

# Juvenile idiopathic arthritis-associated uveitis in the era of biological therapy: how the disease changed in 14 years of observation in a tertiary referral center in Rome (Italy)

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## Research Article

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# Abstract

## Objectives

To describe the ophthalmological characteristics in a Juvenile idiopathic arthritis (JIA) cohort and to evaluate how therapeutic advances have changed the course of the uveitis.

## Methods

Analysis of a retrospective cohort study of consecutive JIA pediatric patients including JIA-associated uveitis (JIA-U) and comparison with a previous study in the same uveitis center assessed before the wide-spread of biological therapy.

## Results

49 JIA patients analyzed, of whom 18 JIA-U, compared with a JIA-U past cohort of 66 patients. Systemic corticosteroids were used significantly less in the current JIA-U group ( $p = 0.008$ ) than in the past one. JIA-U present cohort were on therapy more frequently with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), than the past group ( $p = 0.039$ ), mostly treated with methotrexate (93.3%). Furthermore, a larger use of biologic disease-modifying antirheumatic drugs (bDMARDs) was described in the current JIA-U group ( $p = 0.005$ ) also associated with csDMARDs ( $p = 0.003$ ). Adalimumab was used more (72.7%) in the present JIA-U cohort compared to a larger treatment with infliximab (61.5%) in the past ( $p = 0.005$ ). Higher number of uveitis recurrences was observed in the previous cohort compared to the current one ( $p = 0.005$ ). Fewer complications were described in this study than in the previous: posterior synechiae ( $p = 0.007$ ), cataract ( $p < 0.001$ ), band keratopathy ( $p < 0.001$ ), elevated intraocular pressure (IOP) ( $p = 0.047$ )

## Conclusion.

Current therapies reduced the uveitis recurrences and ocular complications including cataract due also to the lower use of corticosteroids. The new close collaboration with the pediatric rheumatologic center in the same University has contributed to the care improvement and decrease of uveitis complications.

## Introduction

JIA is the most common chronic rheumatic disease in children with an incidence of 8.2 (7.5–9.0)/100000 cases under 16 years of age, and an annual prevalence of approximately 70.2 (16–140)/100000 [1]. Chronic Anterior Uveitis (CAU) is the most frequent extra-articular manifestation of JIA and its incidence is thought to be approximately 1/10000 with some evidence that it is less frequent in Asian populations affected from JIA [2–3]

The reduction of visual acuity is mainly due to complications resulting from CAU as well as side effects owed to local steroid drugs used to contrast it [4]. The main risk factor for visual impairment is chronic intraocular inflammation, therefore all the therapeutic options are aimed to reduce or to resolve it. Nevertheless, the management strategies of JIA-related uveitis remain a relevant clinical challenge [5].

The first line standard therapy is topical corticosteroid, even though up to 60% of the children need further therapies to achieve quiescence [6]. Sometimes systemic corticosteroids are also used for a short time in severe disease, but the next step is usually the immunosuppressive therapy, as disease-modifying antirheumatic drugs (DMARDs), mainly using methotrexate (MTX), or others immunosuppressive drugs in MTX-resistant cases [6]. This therapy is usually able to solve the recalcitrant cases achieving a good control of the uveitis in approximately 70–80% of patients within 3–4 months [7–8]. However, if the DMARDs are not effective, the biological therapies are considered an appropriate third-line treatment [4]. Currently, TNF- $\alpha$  blocking agents are the main biologics used as treatment of chronic childhood uveitis although in unresponsive JIA uveitis cases other biological drugs options are available [9–12].

The aim of the study was to describe the characteristics of a JIA pediatric population and to assess how therapeutic advances have changed the uveitis course by comparing with a previous cohort evaluated before the widespread use of biological therapy in the same uveitis center.

## Methods

### Patients and study design

We conducted a retrospective analysis of all consecutive pediatric patients with suspected diagnosis of JIA referred to the Department of Pediatrics and to the Department of Sense Organs, Eye Clinic, Uveitis Unit (Policlinico Umberto I, Sapienza University of Rome), from April 2012 to July 2018. Patients with diagnosis of JIA according to the International League of Associations for Rheumatology criteria were eligible to participate [12-13]. The whole cohort was subdivided in two groups: patients with only JIA (group I) and patients with JIA-associated uveitis (JIA-U) (group II). Moreover data about the JIA-U group were compared to a previous JIA-U cohort observed from July 1995 to March 2012 in the same referral uveitis center already reported in a published study [14].

Following the close collaboration with the pediatric rheumatologic center in the same University, all JIA patients were assessed by a pediatric rheumatologist and an ophthalmologist at JIA diagnosis and then at every follow up. All examinations were performed in the same center and by the same group of physicians.

Active uveitis was defined when at least one eye showed an anterior chamber (AC) cells grade above 0 according to the SUN (Standardisation of Uveitis Nomenclature) criteria as indicated from the ophthalmologist [15].

Each patient was observed according to the ophthalmological screening uveitis risk for JIA, whereby checks depend on age at disease onset, ILAR reference category, ANA (antinuclear antibodies) positivity and disease duration [10,16-17].

Demographic data and disease related variables including sex, JIA disease subtype according to ILAR category [12], age at JIA diagnosis and uveitis diagnosis, JIA and uveitis disease duration, were assessed for each patient.

The JIA uveitis characteristics and visual acuity were described: uveitis diagnosis date, anatomical involvement (anterior, intermediate, posterior, panuveitis), laterality, as well as presence of ocular complications and rates of uveitis relapses. Moreover the activity ocular indices were collected for each affected eye according to the SUN International Working Group: the total number of AC (anterior chamber) cells, AC cell grade before and after pupil dilatation (grade 0 (< 1 cells), grade 0.5+ (1–5 cells), 1+ (6–15 cells), 2+ (16–25 cells), 3+ (26–50 cells), 4+ (> 50 cells) [15,18]. Each patient underwent a routine laboratory examination at the first examination and during follow-up. According to clinical history, JIA subtypes and uveitis features, other serological and immunological exams were analyzed, such as erythrocyte sedimentation rate [ESR], C-reactive Protein [CRP], ANA [antinuclear antibodies]).

Furthermore, data about the use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biologic disease-modifying antirheumatic drugs (bDMARDs) or a combination therapy (csDMARD plus bDMARD) were analyzed. Information about the csDMARD used (methotrexate [MTX], azathioprine [AZA], salazopyrine [SSZ]) and bDMARD (adalimumab, infliximab, etanercept, tocilizumab, abatacept), as well as concomitant treatment with mydriatic drops and corticosteroids (topical and/or systemic), non-steroidal anti-inflammatory drugs (NSAIDs), mean therapy duration and mean time between the introduction of csDMARD and the bDMARD were also recorded.

According to the current guidelines, the first line treatment approach was the use of topical steroids and mydriatics, then systemic immunosuppressive therapy (mostly methotrexate), and, in case of limited clinical response, the additional use of a biological agent, largely TNF alfa blockers. Within the biological therapy, different possibilities of switch were considered according to the literature in case of inadequate response to one monoclonal antibody [4,10].

All JIA patients underwent ophthalmological examinations following the international recommendations: high-risk children screening every three months (oligoarthritis, polyarthritis rheumatoid factor negative, psoriatic arthritis, or undifferentiated arthritis who are also antinuclear antibody (ANA) positive, younger than 7 years of age at JIA onset, and have JIA duration of 4 years or less); low or moderate risk children screening every 6–12 months (those with high-risk JIA categories but with ANA negative, age of 7 years or older at JIA onset, or have JIA duration of more than 4 years, or systemic JIA or polyarthritis rheumatoid factor positive or enthesitis-related arthritis) [10].

JIA patients with uveitis were then examined at variable interval time depending on therapeutic response and uveitis severity.

The ophthalmological examination included measurement of BCVA (best correct visual acuity) with Snellen's chart at 3 metres; examination of the anterior segment with slit lamp biomicroscopy and intraocular pressure assessment using Goldmann applanation tonometer; fundus examination using bilateral indirect ophthalmoscope. The evaluation of ocular inflammation was based on the cellular activity in the anterior chamber (PK, cells and flare) according to SUN criteria. In some patients additional instrumental examinations were needed as: spectral domain optic coherence tomography (OCT), retinal fluorangiography (FA) and indocyanine angiography (ICGA).

## Statistical analysis

All data were summarized and displayed as mean  $\pm$  SD for the continuous variables. Categorical data were expressed as frequencies and percentages.

Comparison of groups was performed using the Student t test for continuous variables normally distributed and Mann–Whitney U test for not normally distributed. The chi-square test was used to evaluate the differences for categorical variables.

An assessment of the correlation between JIA and JIA-U groups and specific variables was performed using the Pearson and Spearman rank correlation. Finally, we performed a stepwise multivariate linear regression analysis that evaluated all variables with a significant bivariate relationship (defined by  $p < 0.05$ ) with JIA or JIA-U, as well as variables known to influence uveitis, for inclusion in the model. Statistical significance was set at  $p$  value  $< 0.05$ .

The SPSS statistical package version 25 was used to perform all statistical evaluations (SPSS Inc., Chicago, IL).

## Ethical considerations

The study complied with the Declaration of Helsinki and was approved from ethic committee.

## Results

The baseline characteristics of the present cohort are shown in Table 1 and all study sample including the past JIA-U cohort in Table 2.

Table 1  
Main baseline patients' characteristics of the present cohort

	All Cohort (n = 49)		
	JIA (n = 31)	JIA-U (n = 18)	p value
Female sex, n (%)	20 (64.5%)	15 (83.3%)	0.140
Oligoarthritis, n (%)	18 (58%)	11 (61.1%)	0.834
Age at JIA diagnosis (mean ± SD), years	7.9 ± 4.3	3.9 ± 2.4	< 0.001
Age at uveitis diagnosis (mean ± SD), years	-	4.9 ± 3.0	-
Time between JIA and uveitis diagnosis (mean ± SD), years	-	1.8 ± 2.1	-
ANA positive, n (%)	16 (51.6%)	13 (72.2%)	0.0157
CRP (≥6000 µg/L) at the time of uveitis diagnosis, n (%)	11 (35.5%)	7 (38.8%)	0.539
ESR (≥ 20 mm/h) at the time of uveitis diagnosis, n (%)	13 (41.9%)	10 (55.6%)	0.253
CRP (≥6000 µg/L) at 6 months follow up from uveitis diagnosis, n (%)	19 (61.3%)	12 (66.7%)	> 0.99
ESR (≥ 20 mm/h) at 6 months follow up from uveitis diagnosis, n (%)	12 (38.7%)	10 (55.5%)	0.41
ANA antinuclear antibody; CRP C-reactive Protein; ESR erythrocyte sedimentation rate			

Table 2

Main baseline patients' characteristics comparing the present cohort to the cohort pre-dating wide-spread use of biologic therapies

	<b>JIA-U present cohort (n = 18)</b>	<b>JIA-U past cohort (n = 69)</b>	<b>p value</b>
<b>Female sex</b>	15 (83.3%)	55 (79.7%)	0.512
<b>Age at JIA diagnosis (mean ± SD), years</b>	3.9 ± 2.4	4.0 ± 0.8	0.730
<b>Age at uveitis diagnosis (mean ± SD), years</b>	4.9 ± 3.0	3.0 ± 0.5	< 0.001
<b>Time interval between JIA and uveitis diagnosis (mean ± SD), years</b>	1.8 ± 2.1	1.2 ± 0.25	0.017
<b>Follow up duration (mean ± SD), years</b>	5.1 ± 3.8	3.17 ± 4.3	0.086
<b>ANA positive</b>	13 (72.2%)	61 (88.4%)	0.09
<b>Patients on therapy at the last evaluation</b>	18 (100%)	69 (100%)	1.00
<b>Ocular topical therapy</b>	18 (100%)	69 (100%)	1.00
<b>NSAIDs</b>	13 (72.2%)	47 (68.1%)	0.489
<b>Systemic corticosteroids</b>	6 (33.3%)	47 (68.1%)	0.008
<b>csDMARDs monotherapy</b>	5 (27.8%)	27 (39.1%)	0.373
<b>csDMARDS</b>	15 (83.3%)	40 (58%)	0.039
<b>Type of medications: csDMARDs</b>	14 (93.3%)	23 (57.5%)	0.035
MTX	-	-	
SSZ	1 (6.7%)	1 (2.5%)	
AZA	-	5 (12.5%)	
CsA	-	11 (27.5%)	
MTX + CsA			
<b>bDMARDs monotherapy</b>	1 (5.6%)	-	-
<b>bDMARD + csDMARD</b>	10 (55.6%)	13 (18.8%)	0.003

Except where indicated otherwise, values are the number (%).

Abbreviations: JIA juvenile idiopathic arthritis; ANA antinuclear antibody; NSAIDs nonsteroidal antiinflammatory drugs; MTX methotrexate; SSZ salazopyrine; AZA azathioprine; CsA Cyclosporine; csDMARDS conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs biologic disease-modifying antirheumatic drugs

	JIA-U present cohort (n = 18)	JIA-U past cohort (n = 69)	p value
<b>Type of medications: bDMARDs</b>	8 (72.7%)	1 (7.7%)	0.005
Adalimumab	1 (9.1%)	8 (61.5%)	
Infliximab	-	3 (23.1%)	
Etanercept	1 (9.1%)	1 (7.7%)	
Tocilizumab	1 (9.1%)	-	
Abatacept			
Except where indicated otherwise, values are the number (%).			
Abbreviations: JIA juvenile idiopathic arthritis; ANA antinuclear antibody; NSAIDs nonsteroidal antiinflammatory drugs; MTX methotrexate; SSZ salazopyrine; AZA azathioprine; CsA Cyclosporine; csDMARDs conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs biologic disease-modifying antirheumatic drugs			

The present cohort included 49 children with a diagnosis of JIA according to the International League of Associations for Rheumatology criteria [12].

Patients affected from JIA associated with uveitis were 18/49 (36.7%) (on a total of 31 eyes) (group II, JIA-U) while 31/49 (63.3%) children had only a diagnosis of JIA (group I, JIA).

Overall, the present study cohort was characterized by marked female prevalence in both groups, although mostly in the group II, as well as a higher frequency of oligoarthritis and ANA positive according to ILAR criteria. In all cohort the mean follow up duration was  $5.1 \pm 3.8$  years. The mean age at the JIA diagnosis was  $6.3 \pm 4.3$  years with a JIA disease duration at last follow up of  $5.3 \pm 3.7$  years. The mean interval between JIA and uveitis diagnosis was  $1.8 \pm 2.1$  years. A lower age at JIA diagnosis was observed in patients with associated uveitis, in particular a mean age at diagnosis of JIA less than 8 years ( $p = 0.0001$ ). In 15/18 (83.3%) patients of the group II, the JIA diagnosis preceded the uveitis, while only in one patient (5.6%) the ocular involvement appeared one year before arthritis, and in two patients (11.1%) uveitis was detected at the same time of initial diagnosis of JIA. JIA was diagnosed mostly between 6 and 10 years of age in 38.7% of the whole cohort of 49 patients. Laboratory tests such as the mean value of (CRP) and (ESR) at uveitis' diagnosis and at 6 months of follow up were compared between two groups, JIA and JIA-U, showing not significant differences.

Therefore, the data were analyzed to compare JIA-U current cohort with the JIA-U past cohort referred to patients enrolled in the same uveitis center [14], as shown in Table 2. The past JIA-U cohort of patients presented with lower age at uveitis diagnosis and a shorter time interval between JIA and uveitis diagnosis than the current JIA-U cohort.

All patients in both JIA-U cohort were on therapy with topical corticosteroid medications (dexamethasone eyedrops, 1 to 6 drops/day, depending on severity of uveitis) and mydriatic eyedrops (homatropine

and/or tropicamide). Almost 70% of JIA-U past cohort used systemic corticosteroids, significantly more than the current JIA-U group ( $p = 0.008$ ). JIA-U present cohort were on therapy more frequently with csDMARDs than the past group ( $p = 0.039$ ), mostly treated with methotrexate (93.3%). Furthermore a larger use of bDMARDs was described in the current JIA-U group ( $p = 0.005$ ) also associated with csDMARDs ( $p = 0.003$ ). A larger use of adalimumab (72.7%) was observed in the present JIA-U cohort compared to a greater treatment with infliximab (61.5%) in the past ( $p = 0.005$ ) (Table 2).

During the study period (April 2012-July 2018), a bilateral eye involvement was reported for 13/18 (72.2%) patients with a total number of 31 eyes with uveitis. The baseline characteristics of JIA-U patients and related JIA uveitis features are summarized in Table 3.

Table 3

JIA-U patients and uveitis characteristics comparing the present cohort to the cohort pre-dating wide-spread use of biologic therapies\*

	JIA-U present cohort (n = 18)	JIA-U past cohort (n = 69)	p value
Female sex n (%)	15 (83.3%)	55 (79.7%)	0.512
<b>JIA subtype and frequency of uveitis, n (%)</b>	11 (61.1%)	44 (63.8%)	0.924
Oligoarthritis	3 (16.7%)	9 (13%)	
Polyarthritis RF+	4 (22.2%)	16 (23.2%)	
Polyarthritis RF-			
<b>Uveitis involvement, n (%)</b>	5 (27.8%)	22 (32%)	0.489
Unilateral	13 (72.2%)	47 (68%)	
Bilateral			
<b>Uveitis course **, n (%)</b>	3 (16.7%)	9 (13.0%)	0.924
Acute	1 (5.6%)	4 (5.8%)	
Recurrent	14 (77.8%)	56 (81.2%)	
Chronic			
<b>Affected eyes, n (%)</b>	31 (86.1%)	116 (84.1%)	0.761
<b>Ocular complications, n (%)</b>	11 (35.5%)	76 (65.5%)	0.007
posterior synechiae	2 (6.5%)	63 (54.3%)	< 0.001
cataract	3 (9.7%)	63 (54.3%)	< 0.001
band keratopathy	2 (6.5%)	25 (21.5%)	0.047
elevated IOP	4 (12.9%)	18 (15.5%)	0.505
macular edema	-	21 (18.1%)	-
hypotonia			

\* Paroli MP et al. *Ocul Immunol Inflamm.* 2015 Feb, p. 23(1):74–81

\*\* Uveitis Course (defined by Standardization of uveitis nomenclature 2005): acute an episode characterized by sudden onset and limited duration; recurrent repeated episodes separated by periods of inactivity without treatment  $\geq 3$  months in duration; chronic persistent uveitis with relapse within < 3 months after discontinuing treatment. Jabs DA et al. *Am J Ophthalmol* 2005, 140(3):509e16

	JIA-U present cohort (n = 18)	JIA-U past cohort (n = 69)	p value
<b>Ocular complications at presentation, n (%)</b>	-	60 (51.7%)	-
posterior synechiae	-	14 (12.1%)	
cataract	-	44 (37.9%)	
band keratopathy	-	3 (2.6%)	
elevated IOP	-	2 (1.7%)	
macular edema	-	5 (4.3%)	
hypotonia			
<b>Ocular complications during follow-up, n (%)</b>	11 (35.5%)	16 (13.8%)	0.008
posterior synechiae	2 (6.5%)	49 (42.2%)	< 0.001
cataract	3 (9.7%)	19 (16.4%)	0.287
band keratopathy	2 (6.5%)	22 (19%)	0.068
elevated IOP	4 (12.9%)	16 (13.8%)	0.558
macular edema	-	16 (13.8%)	-
hypotonia			
<b>Uveitis recurrences during follow up (mean ± SD)</b>	4.53 ± 4.47	31.6 ± 40.7	0.005
<b>Patients who required eye surgery, n (%)</b>	2 patients	16 patients	0.216
Cataract surgery	1 eye	21 eyes	
Vitrectomy	-	4 eyes	
Trabeculectomy	-	1 eye	
Deep sclerectomy	2 eyes	-	
<i>* Paroli MP et al. Ocul Immunol Inflamm. 2015 Feb, p. 23(1):74–81</i>			
<i>** Uveitis Course (defined by Standardization of uveitis nomenclature 2005): acute an episode characterized by sudden onset and limited duration; recurrent repeated episodes separated by periods of inactivity without treatment ≥ 3 months in duration; chronic persistent uveitis with relapse within &lt; 3 months after discontinuing treatment. Jabs DA et al. Am J Ophthalmol 2005, 140(3):509e16</i>			

Ocular complications were observed more frequently in oligoarticular JIA subtype and the mean age at the time of first ocular complications was  $6 \pm 2.7$  years. Moreover, structural ocular complications were observed all at follow up, in 8/18 (44.4%) patients and 13 eyes (41.9% of 31).

The majority of JIA-U patients (62.5%) developed only one structural ocular complication, while 12.5% and 25% children respectively had two or three of them. The frequencies of ocular complications were 37.5% at 3 months, 12.5% at 6 months and 50% at > 1 year from the uveitis diagnosis, with a mean interval time between them of  $19.3 \pm 18.3$  months. More than two thirds of JIA-U patients (13/18, 72.2%) were ANA positive and 6 of whom (6/13, 46.2%) developed ocular complications mainly synechiae (83.3%).

The visual prognosis of the patients examined appears favorable. In fact, at the end of the follow-up, 83.9% eyes reached a vision of 20/20 while low vision of 20/100 was observed in only one eye of a patient with bilateral uveitis, with preservation of a vision of 20/20 in the contralateral eye.

Analyzing the data on visual acuity at the beginning and at the end of the follow-up, it emerges that of the 31 eyes affected by uveitis, 25/31 (80.6%) eyes had visual acuity between 20/20 and 20/30, 4/31 (12.9%) eyes between 20/40 and 20/70 and 2/31 (6.5%) eyes visual acuity reduced to 20/200; while at follow-up 28/31 (90.3%) eyes had vision between 20/20 and 20/30, 2/31 (6.4%) eyes between 20/40 and 20/70 and one eye (3.2%) visual equal to 20/100. During the follow-up, there was also an improvement in vision in 12 eyes with a mean of  $4.5 \pm 2.5$  SD Snellen lines (min 2-max 9) while in 5 a worsening of  $5 \pm 2.6$  SD Snellen lines (min 2-max 9).

15/18 (83.3%) JIA-U patients were on therapy with a csDMARD and in 10/18 (66.7%) ocular relapses were reported.

In 10/18 (55.6%) patients a combination therapy with bDMARD was needed, due to lack of uveitis remission. A total of 11 patients were on therapy with bDMARDs, as shown in Fig. 1. Eight JIA-U patients maintained ocular remission on therapy with adalimumab. Only one patient was on monotherapy with bDMARD (adalimumab) due to methotrexate intolerance. In this patient synechiae were described 5 years before initiation of adalimumab. Furthermore, one patient started therapy with adalimumab and then switched to infliximab to obtain ocular remission. Due to failure or loss of efficacy during anti-TNF $\alpha$  therapy, the use of abatacept or tocilizumab in two children was needed to achieve the uveitis control (Fig. 1). Despite csDMARDs-bDMARDs combination therapy, 6/10 (60%) patients had ocular relapses.

In the present JIA-U cohort on biological medications, we observed a reduction of AC cell grade at follow up compared to the uveitis diagnosis, specifically 8/11 (72.7%) were free of ocular inflammation at 3 months after the bDMARD introduction. BCVA also improved in 7 of 11 patients (63.6%).

Furthermore the patients on therapy with csDMARDs plus bDMARDs showed a statistically significant higher frequency of visual acuity improvement than those treated on just csDMARDs ( $p = 0.042$ ).

Therefore, the JIA-U present cohort was comparing to the cohort pre-dating wide-spread use of biological therapies by Paroli MP et al [14] (Table 3). The mean number of recurrences during follow up were  $31.6 \pm 40.7$  in the previous cohort, compared to the current one  $4.53 \pm 4.47$  ( $p = 0.005$ ). As showed in Table 3a significant higher frequency of ocular complications was observed in the past cohort with already

evidence in the first ophthalmological examination, whereas no ocular complications were present in the current study at the first observation. Only for the macular edema no significant difference was described ( $p = 0.505$ ), and hypotonia was not reported in the present our cohort. In the present cohort the most common ocular complications on the affected eyes were posterior synechiae (35.5%), followed by cystoid macular edema (12.9%), band keratopathy (9.7%), cataract (6.5%), elevated intraocular pressure (IOP) (6.5%).

During the follow up the posterior synechiae were significantly more frequent in current JIA-U group than in the past one ( $p = 0.008$ ), compared to a higher frequency of cataract in the past ( $< 0.001$ ).

Overall, the differences about eye surgery in the JIA-U present group compared to the previous one by Paroli MP et al were described in Table 3.

## Discussion

Despite advances in treatment, the JIA-associated uveitis (JIA-U) is still a disabling condition, with possible long-term complications and risk of blindness [19–21].

About one third of our JIA patients (36.7%) had associated uveitis; oligoarthritis was the most common form of JIA, affecting 59.2% of children in all our cohort and 61.1% of JIA-U, with a definite preference of females (up to 83.3 % in JIA-U) although without statistical difference among JIA children with and without uveitis. A significant higher frequency of ANA positive patients was observed in the JIA-U group (72.2%) ( $p = 0.0157$ ). Moreover, in 83.3% of our cases, the diagnosis of JIA preceded the ocular involvement, and we observed a significant correlation between uveitis onset and younger age at JIA diagnosis [13, 22–24, 23–25]. Calandra et. al [25] reported an uveitis risk related to younger age at JIA onset, ANA positivity but not to the gender and Saurenmann RK et al. [26] described the patient's age at the time of arthritis onset and ANA positivity in girls but not in boys as factors related to uveitis [27]).

In our data the mean age of JIA diagnosis in children who developed uveitis (3.9 years) and the mean interval time between JIA and uveitis diagnosis ( $\pm 20$  months) were in accordance with several studies by Heiligenhaus et al. [17], Papadopoulou M. [28], Taha R. [29] and Cecchin V. [30] (specifically they reported the following data: 3.8 years/21 months, 3.4 years/17 months, 3.3 years/18 months, 4.4 years /1.6 months respectively).

The age of first uveitis manifestation was also analyzed compared to different age groups, and the mean age at uveitis diagnosis at 5 years of age according to the study by Castagna I et al. [31]. Although, Castagna I et al. evidenced two different peaks of age for the ocular involvement, the first occurred between 4 and 6 years old and the second between 10 and 12 years old. Also Hoeve M et al. [32] described a second peak around puberty.

Our study is a continuation of the study by Paroli MP. et al. [14] referred to patients enrolled in previous seven years in the same uveitis center in Policlinico Umberto I Sapienza.

Nevertheless, the JIA cohort in the first study was larger, but the mean follow up was shorter than our new study ( $3.17 \pm 4.3$  years vs  $5.1 \pm 3.8$  years).

A higher frequency of oligoarthritis and a female prevalence in JIA-U patients were confirmed in both studies. A longer time interval between the JIA and uveitis diagnosis was described in the present cohort ( $p = 0.017$ ), maybe due to an early JIA diagnosis and treatment with a delay on ocular inflammation complications.

Regarding the laboratory exams, similarly to the previous study, a higher frequency of ANA positive in JIA-U patients were found: 72.2 % vs 88.4 % of the previous study, while the inflammation index ESR was positive at the uveitis diagnosis in 55.6 % of JIA-U patients in this study compared to 76.5% of the previous one. In the study by Paroli MP et al., 30% of affected eyes had at least one ocular complication at first visit, while in this study no patients presented ocular complications at first ophthalmological evaluation and the majority (50%) developed them at  $> 1$  year from the uveitis diagnosis, with a mean interval time between them of  $19.3 \pm 18.3$  months.

In this study the frequency of ocular complications observed was lower compared to the previous respectively: posterior synechiae (35.5% and 65.5%), cataract (6.5% and 54.3%), band keratopathy (9.7% and 54.3%), elevated IOP (6.5% and 21.5%) and the macular edema (12.9% and 15.5%).

The hypotonia, considered as one of the most frequent cause of low vision and blindness in the past, was not described in our study.

The data about the late and lower development of ocular complications such as posterior synechiae, cataract and band keratopathy could be due to an early diagnosis and the ophthalmological screening for JIA in the last decade. In the past cohort many patients came from rheumatological centers from different parts of Italy or directly from ophthalmologists with an inevitable delay in JIA diagnosis, while the close collaboration with the pediatric rheumatologic center in the same University has contributed to the care improvement and decrease of ocular complications. Moreover, the reduction and prevalence of the uveitis severity in JIA patients could be related to greater knowledge about JIA uveitis, an early treatment and the introduction of new therapies including biological agents. In fact, the treatment with systemic corticosteroid therapy was significantly decreased in our current cohort compared to the past one ( $p = 0.008$ ) for the use of csDMARDs and bDMARDs, being another possible cause of reductions of cataracts in the most recent cohort.

## Conclusion

Although new drugs improved significantly the course of JIA and visual prognosis of associated uveitis, the disease remains a challenge for pediatric rheumatologists and ophthalmologists, and patients are still developing sight-threatening ocular complications. A routine ophthalmological follow up is therefore required at regular intervals, in order to identify early ocular involvement.

Further studies are needed to better characterize a target therapeutic approach. The appropriate treatment is necessary to reduce the long-term disability and improve the quality of life in JIA-U.

Optimal care of children with JIA and uveitis requires careful and close collaboration between ophthalmologists and rheumatologists to choose the most appropriate systemic therapy. New discoveries on the pathogenesis of JIA-U and the identification of predictive biomarkers could help find a target therapy tailored to individual patients and based on their predicted response or risk of disease.

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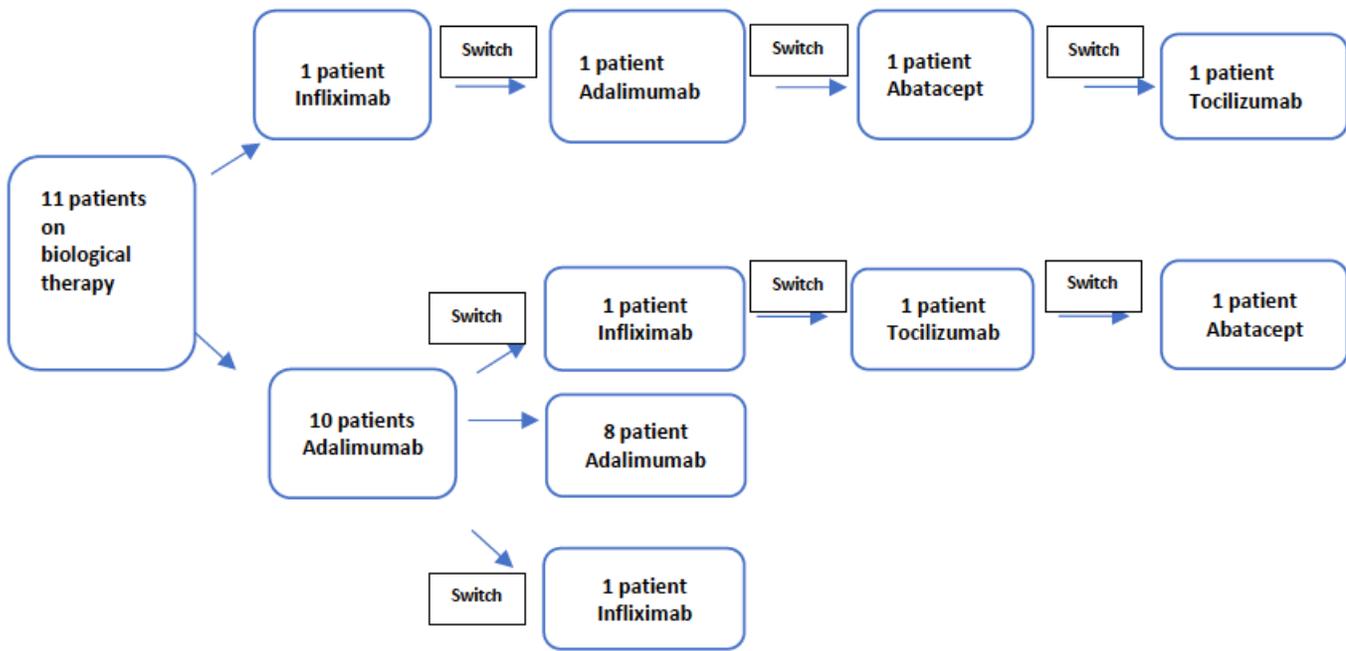
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## Figures



**Figure 1**

Biological therapy in JIA-U patients