cases attended the 18-year follow-up. On the other hand, we may also have lost some late diagnosed uveitis cases, which implies that the true cumulative incidence might be somewhere between those figures. There is some missing information for specific uveitis variables, reducing the total number of assessable patients. The relatively small sample size in subgroups may limit identification of relevant risk factors for complications. Future work should focus on longer follow-up and developing prediction rules for prediction of severe uveitis course to enable targeted screening and treatment strategies adapted to high-risk subgroups.

In conclusion, this unique long-term prospective population-based study found that a considerable proportion of patients with uveitis still develop sight-threatening complications in young adulthood. The patients at highest risk of complications are those who develop uveitis before JIA or closely after the onset of JIA. Screening by an ophthalmologist must start urgently in all children when JIA is suspected and diagnosed. Our study shows that uveitis may develop up to 18 years after the onset of JIA. We suggest screening to be extended for a longer period than recommended in most established screening programs to identify late-onset uveitis.^{9,10,12} The high prevalence of uveitis and ocular complications emphasizes the need for interdisciplinary care, with early consideration of systemic immunosuppressive treatment. Ophthalmologists and pediatric rheumatologists should collaborate closely to minimize the risk of visual impairment with potentially severe implications for quality of life in young adults with JIA.

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Abbreviations and Acronyms:

ANA = antinuclear antibody; **BCVA** = best-corrected visual acuity; **bDMARD** = biologic disease-modifying antirheumatic drug; **CI** = confidence interval; **DMARD** = disease-modifying antirheumatic drug; **HLA** = human leukocyte antigen; **IQR** = interquartile range; **JIA** = juvenile idiopathic arthritis; **JIA-U** = juvenile idiopathic arthritis associated uveitis; **OR** = odds ratio; **RF** = rheumatoid factor; **sDMARD** = synthetic disease-modifying antirheumatic drug; **SUN** = Standardization of Uveitis Nomenclature; **VA** = visual acuity.

Keywords:

uveitis, juvenile idiopathic arthritis, long-term outcome, prospective, population-based, uveitis cumulative incidence, SUN criteria, ocular complications, risk factors for ocular complications, disease activity, treatment.

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