Temporal change in prevalence and complications of uveitis associated with juvenile idiopathic arthritis: data from a cross-sectional analysis of a prospective nationwide study

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Abstract

Objective

To analyse the nationwide prevalence of uveitis in JIA and its complications over a whole decade.

Methods

We conducted a prospective, observational and cross-sectional study including all JIA patients from a National Paediatric Rheumatological Database (NPRD) with a uveitis add-on module in Germany (2002-2013). Temporal changes in uveitis prevalence, related secondary complications and anti-inflammatory medication were evaluated.

Results

A total of 60 centres including 18,555 JIA patients (mean 3,863 patients/year, SD=837) were documented in the NPRD between 2002 and 2013. The mean age of the patients was 11.4±4.6 years, their mean disease duration 4.4±3.7 years. Among them, 66.9% were female and 51.7% ANA positive. Patients' mean age at arthritis onset was 6.9±4.5 years. Treatment rates with synthetic and biological DMARDs increased during the observation period (sDMARD: 39.8% to 47.2%, bDMARD: 3.3% to 21.8%). Uveitis prevalence decreased significantly from 2002 to 2013 (13.0% to 11.6%, OR = 0.98, p=0.015). The prevalence of secondary uveitis complications also decreased significantly between 2002 and 2013 (33.6% to 23.9%, OR=0.94, p<0.001). Among the complications, the most common ones were posterior synechiae, cataract and band keratopathy. A significant increase in achieving uveitis inactivity was observed at 30.6% in 2002 and 65.3% in 2013 (OR=1.15, p<0.001).

Conclusion

Uveitis prevalence and complications significantly decreased between 2002 and 2013. This may be associated with a more frequent use of DMARDs.

Key words

complications, disease-modifying anti-rheumatic drugs, immunosuppressives, juvenile idiopathic arthritis, population-based study, prevalence, temporal change, uveitis

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Introduction

Juvenile idiopathic arthritis (JIA) is an inflammatory rheumatic disease with onset before 16 years of age, an incidence of 3 to 23 per 100,000 children and a prevalence of 16 to 140 per 100,000 (1-11). In 10–13% of cases, uveitis presents as an extra-articular manifestation of disease (12-20). As vision-threatening complications develop frequently (14, 21-27), anti-inflammatory treatment to prevent visual loss is often necessary.

Few data on the occurrence of JIA-associated uveitis (JIAU) and related complications are available from population-based studies (14, 28, 29). Known risk factors for uveitis in JIA include oligoarthritis, young age at arthritis onset and anti-nuclear antibody (ANA) positivity (13, 14, 30, 31).

Whether uveitis prevalence has changed over time has been the subject of controversial discussion (16, 18, 32-40). One study from Seattle (USA) assessed the occurrence of JIAU over a period of 15 years (32). The frequency of uveitis decreased from 45% in 1975 to 13% in 1989. However, this rate was uncommonly high in the early years, which may indicate a selection bias. In another study from Switzerland, a uveitis rate of 16% was reported in 1972 and one of 13% in 2005 (37). In a study from Finland, the frequency of uveitis in patients with newly diagnosed JIA decreased from 25% to 18% in two 4-year cohorts from 1990-1993 and 2000-2003 (40). Further population-based studies are required, particularly to determine whether changes in treatment patterns, *i.e.* more frequent use of disease-modifying anti-rheumatic drugs (DMARDs), has influenced uveitis prevalence and outcome. Indeed, a previous study indicated that methotrexate treatment in JIA may reduce the risk for uveitis (34). Based on the prospective National Paediatric Rheumatological Database (NPRD) with a uveitis add-on module, we analysed the temporal changes in uveitis prevalence and secondary complications and describe changes in treatment in a large cohort of JIA patients between 2002 and 2013.

Patients and methods

NPRD

The prospective NPRD in Germany collects rheumatological and ophthalmological data from patients each year (14). All cases fulfilling the ILAR criteria for JIA (41) and documented between 1 January 2002 and 31 December 2013 were considered for this analysis.

Paediatric rheumatological documentation

Paediatric rheumatologists annually report patients' age, gender, diagnosis (JIA category), age at onset of arthritis, treatment, global disease activity, number of joints with arthritis, number of joints with limited range of motion (ROM), and extra-articular manifestations, such as the presence of uveitis. The presence of ANA, HLA-B27 antigen and rheumatoid factor (RF) are also documented.

Ophthalmological documentation

The parameters recorded in the ophthalmological documentation (NPRD add-on uveitis module) are age at onset of uveitis, uni- or bilateral uveitis, anatomical type of uveitis, uveitis symptoms, eye involvement, uveitis activity, best-corrected visual acuity and eye complications (14). All this information is collected in agreement with the SUN guidelines (42). Furthermore, topical and systemic anti-inflammatory treatment and previous eye surgery are documented.

Statistical analysis

Clinical and demographic characteristics, treatment rates, prevalence of uveitis and secondary complications and uveitis activity are reported by using standard descriptive statistics for the years 2002 to 2013. Statistical inference is based on generalised linear mixed models in order to investigate time trends in demographic and disease characteristics and also treatment. A patient may have been documented for several years in the NPRD. The correlated data structure was modelled by using the generalised linear mixed models and including patient identification numbers as a level-two variable. Beta co-efficients for continuously distributed variables and odds ratios for dichotomous variables were estimated as an effect measure for a 1-year change in the variable of interest. An odds ratio

lower than 1 indicates a decrease in the rate of interest. Multivariable generalised linear mixed models were used for testing known uveitis risk factors for JIA patients and risk factors of developing secondary ocular complications due to uveitis. An unstructured covariance matrix for the random effects was selected for parameter estimation. A *p*-value of less than 0.05 was considered significant. All statistical analyses were conducted using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA).

Ethics Committee approval

The NPRD was approved by the Ethics Committee in Berlin and the local Ethics Committees, too, if required, and was performed according to the Declaration of Helsinki. The design of the work conforms to the standards currently applied in Germany.

Results

Demographics

Between 2002 and 2013, a total of 18,555 JIA patients were included in the NPRD (year 2002: 27 centres with a mean of 101 patients/centre; year 2013: 60 centres, mean of 88 patients/centre). The demographic and clinical characteristics of JIA patients are summarised in Table I. For the entire observation period, mean age of JIA patients was 11.4±4.6 years (66.9% female, 51.7% ANA positive, 5.4% rheumatoid factor positive). The mean age at arthritis onset was 6.9±4.5 years (patients without uveitis 7.3±4.5 years *versus* patients with uveitis 4.4±3.4 years). The mean duration between arthritis and uveitis onset was 14.8±29.7 months, without any significant change between 2002 and 2013 (p=0.314). Patients' age at documentation, age at JIA onset, disease duration, ANA positivity and rheumatoid factor positivity fluctuated slightly during the observation period (each p<0.05). However, known risk factors for uveitis such as JIA subgroup (β=-0.08,; 95%CI -0.092, -0.069, p=0.001), ANA positivity (OR=1.04,; 95%CI 1.03, 1.06, p=0.001), age at onset of JIA (β=0.02; 95%CI -0.003, 0.040, p=0.101) and duration of JIA disease (β=0.03; 95%CI -0.004, 0.061, p=0.082) did not reveal any relevant change in favour of a reduced uveitis risk between 2002 and 2013. Persistent oligoarthritis, rheumatoid factor-negative polyarthritis and enthesitis-related arthritis were the most prevalent JIA subgroups in all years analysed (Table I).

Prevalence of uveitis

Uveitis prevalence decreased significantly from 2002 to 2013 (OR=0.98, 95%CI: 0.975; 0.991, p=0.015), revealing rates of 13.0%, 12.7% and 11.6% in the years 2002, 2007 and 2013, respectively (Table II). This decrease was more evident when analysing only JIA subgroups at high risk for uveitis, namely extended and persistent oligoarthritis and rheumatoid factor-negative polyarthritis (change in uveitis prevalence between 2002 and 2013 from 16.5% to 13.9%; OR=0.98, 95%CI: 0.971; 0.993, p=0.004).

In a multivariable regression analysis, the following risk factors for uveitis were identified: persistent oligoarthritis (OR=2.40, 95%CI: 2.21; 2.62), extended oligoarthritis (OR=1.80, 95%CI: 1.62; 1.99), and enthesitis-related arthritis (OR=2.02, 95%CI: 1.79; 2.28), longer disease duration (OR=1.10, 95%CI: 1.09; 1.11), ANA positivity (OR=2.61, 95%CI: 2.39; 2.87) and higher disease activity as measured by the cJADAS-10 (OR=1.02, 95%CI: 1.01; 1.03). In contrast, higher age at JIA onset was negatively associated with the onset of uveitis (OR=0.90, 95%CI: 0.89; 0.91).

Uveitis documentation – risk factors for uveitis onset

Between 2002 and 2013, ophthalmologists also documented 1,381 (24.6%) of the total patients with uveitis (n=5,620) by using the uveitis module. This corresponds to a mean of 115±29 uveitis patients per year. In these patients the sociodemographic parameters were different from those in the total group of uveitis patients in the rheumatological database concerning age at documentation (10.3 yrs *vs*. 11.3, p<0.001), JIA subgroup (p<0.001), ANA positivity (86.6% *vs*. 76.9%, p<0.001) and

Table I. Epidemiological characteristics of patients with juvenile idiopathic arthritis from a national prospective database with data from 60 rheumtological centres (years 2002–2013; representative years 2002, 2005, 2007, 2009, 2011 and 2013 are shown).

	2002	2005	2007	2009	2011	2013
No. of JIA patients	2,705	3,497	3,399	3,751	4,783	5,303
Female sex, n (%)	1,773 (65.6%)	2,342 (67.0%)	2,251 (66.3%)	2,495 (66.5%)	3,214 (67.2%)	3,613 (68.2%)
Age, mean (SD)	11.5 (4.7)	11.4 (4.7)	11.3 (4.8)	11.1 (4.5)	11.4 (4.5)	11.7 (4.6)
Age at JIA onset, mean (SD)	7.0 (4.4)	6.9 (4.4)	6.8 (4.4)	7.0 (4.4)	7.1 (4.5)	7.1 (4.6)
Disease duration of JIA (years), mean (SD)	4.5 (3.7)	4.5 (3.7)	4.3 (3.6)	4.1 (3.5)	4.3 (3.7)	4.5 (3.7)
Polyarthritis RF positive	69 (2.6%)	71 (2.0%)	90 (2.7%)	100 (2.7%)	105 (2.2%)	125 (2.4%)
Polyarthritis RF negative	390 (14.4%)	498 (14.2%)	523 (15.4%)	586 (15.6%)	873 (18.3%)	1,060 (20.0%)
Systemic arthritis	180 (6.7%)	230 (6.6%)	212 (6.2%)	221 (5.9%)	242 (5.1%)	234 (4.4%)
Oligoarthritis, persistent	1,046 (38.7%)	1,526 (43.7%)	1,654 (48.7%)	1,832 (48.9%)	2,127 (44.5%)	2,264 (42.7%)
Oligoarthritis, extended	210 (7.8%)	274 (7.8%)	261 (7.7%)	270 (7.2%)	415 (8.7%)	605 (11.4%)
Psoriatic arthritis	174 (6.4%)	265 (7.6%)	69 (2.0%)	202 (5.4%)	315 (6.6%)	343 (6.5%)
Enthesitis-related arthritis	324 (12.0%)	493 (14.1%)	449 (13.2%)	423 (11.3%)	532 (11.1%)	527 (9.9%)
Undifferentiated arthritis	312 (11.5%)	139 (4.0%)	140 (4.1%)	115 (3.1%)	170 (3.6%)	143 (2.7%)
ANA positive, n (%)	779 (42.6%)	1,243 (51.9%)	1,194 (51.8%)	1,270 (52.4%)	1,724 (53.1%)	2,005 (54.9%)
HLA-B27, n (%)	513 (23.9%)	606 (21.5%)	562 (21.1%)	584 (21.0%)	719 (19.9%)	761 (18.7%)

Table II. Change in uveitis prevalence between 2002 and 2013. A significant decrease in uveitis frequency is observed when analysing all JIA patients (OR=0.98, 95%CI: 0.975; 0.991, *p*=0.015) as well as JIA patients at high risk for uveitis, namely polyarthritis rheumatoid factor-negative (PA RF neg), persistent and extended oligoarthritis (OA pers/ext) (OR=0.98, 95%CI: 0.971; 0.993, *p*=0.004).

Year	JIA Uveitis		OA pers/ext PA RF neg Uveitis	
	n	%	n	%
2002	352	13.0	271	16.5
2003	333	12.6	265	15.9
2004	406	12.1	325	14.8
2005	415	11.9	336	14.6
2006	455	12.4	369	15.1
2007	433	12.7	377	15.5
2008	442	12.3	349	14.0
2009	446	11.9	381	14.2
2010	602	13.0	521	15.7
2011	550	11.5	468	13.7
2012	569	11.3	492	13.5
2013	617	11.6	547	13.9
Test for trend unadjusted				
OR	0.98		0.98	
95% CI	0.975 ; 0.991		0.967 ; 0.993	
p-value	0.026		0.004	
Test for trend adjusted[1]				
OR	0.98		0.98	
95% CI	0.975 ; 0.997		0.971 ; 0.997	
p-value	0.015		0.023	

CI: confidence interval; OR: odds ratio
[1]adjusted for JIA subgroup, duration of disease, age at disease onset.

age at onset of JIA (4.0 *vs*. 4.6 years, *p*<0.001).

Anatomical type and laterality of uveitis

In a total of 92.9% of patients, uveitis was classified as anterior uveitis, 3.7% as intermediate and 0.9% as posterior uveitis, whereas panuveitis was only documented in 2.5% (all without any significant change over time). Unilateral *versus* bilateral eye involvement was observed in 39% and 61% of the patients, respectively. The rate of patients with bilateral involvement (2003: 69.7%; 2013: 66.3%) did not significantly differ between 2002 and 2013 (OR=0.98, 95%CI: 0.94 ; 1.02, *p*=0.248).

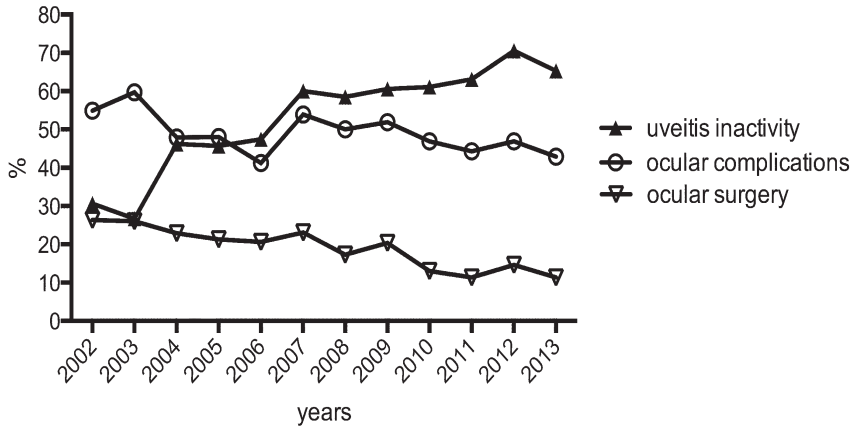

Fig. 1. In documentation for patients using the uveitis module (n=1,381) the proportion of patients in whom uveitis inactivity was achieved increased significantly between 2002 and 2013 (*p*<0.001). Furthermore, a decreasing rate of ocular surgery (*p*<0.001) and a trend for a decreasing proportion of patients with secondary uveitis complications (*p*=0.072) were reported.

Visual acuity

At the yearly documentation, mean visual acuity in the worse eye was 0.35±0.59 logMar (*i.e*. 20/40–20/50) in 2002 and 0.20±0.43 logMar (*i.e*. 20/32) in 2013, revealing a significantly better vision over the 10-year observation period (β=-0.010; 95%CI: -0.016; -0.003; *p*=0.006). In 2002, a visual acuity <20/100 was found in 56.0% of patients, 20/100 to 20/32 in 28.4% and ≥20/25 in 15.6% of patients, whereas in 2013 a visual acuity <20/100 was found in 47.5% of patients, 20/100 to 20/32 in 46.0% and ≥20/25 in 6.6% of patients.

Uveitis-related secondary complications

Cross-sectional analysis of the yearly documentations of all uveitis patients in the NPRD revealed a significant decrease in the prevalence of secondary complications of uveitis between 2002 and 2013, with 33.6% of all uveitis patients presenting with complications in the year 2002 and 23.9% in the year 2013 (OR=0.94, 95%CI: 0.92, 0.96; *p*<0.001).

When analysing only those patients included in the uveitis module, a similar trend for a decreasing complication rate was found from 2002 to 2013 (2002: 50.9%; 2013: 42.9%; OR=0.97, 95%CI: 0.94, 1.00; *p*=0.072; Fig. 1). For these patients, the decrease was pronounced between 2009 and 2013. The most common complications were posterior synechiae (2002: 23.6%; 2013: 25.0%, OR=1.01, 95CI: 0.98; 1.05; *p*=0.460), cataract (2002: 23.6%; 2013: 15.7%, OR=0.97, 95%CI: 0.93; 1.00, *p*=0.067), band keratopathy (2002: 24.6%; 2013: 7.1%; OR=0.84, 95%CI: 0.79; 0.89, *p*<0.001) and glaucoma (2002: 7.3%; 2013: 5.0%; OR=0.93, 95%CI: 0.88, 1.05; *p*=0.151). An overview of the presence of uveitic secondary complications at the yearly documentation is shown in Table III.

Systemic anti-inflammatory treatment

Systemic treatment patterns changed significantly between 2002 and 2013 in the cohort of all JIA patients. In 2002, the most common synthetic DMARD (sDMARD), methotrexate, was used in 39.8% of JIA patients, whereas the

Table III. Prevalence of secondary uveitis complications (n / %) in the uveitis add-on module (n=1,381).

	Cataract	Synechiae	Macular oedema	Glaucoma	Ocular hypotony	Band keratopathy	Drug-induced complications	Other complications
2002	26 (23.6)	26 (23.6)	4 (3.6)	8 (7.3)	2 (1.8)	27 (24.6)	10 (9.1)	20 (18.2)
2003	22 (28.6)	22 (28.6)	2 (2.6)	6 (7.8)	2 (2.6)	23 (29.9)	5 (6.5)	17 (22.1)
2004	24 (25.0)	19 (19.8)	5 (5.2)	12 (12.5)	2 (2.1)	22 (22.9)	8 (8.3)	12 (12.5)
2005	14 (18.7)	15 (20.0)	1 (1.3)	10 (13.3)	1 (1.3)	18 (24.0)	8 (10.7)	16 (21.3)
2006	21 (20.6)	19 (18.6)	5 (4.9)	10 (9.8)	1 (1.0)	18 (17.7)	2 (2.0)	10 (10.8)
2007	27 (26.0)	34 (32.7)	6 (5.8)	13 (12.5)	2 (1.9)	19 (18.3)	12 (11.5)	25 (24.0)
2008	29 (27.9)	28 (26.9)	3 (2.9)	9 (8.7)	3 (2.9)	19 (18.3)	6 (5.8)	23 (22.1)
2009	30 (27.8)	28 (25.9)	6 (5.6)	11 (10.2)	3 (2.8)	22 (20.4)	8 (7.4)	25 (23.2)
2010	31 (19.1)	40 (24.7)	3 (1.9)	5 (3.1)	3 (1.9)	11 (6.8)	7 (4.3)	38 (23.5)
2011	34 (21.5)	40 (25.3)	3 (1.9)	9 (5.7)	4 (2.5)	6 (3.8)	12 (7.6)	37 (23.4)
2012	30 (20.7)	38 (26.2)	8 (5.5)	10 (6.9)	1 (0.7)	8 (5.5)	16 (11.0)	36 (24.8)
2013	22 (15.7)	35 (25.0)	2 (1.4)	7 (5.0)	2 (1.4)	10 (7.1)	7 (5.0)	25 (17.9)
OR	0.97	1.01	0.97	0.93	0.98	0.84	0.69	1.03
95% CI	0.93 ; 1.00	0.98 ; 1.05	0.89 ; 1.05	0.88 ; 1.05	0.88 ; 1.10	0.79 ; 0.89	0.55 ; 0.86	0.99 ; 1.07
p-value	0.067	0.460	0.455	0.151	0.726	<0.001	0.001	0.101

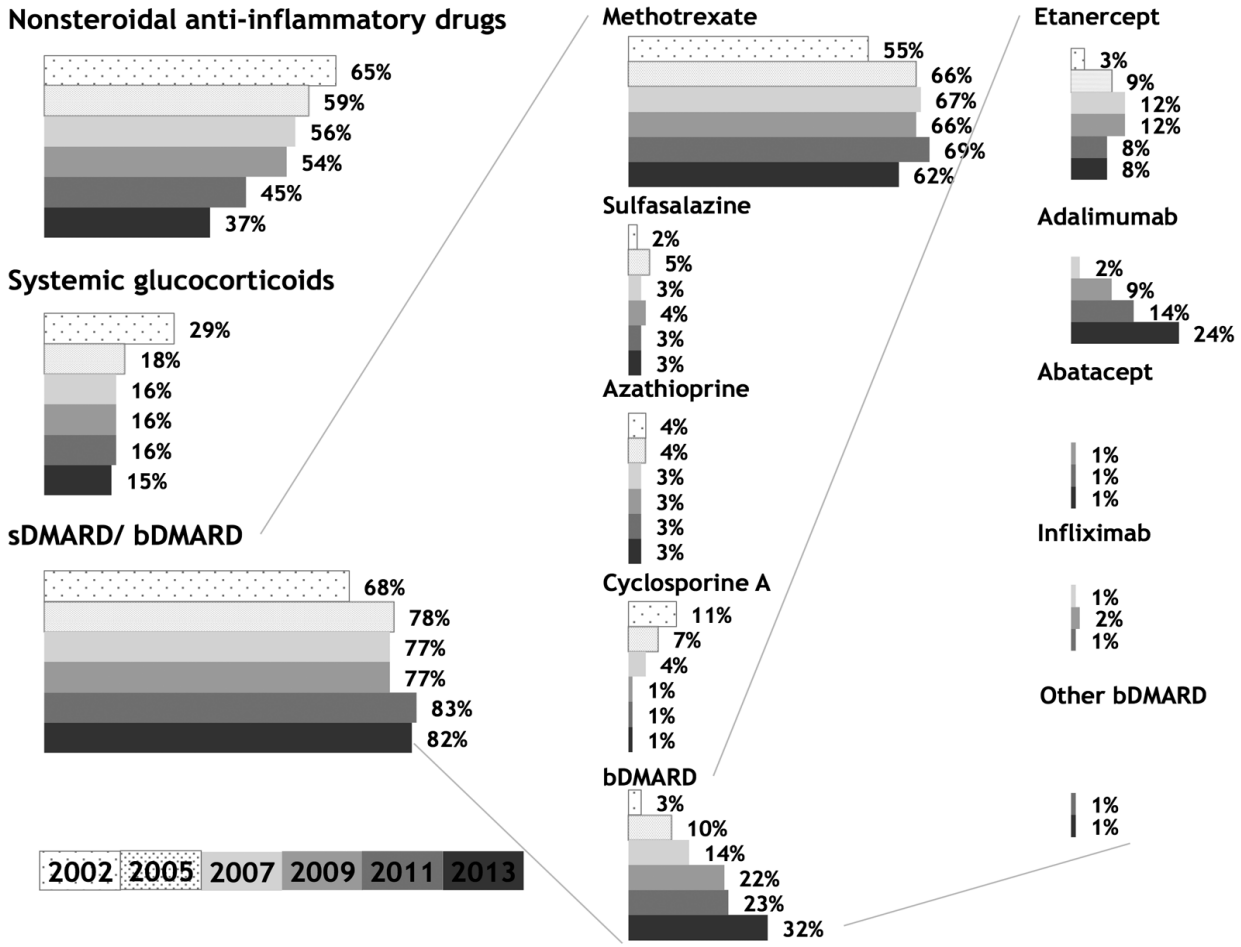

Fig. 2. Systemic treatment of uveitis patients (uveitis patients in NPRD; n=5,620) is shown for representative years 2002, 2005, 2007, 2009, 2011 and 2013. sDMARD: synthetic disease-modifying drug; bDMARD: biological disease-modifying drug.

use of this drug increased to 47.2% of JIA patients in 2013 (OR=1.03; 95%CI: 1.01 ; 1.05; p=0.002). Other sDMARDs such as cyclosporine A (2002: 67 patients; 2.8% – 2013: 4 patients; 0.1) or azathioprine (2002: 70 patients; 2.9% – 2013: 37 patients; 0.8) were used in only a minority of patients. In the same period, the use of systemic corticosteroids decreased from 24.0% to 13.5% (OR=0.94; 95%CI: 0.92; 0.96; p<0.001). Whereas in 2002, 79 patients (3.3%) were treated with etanercept, in 2006 already 289 patients (7.9%) were being treated with this TNF inhibitor. During that period of time, infliximab or adalimumab was not approved for JIA. In 2013, a total of 21.8% of patients were treated with biological disease-modifying drugs (bDMARDs), mainly with etanercept (13.9%), infliximab

Table IV. History of ocular surgery at any time prior to documentation in patients using the uveitis module (n=1,381).

	Any ocular surgery	Cataract surgery	EDTA abrasio	Vitrectomy	IOL -implantation	Retinal surgery	Glaucoma surgery	Retinal cryocoagulation
2002	29 (26.4%)	27 (24.6%)	3 (2.7%)	8 (7.3%)	8 (7.3%)	2 (1.8%)	4 (3.6%)	1 (0.9%)
2003	20 (26.0%)	18 (23.4%)	3 (3.9%)	6 (7.8%)	6 (7.8%)	2 (2.6%)	3 (3.9%)	1 (1.3%)
2004	22 (22.9%)	18 (18.8%)	4 (4.2%)	4 (4.2%)	8 (8.3%)	1 (1.0%)	5 (5.2%)	0 (0.0%)
2005	16 (21.3%)	15 (20.0%)	3 (4.0%)	3 (4.0%)	1 (1.3%)	3 (4.0%)	2 (2.7%)	0 (0.0%)
2006	21 (20.6%)	20 (19.6%)	1 (1.0%)	2 (2.0%)	3 (2.9%)	1 (1.0%)	8 (7.8%)	0 (0.0%)
2007	24 (23.1%)	20 (19.2%)	4 (3.9%)	9 (8.7%)	11 (10.6%)	3 (2.9%)	7 (6.7%)	0 (0.0%)
2008	18 (17.3%)	13 (12.5%)	0 (0.0%)	1 (1.0%)	7 (6.7%)	4 (3.9%)	6 (5.8%)	0 (0.0%)
2009	22 (20.4%)	20 (18.5%)	6 (5.6%)	4 (3.7%)	9 (8.3%)	2 (1.9%)	5 (4.6%)	0 (0.0%)
2010	21 (13.0%)	18 (11.1%)	2 (1.2%)	4 (2.5%)	7 (4.3%)	4 (2.5%)	8 (4.9%)	0 (0.0%)
2011	18 (11.4%)	14 (8.9%)	0 (0.0%)	2 (1.3%)	3 (1.9%)	0 (0.0%)	12 (7.6%)	0 (0.0%)
2012	21 (14.6%)	20 (13.9%)	1 (0.7%)	6 (4.2%)	8 (5.6%)	3 (2.1%)	8 (5.6%)	0 (0.0%)
2013	16 (11.4%)	14 (10.0%)	2 (1.4%)	6 (4.3%)	9 (6.4%)	0 (0.0%)	6 (4.3%)	0 (0.0%)
OR	0.91	0.91	0.87	0.92	0.97	0.93	1.02	0.37
95% CI	0.87 ; 0.95	0.87 ; 0.95	0.77 ; 1.00	0.85 ; 1.00	0.90 ; 1.04	0.83 ; 1.04	0.96 ; 1.10	0.08 ; 1.60
p-value	<0.001	<0.001	0.042	0.062	0.355	0.203	0.508	0.181

mab (0.1%) and adalimumab (7.5%). Treatment regimens combining sDMARDs with bDMARDs increased significantly between 2002 and 2013 for MTX / adalimumab, in 2007 1.9% *versus* 13.0% in 2013 (OR 1.72, 95%CI 1.38, 2.13, $p<0.001$), and MTX/infliximab, in 2007 0.7% *versus* 1.2% in 2013 (OR 1.31, 95%CI 1.03; 1.67, $p=0.031$), whereas no significant difference was found for combined MTX / etanercept treatment when comparing the numbers between years 2003 and 2013 (2003 3.6% *vs*. 2013 1.2%, OR 1.00, 95%CI 0.9, 1.12, $p=0.984$). Similar temporal changes were also observed when analysing only JIA subgroups at high risk for uveitis, namely rheumatoid factor-negative polyarthritis and both extended and persistent oligoarthritis.

Patients with uveitis were treated significantly more often with systemic corticosteroids (OR=1.58; 95%CI: 1.44; 1.73; $p<0.001$) and sDMARDs (OR=2.73; 95%CI: 2.52; 2.95; $p<0.001$). The use of etanercept was significantly lower in patients with uveitis (OR=0.81; 95%CI: 0.72; 0.91; $p<0.001$), whereas adalimumab (OR=7.29; 95%CI: 6.22; 8.55; $p<0.001$) and infliximab (OR=5.62; 95%CI: 2.92; 10.82; $p<0.001$) were used significantly more often if uveitis was present (Fig. 2).

Achievement of inactivity

A significant increase was observed in the rate of patients in whom uveitis inactivity was achieved according to cross-sectional uveitis module data, showing 30.6% of uveitis patients with inactive disease (*i.e*. ocular quiescence, anterior chamber cells 0) in 2002 and 65.3% in 2013 (OR=1.15; 95%CI: 1.11, 1.19; $p<0.001$; Fig. 1).

Eye surgery

A total of 248 patients (18.0% of all uveitis patients from the uveitis module) had undergone ocular surgery prior to enrolment or during reporting in the NPRD. The rate of patients with any ocular surgery significantly decreased between 2002 and 2013 from 26.4% to 11.4% (OR=0.91; 95%CI: 0.87; 0.95; $p<0.001$; Fig. 1). The most common procedures were cataract surgery (2002: 24.6%, 2013: 10%; OR 0.91, 95%CI 0.87; 0.95, $p<0.001$), followed by pars plana vitrectomy (2002: 7.3%; 2013: 4.3%; OR=0.92; 95%CI 0.85; 1.00; $p=0.062$) and glaucoma surgery (2002: 3.6%; 2013: 4.3%, OR=1.02, 95%CI: 0.96; 1.10; $p=0.508$). An overview of surgical interventions for all patients from the uveitis module is shown in Table IV.

Discussion

In the present study, cross-sectional data from the prospective NPRD in Germany were analysed over a period of 12 years. Similar to the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry in the USA (43), prospective rheumatological data are collected from a large JIA cohort. In addition, the NPRD with its uveitis add-on module – *i.e*. completed by ophthalmologists – offers the possibility of analysing standardised ophthalmological data. This cohort of 18,555 JIA patients is unique and one of the largest reported so far.

In general, we found a prevalence of uveitis of between 11.3% and 13.0%, which is similar to previously reported data from the USA at 10.2% (13, 16-20, 44), lower than data from Scandinavia at 18% (13, 28, 45, 46) and quite higher than reports from East or South Asia at 2.9–4.6% (13, 47-52). Our data are also in line with previous cross-sectional data from Germany (2, 14, 53). Prevalence data may differ between publications due to uveitis screening, JIA subgroup composition, follow-up time, genetic background, geographic differences, and treatment patterns and are probably also due to selection bias from tertiary centres compared to national databases and registries. Importantly, our data represent a prospective collection from a population-based cohort.

In our study, a significant decrease in uveitis prevalence from 13.0% to 11.3% was found between 2002 and 2013. This significant change was also found in JIA subgroups known for their high uveitis prevalence. While a decrease in uveitis prevalence over time has already been suggested by some authors (32, 33, 40, 54), a quite stable prevalence of uveitis was reported in other studies (17, 38, 39). The prospective observation of more than 10 years in our study, the high number of patients, the standardised documentation in a population-based cohort for each year analysed provide a sound basis for

making a valid estimation of the temporal change in uveitis prevalence.

There are no indications that the observed decrease in uveitis prevalence over time is caused by changes in risk factors in the study population during the observation period. Although patient age at documentation, age at JIA onset, disease duration, ANA positivity and rheumatoid factor positivity fluctuated during the observation period, these known risk factors for uveitis onset did not reveal any significant change in favour of a reduced uveitis risk between 2002 and 2013 (see *Results* section). Accordingly, the reported decrease in uveitis prevalence remained at the same significance level after adjusting the analysis for gender, JIA subtype, ANA positivity, age at arthritis onset and duration of disease.

Although a variety of studies in JIAU patients and the effect of different DMARDs on uveitis activity have been published, only few data from population-based studies are available from which information can be retrieved about the global rate of patients in whom uveitis inactivity was achieved over time. In the present study, a standardised ophthalmological questionnaire based on the uveitis activity definition according to the SUN classification (42) enabled us to compare uveitis activity over time. Interestingly, the number of patients in whom uveitis inactivity was achieved increased significantly during the last decade.

JIA-associated uveitis frequently leads to ocular complications, with high rates of up to 90% during the course of disease (12, 23, 27, 38, 55-59). Depending on duration of disease and reporting centre, different rates of ocular complications in JIA were reported for cataract (19–81%), glaucoma (8-38%), band keratopathy (7–70%), posterior synechiae (8–75%), ocular hypotony (19%) and macular oedema (14, 23, 39, 59-62). Our analysis revealed a significant decrease in ocular complications in all uveitis patients (NPRD): from 33.6% in 2002 to 23.9% in 2013. According to patient data from the uveitis module, a trend for a decreasing rate of ocular complications was observed for the period 2002–2013, with a more pronounced reduction for the later years (2009–2013). As patients from the uveitis module had a more severe course of disease, the more frequent use of bDMARDs, particularly within the last few years, may explain these findings.

Unfortunately, ocular complications of uveitis may result in impaired visual acuity, with a rate of 9.2% as shown in a recent meta-analysis (13). Variability in visual outcome is high, depending probably – but not only – on differences between population-based studies and reports from tertiary referral centres (14, 21, 22, 37-39, 55, 63-68). A previous study by Saurenmann *et al*. reported legal blindness in 17.6% of JIAU patients in 1992 as compared to 5.6% in 2005, suggesting that this might be the result of an increased usage of immunosuppressive treatments in JIA patients (37). Similarly improving visual outcomes were found in our study. As a result of the better outcome of JIAU reported after early use of immunosuppressive treatment, new treatment recommendations were recently published (69).

Monotherapy and also combination treatments of methotrexate, adalimumab or infliximab in uveitis patients increased significantly in the last decade. Interestingly, a previous study also suggested that methotrexate treatment in JIA may reduce the risk for uveitis onset (34). Due to the cross-sectional design of our study, a causal role of methotrexate and other DMARDs to prevent uveitis manifestation in JIA cannot be proven. However, it may be speculated that the more frequent use of synthetic and biological DMARDs have influenced the rate of uveitis manifestation, as no relevant change in uveitis risk factors were observed during this period.

The present study is one of the largest prospective population-based analyses for uveitis in JIA, now offering a follow-up of more than 10 years. Currently accepted, standardised methods of rheumatological (70) and ophthalmological documentation (42) were applied. However, the NPRD also has certain limitations. Each patient is only documented once a year. As this applies to the entire study period, though, it has no impact on the temporal changes described. The strength of our estimation of uveitis prevalence lies in the large numbers of over 3,500 patients documented per year. However, the detailed ophthalmological dataset, which provides information on uveitis activity, visual function, secondary complications and eye surgery, was only completed in 25% of uveitis patients. Nonetheless, as this refers to all years during the entire study period, it does not impair the estimation of the longitudinal changes that were observed.

Our prospective cross-sectional analysis of a national database shows a significant decrease in uveitis prevalence in the last decade. Furthermore, achievement of uveitis inactivity increased significantly over time. Moreover, the prevalence of ocular complications and rate of ocular surgery decreased in JIAU patients. This may be associated with an increasing rate of both synthetic (mostly methotrexate) and biological DMARD treatment between 2002 and 2013. Further longitudinal analysis is required to verify the causal association of such treatments for the onset and course of uveitis in JIA.

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