Improved clinical outcomes in patients with juvenile idiopathic arthritis associated uveitis in the last decade

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ABSTRACT.

Purpose: The purpose of the study was to analyse the development of ocular complications and visual prognosis in juvenile idiopathic arthritis associated uveitis (JIA-uveitis) compared to the previous decade in the light of new treatment guidelines.

Methods: In this retrospective cohort, 143 patients with JIA-uveitis were stratified into two cohorts based on the year of diagnosis of uveitis, <2010 (n = 61) and ≥2010 (n = 82). Development of ocular complications and visual outcomes were analysed by univariate and multivariate methods. Treatment with systemic corticosteroids and immunomodifying medication (IMT) were documented.

Results: In total, 109 and 133 affected eyes, respectively, for cohort 1 (<2010) and cohort 2 (≥2010) were included for analysis. In the multivariate analysis with correction for paired eyes, patients in cohort 1 were at higher risk for cataract surgery (p = 0.03) and secondary glaucoma (p = 5.15 x 10^-3). Also, the number of eyes that were legally blind and visually impaired at 5 years of follow-up was significantly higher in cohort 1 (7% versus 2% and 8% versus 0%, p = 0.01 respectively). The number of patients that started IMT was significantly higher in cohort 2 (57% versus 98%, p = 2.17 x 10^-3). In cohort 2, both methotrexate and anti-TNF-α therapy were prescribed earlier in the disease course (1.41 versus 0.05 years, p = 8.31 x 10^-6 and 6.07 versus 1.84 years, p = 5.14 x 10^-5 respectively).

Conclusions: The prognosis of JIA-uveitis has improved during the last decade. There is a reduction in the number of cataract surgeries and secondary glaucoma and fewer patients lose their vision parallel with earlier access to tertiary care and earlier introduction of IMT.

Key words: cataract – glaucoma – juvenile idiopathic arthritis – uveitis

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children with some genetic predisposition but still unclarified triggers (Angeles-Han et al. 2015a, 2015b, 2015c, Haasnoot et al. 2018). Depending on JIA subtype, approximately one-third of JIA patients develops uveitis within 4 years after JIA onset (Heiligenhaus et al. 2007; Angeles-Han et al. 2015a). Uveitis in JIA (JIA-uveitis) is the leading cause of uveitis in children, with high risk of development of complications (e.g. cataract and glaucoma). (Tugal-Tutkun 2011, Edelsten et al. 2006, Saurenmann et al. 2007, Thorne et al. 2007, Bolt et al. 2008, Skarin et al. 2009, Cann et al. 2018, Heiligenhaus et al. 2019, Sen & Ramanan 2020, Rypdal et al. 2021). Consequently, by adulthood, approximately 30% of the eyes with JIA-uveitis become visually impaired which poses a significant burden on the quality of life (Angeles-Han et al. 2015a, 2015c; Haasnoot et al. 2016). Male gender, short interval between arthritis and uveitis diagnosis, uveitis diagnosis prior to arthritis diagnosis, young age at uveitis onset, disease severity and presence of complications at first ophthalmological visit have been reported as risk factors for visual impairment and ocular complications (Edelsten et al. 2002, Zulian et al. 2002; Heiligenhaus et al. 2007; Thorne et al. 2007; Woreta et al. 2007; Holland
et al. 2009; Kalinina Ayuso et al. 2010; Angeles-Han et al. 2013; Heiligenhaus et al. 2019; Sen & Ramanan 2020; Rydpal et al. 2021). Therefore, the combination of established standard-ized uveitis screening for early detection, specialized care by a uveitis expert and the development of novel immunomodifying treatments are expected to improve outcomes. Formerly, topical and/or systemic corticosteroids were used for rapid control of intraocular inflammation (Simionini et al. 2010, Heiligenhaus et al. 2012a, Constantin et al. 2018). However, given the potentially severe side effects of both topical (cataract and glaucoma) and systemic corticosteroids (e.g. Cushing’s syndrome), adding immunomodifying treatment (IMT) like methotrexate (MTX) earlier in the disease course is widely recommended nowadays so that topical and systemic corticosteroids can be tapered (Hoes et al. 2009, Simionini et al. 2010, 2013, Thorne et al. 2010, Gregory et al. 2013, Heiligenhaus et al., 2012a, Kothari et al. 2015, Blum-Hareuveni et al. 2017, Constantin et al. 2018, Angeles-Han et al. 2019). Further, the therapeutic potential of tumour necrosis factor alpha (TNF-α) inhibitors, in addition to methotrexate, is significant (Ramanan et al. 2017). Treatment with biologics in JIA has been registered since 2010 and changed the clinical practices completely. Therefore, in this retrospective study, we compared the clinical outcomes in children with JIA-uveitis diagnosed before 2010 to children diagnosed in 2010 and after.

Methods

Patient and data collection

The study was approved by the Medical Ethical Research Committee of the University Medical Center Utrecht in concordance with the Declaration of Helsinki. In this retrospective study, we compared the clinical outcomes of a previously reported cohort of children with JIA-uveitis diagnosed <2010 to a new cohort of children diagnosed ≥2010 (Kalinina Ayuso et al. 2010). All patients were seen by a paediatric rheumatologist who diagnosed the patients with JIA based on the criteria of the International League of Associations for Rheumatology or by former criteria [e.g. European League Against Rheumatism (EULAR)] (Wood 1978; Berntson et al. 2001; Petty et al. 2004). All patients had an uveitis screening according to the guideline the of American Academy of Paediatrics (AAPS 1993). Uveitis was diagnosed by an ophthalmologist specialized in paediatric uveitis at the Department of Ophthalmology, University Medical Centre, Utrecht, the Netherlands, a tertiary referral centre. Patients with SUN ≥1+ cells or more in the anterior chamber were diagnosed with JIA-associated anterior uveitis (Jabs et al. 2005).

Clinical data were retrospectively collected from the patient files. The following information from the medical data of the patients were recorded: gender, age of onset of uveitis, age of onset of JIA, laterality, laboratory results of antinuclear antibodies (ANA), ocular complications, best-corrected visual acuities (BCVA) and systemic treatment. The following ocular complications were registered: ocular hypertension, posterior synechiae, secondary glaucoma, glaucoma requiring surgery, cataract requiring surgery, cystoid macula oedema (CME), papillitis and hypotony. Ocular hypertension was defined as three successive intraocular pressure measurements higher than 21 mmHg for which anti-glaucomatous treatment had been started in the absence of pathologic optic disc cupping or visual field changes (Sijssens et al. 2006). Secondary glaucoma was classified as the presence of pathologic disc cupping and/or glaucomatous visual field, in combination with history of intraocular pressure higher than 21 mmHg. Preperimetric glaucoma was defined as glaucomatous changes on the optical coherence tomography (OCT) retinal nerve fibre layer (RNFL). Since the OCT was not available in our clinic until 2003, CME was defined as the presence of macular thickening with cyst formation observed by fundoscopy or by OCT, before and after 2003 respectively. Visual impairment was defined as BCVA between 20/50 and 20/200, and legal blindness as BCVA of 20/200 or worse or a visual field less than 10 degrees (Kalinina Ayuso et al. 2010).

The data regarding treatment with corticosteroid and IMT were collected. Because of missing values regarding the amount of drops and duration of treatment with topical corticosteroids was excluded from the analysis.

Statistical analyses

Statistical analyses of the data were performed using r software version 3.6.1. Baseline characteristics and administration of therapy were analysed per patient. Data are presented as medians with an interquartile range. The Pearson chi-squared test or Fisher exact test was used for univariate analysis of categorical variables, and the Mann-Whitney U test was used to compare medians. Statistical analysis of ocular complications and BCVA were performed ‘by eye’, only including affected eyes with a 4-year follow-up with correction for paired eyes. Generalized estimating equations (GEE) was used for correction of paired eyes (Katz et al. 1994). A Cox proportion hazard regression was applied for multivariate analysis including all affected eyes with correction of standard error with clustering using robust method (Lin & Wei 1989). The model was adjusted for age of onset of uveitis (numeric variable), gender and uveitis diagnosis before arthritis onset. P-values of <0.05 were considered statistically significant. All tests were two-tailed.

Results

General characteristics of the study population

Sixty-one patients diagnosed with JIA-uveitis before 2010 were included in cohort 1. Cohort 2 included 82 patients diagnosed with JIA-uveitis in 2010 and after (Table 1) (Kalinina Ayuso et al. 2010). Children in cohort 1 were younger at uveitis onset and had a longer interval between diagnosis of uveitis and initial visit at a tertiary referral centre than the children in cohort 2. Other comparisons of baseline characteristics can be seen in Table 1.

Complications

Cohort 1 and cohort 2

Cumulative incidences of ocular complications according to the two different cohorts are presented in Table 2. After adjusting for paired eyes, we found that in cohort 1, cataract surgeries were more common than in cohort 2 at 5 years of follow-up (40% versus 20%, p = 0.02, GEE). No other differences were found after adjusting for paired eyes. Of the eyes that needed glaucoma surgery at 5 years of follow-up, the indications were ocular hypertension (40% versus 50%),
Follow-up at 5 years
The Pearson = CME
Cumulative incidences of ocular complications of patients with juvenile idiopathic arthritis
Table 2.
Timing of uveitis
At diagnosis
Number of eyes 109 133
Posterior synchiae, n (%) 24 (22) 24 (18) 0.44
Cataract surgery, n (%) 0 (0) 0 (0) NA
Ocular hypertension, n (%) 6 (6) 18 (14) 0.04
Secondary glaucoma, n (%) 1 (1) 0 (0) 0.45
Glaucoma surgery, n (%) 0 (0) 1 (1) 1.00
CME, (%) 2 (2) 6 (5) 0.30
Papillitis, n (%) 5 (5) 8 (6) 0.62
Hypotony, n (%) 0 (0) 0 (0) NA
Follow-up at 5 years
Number of eyes 105 76
Posterior synchiae, n (%) 47 (45) 22 (29) 0.03
Cataract surgery, n (%) 42 (40) 15 (20) 3.79 × 10⁻³
Secondary glaucoma, n (%) 22 (21) 8 (10) 0.06
Glaucoma surgery, n (%) 25 (24) 10 (13) 0.07
CME, (%) 20 (19) 9 (12) 0.19
Papillitis, n (%) 16 (15) 15 (20) 0.43
Hypotony, n (%) 3 (4) 0 (0) 1.00

Analysis performed by “eye”. CME = cystoid macular oedema, NA = not applicable.
* The Pearson χ² test or Fisher exact test.

preperimetric glaucoma (32% versus 30%) and secondary glaucoma (28% versus 20%, p = 0.90).

Uveitis diagnosis before arthritis onset
After adjusting for paired eyes, the group with uveitis diagnosis before arthritis onset developed more frequently posterior synchiae (29% versus 74%, p = 6.00 × 10⁻³), CME (10% versus 39%, p = 1.94 × 10⁻⁴) and needed to undergo cataract surgery more frequently (24% versus 59%, p = 2.64 × 10⁻³) at 5 years of follow-up.

Risk factors for ocular complications
Cox proportion hazard regression analysis with correction for age, gender and uveitis diagnosis before arthritis onset, revealed that patients in cohort 1 had an increased risk for cataract surgery (HR = 1.84, 95% CI: 1.06–3.20, p = 0.03; Fig. 1A). Furthermore, male gender and uveitis diagnosis before arthritis onset also appeared to be an independent risk factor for cataract surgery (HR = 1.68, 95% CI: 1.00–2.80, p = 4.79 × 10⁻² and HR = 2.25, 95% CI: 1.33–3.82, p = 2.43 × 10⁻³ respectively). Cohort 1 was the only independent risk factor for secondary glaucoma (HR = 2.81, 95% CI: 1.36–5.79, p = 5.15 × 10⁻³; Fig. 1B). Independent risk factors for posterior synchiae were uveitis diagnosis before arthritis and younger age of uveitis onset (HR = 3.11, 95% CI: 1.95–4.98, p = 2.13 × 10⁻⁶ and HR = 0.90, 95% CI: 0.83–0.99, p = 0.03 respectively).

Next, to identify the potential effect of early start with IMT we compared the interval between diagnosis of uveitis and treatment with methotrexate and anti-TNF-α between patients with and without ocular complications in the two different cohorts (Table 3). In cohort 1, patients with secondary glaucoma and children with cataract requiring surgery had a longer interval between diagnosis of uveitis and start with methotrexate and start with anti-TNF-α therapy compared to patients without these complications, although this was not significant (Table 3). These differences were not observed in cohort 2. Patients from cohort 2 with cataract requiring surgery had a significant shorter time between diagnosis of uveitis and initial visit at the tertiary centre (Table 3).

Visual outcomes
Median BCVA's and categorized BCVA's at standard points of follow-up, analysed according to cohort, are presented in Table 4. After adjusting for paired eyes, the total number of legally blind and visually impaired eyes was higher in cohort 1 (7% versus 2% and 8% versus 0%, p = 0.02, GEE). No other differences were identified (Table 4).

Treatment
The differences in treatment with systemic corticosteroids and IMT at 5 years of follow-up are presented in Table 5. There was no difference in the
number of patients that were treated with systemic corticosteroids; however, in cohort 2, systemic corticosteroids were predominately prescribed between 2011 and 2014. All patients requiring systemic treatment were initiated with methotrexate. In cohort 2, both methotrexate and anti-TNF-α therapy were prescribed earlier in the disease course compared to cohort 1 (1.41 [0.07–4.72] years versus 0.05 [0.00–0.37] years, \( p = 8.31 \times 10^{-6} \) and 6.07 [3.40–9.23] years versus 1.84 [0.66–4.28] years, \( p = 5.14 \times 10^{-5} \) respectively; Fig. 2).

### Discussion

Our retrospective cohort study shows a reduction in the rates of cataract surgeries, secondary glaucoma development, visual impairment and blindness among patients with JIA-uveitis diagnosed...
Compared with patients diagnosed < 2010 along with more intensive therapy and earlier access to a tertiary centre. Since most of the prognostic studies in patients with JIA-uveitis are from the previous decade, before the new treatment guidelines, a new prognostic study is of great value both for ophthalmologists and patients (Constantin et al. 2018).

In our study, the rate of visual impairment reduced substantially from 8% to 0%. A reduction in the number of eyes with visual impairment was also reported in an earlier study by Tappeiner (Tappeiner et al. 2015). According to studies from previous decades, cataract occurs in 15–46% and glaucoma in 7–27% of affected eyes of patients with JIA-uveitis, depending on follow-up (Kanski 1977; Wolf et al. 1987; Carvounis et al. 2006; Sijssens et al. 2007; Thorne et al. 2007; Bolt et al. 2008; Papadopoulou et al. 2017; Cann et al. 2018; Rypdal et al. 2021). A recent study by Tappeiner revealed a significant decrease in the prevalence of cataract (from 28% to 16%) and secondary glaucoma (from 10% to 5%) between 2009 and 2013 (Tappeiner et al. 2015). In our study, the rate of cataract surgery (20% in cohort 2) and secondary glaucoma (10% in cohort 2) were higher than the recent studies of Tappeiner et al. (2015) and Heiligenhaus et al. (2019). The difference in the number of complications between studies can be caused by a difference in corticosteroid treatment, follow-up or definition of a complication which is not always reported in the studies (Kanski 1977; Wolf et al. 1987; Carvounis et al. 2006; Sijssens et al. 2007; Thorne et al. 2007; Bolt et al. 2008; Tappeiner et al. 2015; Papadopoulou et al. 2017; Cann et al. 2018; Heiligenhaus et al. 2019; Rypdal et al. 2021). This emphasizes the unmet need for a study that describes the prognostic changes in children with JIA-uveitis using the recommended standardized outcomes (Heiligenhaus et al. 2012b; Foeldvari et al. 2019).

Table 4. Median best-corrected visual acuity and categorized visual outcomes in eyes affected by juvenile idiopathic arthritis associated uveitis, according to cohort.

| Timing of uveitis | Cohort 1 | Cohort 2 | p-value* |
|-------------------|----------|----------|----------|
| At diagnosis      |          |          |          |
| Number of eyes    | 109      | 133      |          |
| BCVA, median (range) | 1.0 (0.8–1.0) | 1.00 (0.8–1.0) | 0.22 |
| ≤20/200, n (%)    | 3 (5)    | 3 (5)    | 0.98     |
| 20/100–20/50, n (%) | 4 (7)    | 5 (8)    |          |
| ≥20/40, n (%)     | 50 (88)  | 58 (88)  |          |
| Follow-up at 5 years |        |          |          |
| Number of eyes    | 105      | 76       |          |
| BCVA, median (range) | 1.0 (0.6–1.0) | 1.20 (1.0–1.2) | 1.48 × 10⁻⁹ |
| ≤20/200, n (%)    | 6 (7)    | 1 (2)    | 0.01     |
| 20/100–20/50, n (%) | 8 (8)    | 0 (0)    |          |
| ≥20/40, n (%)     | 78 (85)  | 63 (98)  |          |

Analysis performed “by eye”.
BCVA = best-corrected visual acuity.
* The Pearson χ² test or Fisher exact test.

Table 5. Treatment with systemic corticosteroids and immunomodifying treatment at 5 years of follow-up according to cohort.

| Timing of uveitis | Cohort 1 | Cohort 2 | p-value |
|-------------------|----------|----------|---------|
| Follow-up at 5 years |        |          |         |
| Number of patients, n (%) | 58 (95) | 45 (55) | 0.65 |
| Systemic corticosteroids, n (%)* | 13 (23) | 12 (27) |          |
| Methotrexate, n (%) | 33 (57) | 44 (98) | 2.17 × 10⁻⁶ |
| Anti-TNF-α therapy | 6 (10) | 22 (49) | 1.30 × 10⁻⁵ |
| Adalimumab, n (%) | 6 (100) | 20 (91) |          |
| Infliximab, n (%) | 0 (0) | 2 (9) |          |

anti-TNF-α = anti-tumour necrosis factor alpha.
* Perioperative use of systemic corticosteroids was not included.

Lowest compared with patients diagnosed < 2010 along with more intensive therapy and earlier access to a tertiary centre. Since most of the prognostic studies in patients with JIA-uveitis are from the previous decade, before the new treatment guidelines, a new prognostic study is of great value both for ophthalmologists and patients (Constantin et al. 2018).

In our study, the rate of visual impairment reduced substantially from

![Fig. 2. Time to immunomodifying treatment. (A) Time to treatment with methotrexate. HR = 0.34, 95% CI: 0.22–0.52, p = 1.04 × 10⁻⁶. (B) Time to treatment with anti-TNF-α therapy. HR = 0.10, 95% CI: 0.05–0.20, p = 1.98 × 10⁻⁸. Analysis is adjusted for age of uveitis, uveitis diagnosis before arthritis onset and gender. The dotted line represents the median survival. CI = confidence interval; HR, hazard ratio.](image-url)
diagnosis prior to arthritis diagnosis, young age at uveitis onset and disease severity are associated with a poor prognosis (Edelsten et al. 2002; Zulian et al. 2002; Heiligenhaus et al. 2007; Thorne et al. 2007; Woreta et al. 2007; Holland et al. 2009; Kalimina Ayuso et al. 2010; Angeles-Han et al. 2013; Heiligenhaus et al. 2019; Sen & Ramanan 2020; Rydal et al. 2021). In our study, patients in cohort 1 were significantly younger of age at uveitis diagnosis. The difference in age at uveitis diagnosis might be explained by the fact that nowadays MTX is well-established as first-line treatment in the management of JIA (Ramanan et al. 2017) which might delay or even prevent the occurrence of uveitis.

General opinion is that early treatment with immunomodifying agents can reduce the rate of complications and this is in line with this study (Sijssens et al. 2007, Heiligenhaus et al. 2012a, Gregory 2nd et al. 2013, Constantin et al. 2018). However, due to the retrospective design of our study, a causal role of immunomodifying therapy to prevent ocular complications cannot be proven. Early treatment with immunomodifying agents is also recommended so that topical and systemic corticosteroids can be tapered to prevent long-term treatment with corticosteroids. In our study, there was no difference in the number of patients that were treated with systemic corticosteroids between the cohorts. Besides earlier treatment with immunomodifying agents, we hypothesize that the clinical improvement is also influenced by better access to multidisciplinary specialized care between ophthalmologists and paediatric rheumatologists.

Unfortunately, due to the retrospective design of the study, we were unable to take into account the use of topical corticosteroids. The number of corticosteroid drops and duration of treatment is related to cataract and glaucoma development as has been shown in several studies (Thorne et al. 2010; Blum-Hareuveni et al. 2017).

In conclusion, our study reports a significant decrease in the number of cataract surgeries, secondary glaucoma development and lower rates of visual impairment parallel with earlier access to a tertiary referral centre and more intensive IMT. These data on clinical outcome and visual prognosis are relevant for ophthalmologists who need to counsel the child and their parents for the need of intensive IMT for uveitis. Additionally, our study will contribute in creating awareness among ophthalmologists about the increased risks of complications in patients with JIA-uveitis. Further studies are required to verify the causal association of early IMT on the course of uveitis in JIA.

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