Uveitis as predictor of disease flare after the first anti-TNF withdrawal in oligoarticular and polyarticular juvenile idiopathic arthritis: a multicentric Italian experience

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Abstract

Objective

TNF inhibitors (TNFi) have dramatically changed the prognosis of juvenile idiopathic arthritis (JIA), but it is not clear how and when to stop therapy. We aim to describe a multicentric cohort of JIA treated with adalimumab or etanercept who discontinued the treatment for persistent inactivity and to identify factors associated with relapse.

Methods

In a multicentric Italian retrospective cohort study, medical records of patients with oligoarticular and polyarticular JIA were evaluated if they stopped therapy for persistent inactivity after the first TNFi.

Results

136 patients were enrolled (102 female, median age at onset 3 years (range 1–15), of whom 55.9% had oligoarticular JIA, 40.4% uveitis and 72.8% ANA positivity. Adalimumab (59.3%) and etanercept (40.7%) were started at a median age of 6 years (range 1–16), TNFi were discontinued after a median time of 30 months (range 6–90), increasing the interval (76.5%), reducing the dose (18.4%) and abrupt discontinuation (16.9%). 79.4% of patients relapsed after a median time of 5 months (range 0.5–66). Patients with uveitis relapsed earlier (log rank χ^2 16.4 $p<0.0001$), while patients who lengthened the interval of administration showed a later relapse (log rank χ^2 6.95 $p=0.008$). Uveitis (HR 2.11 CI 1.34–3.31), age at onset (HR 0.909 CI 0.836–0.987), duration of tapering (HR 0.938 CI 0.893–0.985) and to have a persistent oligoarticular JIA (HR 0.597 CI 0.368–0.968) are significant predictors of disease relapse (Mantel-Cox χ^2 34.23 $p<0.001$).

Conclusion

Younger age at onset, uveitis, duration of tapering, and non-persistent oligoarticular JIA seem to be independent risk factors for earlier relapse after the first TNFi withdrawal.

Key words

uveitis, tumour necrosis factor inhibitors, withdrawal, juvenile idiopathic arthritis, adalimumab, etanercept

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Introduction

Juvenile idiopathic arthritis (JIA), the most common chronic rheumatic disease in childhood, features persistent arthritis (>6 weeks) of unknown origin with disease onset before 16 years old (1). Uveitis, the most frequent comorbidity of JIA, burdened up to 30% of children (1).

The treatment and prognosis of JIA have been dramatically changed in the past twenty years with the introduction of anti-TNF-α (*i.e.* etanercept or adalimumab) (2, 3). Since then, a significant cohort of patients achieves persistent clinical remission, and therefore systemic glucocorticoids are less used and articular damage rarely seen (2, 3). Large studies showed that up to 80% of patients achieved remission after one year of treatment. However, more than a half of them relapsed after drug weaning (2-8). Even though long-term use of anti-TNF-α is effective and safe, now-adays it is controversial whether to continue or withdraw treatment in patients under remission, due to its costs and long-life administration (9). Controversial reports about predictive factors of relapses after anti-TNF withdrawal in JIA are available in the literature (4, 7, 9-13). Several demographical and clinical factors, such as early age at JIA onset, biological sex, anti-nuclear antibody (ANA), rheumatoid-factor (RF) positivity, and a higher articular score at onset have been associated to an increased risk of relapses after drug withdrawal (6, 7, 11, 14). Additionally, longer time between disease onset and anti-TNF-α initiation and longer time to reach clinical inactive disease seem to indicate an increased risk of relapse (8, 13, 15). However, there is no agreement about the specific time and modality of anti-TNF withdrawal (4, 7, 13, 16).

Along with clinical predictors, over the last years, new biochemical markers and articular ultrasound has been studied as potential indicators of subclinical inflammation, but more studies are needed to use them in the daily practice (12, 17, 18).

This study aims to describe a multicentric, homogenous cohort of JIA patients treated with anti-TNF-α (adalimumab and etanercept) in whom therapy was discontinued for persistent remission, and to identify predictive factors associated with disease flare.

Materials and methods

Study design and patient flow

This is a multi-centre Italian, retrospective cohort study that involved the Paediatric Rheumatology of Meyer Children's Hospital IRCCS (Florence), Giovanni XXIII Hospital (Bari), Spedali Civili of Brescia (Brescia) and Institute for Maternal and Child Health IRCCS Burlo Garofolo (Trieste) up to September 2022.

In order to properly set and define the variables to be considered and entered, a consensus agreement meeting was held prior to data collection.

Study population

Patients were considered eligible for this study if they fulfilled the following inclusion criteria:

- A diagnosis of polyarticular or oligoarticular JIA according to the ILAR criteria (1),
- Patients who were able to stop the first course of biologic therapy with anti-TNF-α (adalimumab or etanercept) for persistent inactivity,
- Administration of anti-TNF-α before the age of 18.
- A follow-up of at least of 6±2 months after anti-TNF-α withdrawal
- Being currently followed at the participating paediatric rheumatology units up to September 2022.

Uveitis, and concomitant medications other that anti-TNF-α therapy (*i.e.* traditional DMARDs) were not considered exclusion criteria. Conversely, JIA patients with different diagnosis from oligoarticular or polyarticular JIA or who were previously treated with another biologic were excluded from this cohort.

The study obtained approval from Meyer Children's Hospital IRB (175/2022) and patientsgave their signed informed consent to participate in the study.

Data collection and outcomes

- Variables collected

The following data were collected based on the medical record review: biologic sex, age at onset of symptoms

and diagnosis, JIA subtype according to ILAR classification (1), presence or not of uveitis, autoantibody positivity (ANA and RF), presence of comorbidity (as thyroiditis, diabetes), HLA B27 and B51 positivity, ESR (expressed in mm/hr) and CRP (expressed in mg/dl) at onset and at the time of anti-TNF-α starting, as well as patients/parents and medical global assessment measured on a 10-cm Visual Analogue Scale (VAS), JADAS10 (10-joint Juvenile Arthritis Disease Activity Score) (19), Childhood Health Assessment questionnaire (CHAQ). Additionally, at the time of anti-TNFα starting, the following variables have been recorded: age, concomitant administered therapies, including systemic corticosteroids, number of active joints, activity of uveitis, the time between JIA diagnosis and anti-TNF-α initiation, time to achieve inactive disease, time on persistent inactivity before drug withdrawal, cumulative time on anti-TNF-α therapy with, cumulative time on concomitant therapy, the modality of anti-TNF-α weaning, recorded as lengthening of interval of administration, or reducing drug dose, or abrupt interruption, time to wean anti-TNF-α, time up to the first relapse or at the last available follow-up after anti-TNF-α withdrawal.

In case of disease relapse, the type of relapse (recorded as arthritis, uveitis or both), the concomitant administered drug after anti-TNF-α withdrawal, if any, and its duration

- Primary outcomes

As primary outcomes we considered the disease relapse after drug withdrawal and time free from relapse out of therapy.

Inactive disease was defined as absence of arthritis and anterior chamber cells less than 0.5 at slit lamp evaluation and normal inflammatory biomarkers according to Wallace criteria. Relapse was defined as recurrence of arthritis in at least one joint or uveitis recurrence. We considered relapse in therapy and off therapy. Time free from relapse after drug withdrawal was defined as time between anti-TNF-α discontinuation and the first disease flare articular as well as ocular.

Statistical analysis

All data were stored and organised using Microsoft Excel, and statistical analysis was performed with SPSS v. 27 for Microsoft.

Continuous variables were summarised with medians and ranges (R), while categorical variables were summarised with frequencies and percentages. Demographic and clinical features were compared between the relapse group and non-relapse group using the chi square or the Fisher exact test or with Kruskal Wallis or Mann-Whitney U-test as appropriate.

The following data were considered as variables for correlations, and as covariates for the survival curves: persistent oligoarticular JIA (pOligo), extended oligo JIA (eOligo), polyarticular JIA (poly), time between diagnosis and biologic initiation, duration of inactivity on therapy, continuation of concomitant therapy, duration of biologic therapy, duration of biologic tapering, and biologic tapering modality, antinuclear antibody (ANA) presence and sex.

To identify predictors of outcome, Cox regression model and Kaplan-Meier curves were constructed, each at the mean of the above-reported covariates. Kaplan-Meier survival curves were generated to estimate rate of flare over time following anti-TNF withdrawal for the study population. Log rank test was used to compare the survivorship functions among groups. Cox regression analysis was used to identify independent variables that could significantly predict flare by time and to calculate the hazard ratio of relapse adjusted for the above-mentioned co-variates.

Results

The medical records of 136 patients (102 female, 75%) who met the inclusion criteria were reviewed (73 from Florence, 26 from Brescia, 24 from Trieste and 13 from Bari). The median age at diagnosis was 3 years old (range 1–15). Fifty-five patients received a diagnosis of persistent oligoarticular JIA (40.4%), 21 extended oligoarticular JIA (15.4%), and 60 polyarticular JIA (44.1%). Among all patients, 55 had a history of uveitis (40.4%) and 99 ANA positivity (72.8%) (Table I). Seventy-nine patients were treated with ADA (58%) and 57 with ETA (41.9%) after a median time from onset of 12 months (R 0-127). Inactivity was achieved after a median time of 4 months (range 1–32), and TNFi were discontinued after a median time of 30 months (range 6–90). Considering the whole cohort, 104 children extended the interval of administration (76.5%), 25 weaned the TNFi dose (18.4%), and 16 stopped medication abruptly (11.8%) (Table I). TNFi was discontinued in a median time of 6 months (range 0–22 months). After drug withdrawal, 106 patients relapsed (79.4%) after a median time of 5 months (range 0.5–66), because of arthritis in 71 (66.9%), uveitis in 19 (17.9%) and both in 18 (16.9%).

Significant differences in the characteristic of population treated with adalimumab and etanercept have been reported in Table I.

Among the different JIA subtypes, patients with pOligo had lower age at JIA onset ($p<0.04$), more frequently uveitis (χ^2 =13.17 $p<0.001$), active uveitis at drug initiation (χ^2 17.2 $p<0.001$), treated with adalimumab (χ^2 13.3 $p=0.001$), and flared for uveitis off therapy (χ^2 9.7 $p=0.04$). While patients with polyarticular JIA had shorter duration of disease when they started anti-TNF ($p<0.001$) (Supplementary Table S1).

Considering JIA uveitis patients, they seemed to have an early onset of disease (median 2 *vs*. 4, $p<0.001$), ANA positivity (χ^2 5.4 $p<0.0001$), they were treated with adalimumab (χ^2 32.3 $p<0.001$), lower number of active joints at drug initiation ($p<0.001$), increased time intercourse between JIA diagnosis and TNFi administration ($p<0.001$), but shorter time to achieve inactivity ($p<0.045$) and to remain free from relapse after drug withdrawal ($p<0.001$) (Suppl. Table S2).

The population of patients who relapsed after drug withdrawal were more frequently female (χ^2 5.9 $p=0.014$), had younger age at JIA onset (3 *vs*. 7 years old $p<0.001$) and at TNFi initiation (6 *vs*. 9.5 $p=0.02$), longer duration of JIA before TNFi initiation (13 *vs*. 8.5 months, $p=0.02$), uveitis history (χ^2 7.4 $p<0.006$), and ANA positivity (χ^2 4.3 $p<0.03$) (Table II). Moreover,

Table I. Characteristics of the whole cohort, and its distribution according to the treatment.

	Entire cohort (136)	Adalimumab (79)	Etanercept (57)	Test and *p*-value
Female n, %	102 (75%)	59 (74.7%)	43 (75.4%)	
Age at diagnosis m (R)	3 (1-15)	3 (1-13)	4 (1-15)	
Type of JIA				
pOligo, n	55 (40.4%)	42 (53.2%)	13 (22.8%)	
eOligo, n	21 (15.4%)	8 (10.1%)	13 (22.8%)	
Poli, n	60 (44.1%)	29 (36.7%)	31 (54.4&)	
Uveitis history, n (%)	55 (40.4%)	**48 (60.8%)**	7 (12.3%)	χ^2 **32.3** ***p*<0.0001**
ANA positivity	99 (72.8%)	**63 (79.7%)**	36 (63.2%)	χ^2 **4.6** ***p*<0.03**
RF, n (%)	3 (2.2%)	2 (3.1%)	1 (2%)	
JADAS10 onset, m (R)	17.3 (2-41.7)	16.5 (2-41.7)	18.75 (3-34.7)	
CHAQ onset, m (R)	0.87 (0-2.4)	0.87 (0-2.4)	1 (0-2.3)	
ESR onset mm/h, m (R)	45 (2-120)	45 (2-120)	46 (2-120)	
CRP onset mg/dl, m (R)	1.29 (0-17)	1.2 (0-17)	1.4 (0-7.9)	
HLA B27, n (%), performed in 51	13 (9.6%)	10 (12.7%)	3 (5.3%)	
Characteristics of population when the biologic was started				
Age, m (R)	6 (1-16)	7 (2-16)	5 (1-15)	
n. of active joints	4 (0-18)	2 (0-18)	5 (0-16)	*p*<0.0037
Active uveitis	36 (26.5%)	**36 (45.2%)**	0	χ^2 **35.8** ***p*<0.0001**
ESR	21.5 (0-120)	23.5 (0-120)	18 (0-120)	
CRP	0.41 (0.02-32)	0.45 (0.05-32)	0.41 (0.02-11)	
JADAS10	17.2 (0-34.4)	15.2 (0-34.4)	27.9 (2-26.7)	
CHAQ	1 (0-2.5)	0.8 (0-2.5)	1.2 (0.25)	
Concomitant therapy	111 MTX (81.6%)	65 (82.3%)	46 (80.7%)	
Systemic corticosteroids	28 (20.6%)	14 (17.7%)	14 (24.6%)	
Time between diagnosis and B (months)	12 (0-127)	20 (0-127)	10 (0-92)	*p*<0.001
Time to achieve inactivity on therapy months	4 (1-32)	4 (1-32)	3 (1-24)	
Last item that achieves remission				
Arthritis	108	51	57	χ^2 **25.4** ***p*<0.0001**
Uveitis	23	**23**	0	
Both	5	**5**	0	
Duration of inactivity on Tp months	23 (3-64)	24 (3-64)	22 (3.5-58)	
Duration of therapy	30 (6-90)	30 (7-90)	30 (6-72)	
n. of pts who relapsed	106 (79.4%)	66 (83.5%)	42 (73.7%)	
Time free from relapse out of therapy months	6 (0.5-96)	6 (0.5-60)	5 (0.5-96)	
Type of flare				
Arthritis	71 (66.9%)	33 (50%)	**38 (90.5%)**	
Uveitis	19 (17.9%)	**16 (24.2%)**	3 (7.1%)	
Both	18 (16.9%)	**17 (25.8%)**	1 (2.4%)	χ^2 **19.07** ***p*<0.0001**
n. of months to stop B	6 (0-22)	6 (0-22)	6 (0-22)	
n. of months to stop concomitant	3 (0-36)	4 (0-36)	0 (0-25)	
Modality to stop B				
Lengthening intervals	104 (76.5%)	61 (77.2%)	43 (75.4%)	χ^2 **3.9** ***p*<0.04**
Reduction of dose	25 (18.4)	12 (15.2%)	13 (22.8%)	
Abrupt	16 (11.8%)	**13 (16.5%)**	3 (5.3%)	

m: median, n: number, R: range, pOligo: persistent oligoarthritis, eOligo: extended oligoarthritis, Poli: polyarticular, JIA: juvenile idiopathic arthritis, JADAS10: Juvenile Arthritis Disease Activity Score 10, CHAQ: Childhood Health Assessment Questionnaire, ESR: erythrosedimentation rate, CRP: C-reactive protein, B: biologics, Tp: therapy.

this population had stopped therapy faster than the others (6 *vs*. 9 months, *p*=0.005). Lengthening the interval of administration seems to be protective compared to the other modality of drug withdrawal (χ^2 5.2 *p*=0.02, Odd ratio 0.42 CI 0.15–1,17). Relapse happened more frequently in the first months after drug withdrawal (Mann-Whitney U-test *p*<0.001) (Table II). No significant difference has been found in the proportion of relapse between the two TNFi used.

Figure 1 represents the survival functions from Kaplan-Meier curve, showing the time up to the first relapse after discontinuing therapy among enrolled patients. Using Kaplan-Meier curves to evaluate time free from relapse after drug withdrawal, we showed that patients with uveitis had a significantly earlier relapse (log rank χ^2 = 16.4 *p*<0.0001) (Fig. 2A). Patients who extended the interval of administration during drug withdrawal have a longer period free from relapse after TNFi withdrawing (log rank χ^2 = 6.95 *p*=0.008) (Fig. 2B). This difference persists also if we stratified these curves for uveitis history (log rank χ^2 = 8.97 *p*=0.002) (Fig. 2C-D).

Uveitis (HR 2.11 CI 1.34–3.31), age at onset (HR 0.909 CI 0.836–0.987), du-

Table II. Characteristics of the population according to the event of flare after biologic withdrawal.

	Entire cohort (136)	No relapse (28)	Relapse (108)	Odds ratio (CI)	Test and *p*-value
Female, n	102	16	86	**1.3 (1.03-1.69)**	χ^2 **5.9 p 0.014**
Age at diagnosis, m (R)	3 (1-15)	7 (1-15)	3 (1-11)		***p*<0.001**
Uveitis history, n	55	5	50	**3.97 (1.4-11.2)**	χ^2 **7.4 *p*<0.006**
Type of JIA					
pOligo, n	55	12	43		
eOligo, n	21	3	18	**-**	**ns**
Poli, n	60	13	47		
ANA positivity	99	16	83	**2.49 (1.04-5.95)**	χ^2 **4.3 *p*<0.03**
FR positivity	3	1	2	**0.57 (0.05-6.6)**	**ns**
Comorbdity, n	29	10	19	0.38 (0.15-0.962)	χ^2 4.35 p<0.037
ESR mm/h, m (R)	45 (2-120)	42.5 (2-120)	45 (2-120)		NS
CRP mg/dl, m (R)	1.29 (0-17)	1.17 (0-10.2)	1.34 (0-17)		NS
JADAS10	17.3 (2-41.7)	20.5 (3.7-41)	16.9 (2-34)		NS
Type of biologics	ADA 79 ETA 57	ADA 13 ETA 15	ADA 66 ETA 42	0.552 (0.239-1,27)	NS
Characteristics of population when the biologic was started					
Age, m (R)	6 (1-16)	9.5 (1-15)	6 (1-16)		**p0.002**
Concomitant therapy	111 MTX	20	91	**-**	χ^2 **6.58 *p*<0.03**
Systemic corticosteroids	28 (20.6%)	7	21	0.724 (0.27-1.9)	NS
Active uveitis at B initiation	36	5	31	1.87 (0.6-5.3)	NS
ESR mm/h, m (R)	21.5 (0-120)	11 (0-120)	23 (0-120)	NS	
CRP mg/dl, m (R)	0.41 (0.02-32)	0.4 (0.08-12.5)	0.42 (0.02-32)	NS	
JADAS10	17.2 (0-34.4)	12 (0-34)	17.5 (0-28.9)	NS	
Time between diagnosis and B (months)	12 (0-127)	8.5 (0-117)	13 (1-127)	***p*<0.021**	
Time to achieve remission on therapy	4 (1-32)	3 (1-30)	4 (1-32)	NS	
Duration of therapy	30 (6-90)	30 (9-81)	30 (6-90)	NS	
Duration of remission on therapy	23 (3-64)	23.5 (10-64)	23 (3-60)	NS	
Time free from relapse out of therapy months	6 (0.5-96)	Duration FU 16 (4-96)	5 (0.5-66)		
Type of flare					
Arthritis	71		71	-	
Uveitis	19	-	19		NS
Both	18		18		
Continuation of concomitant therapy after stop bio	39	6	33		NS
n. of months to stop B	6 (0-22)	9 (0-22)	6 (0-22)		***p*<0.005**
Modality to stop B					
Lengthening intervals	104	26	78	**0.2 (0.045-0.89)**	χ^2 **5.2 *p*<0.02**
Reduction of dose	25	4	21	**1.48 (0.4-4.6)**	
Abrupt	16	1	15	**4.35 (0.55-34.4)**	

m: median, n: number, R: range, pOligo: persistent oligoarthritis, eOligo: extended oligoarthritis, Poli: polyarticular, JIA: juvenile idiopathic arthritis, JADAS10: Juvenile Arthritis Disease Activity Score 10, CHAQ: Childhood Health Assessment Questionnaire, ESR: erythro-sedimentation rate, CRP: C-reactive protein, B: biologics, Tp therapy.

ration of tapering (HR 0.938 CI 0.893–0.985) and to have a pOligo (HR 0.597 CI 0.368–0.968) resulted as significant predictors of disease relapse after anti-TNF-α therapy withdrawal (Mantel-Cox $\chi^2 = 34.23$ $p<0.001$)

Cox regression analysis, at mean of the above-reported covariates, showed that JIA children with uveitis (Mantel-Cox $\chi^2 = 20.54$, $p=0.025$), and JIA children who did not lengthen the interval of anti TNF administration (Mantel-Cox $\chi^2=30.3$, $p=0.001$) had a higher probability to relapse after treatment discontinuation. Conversely, after stopping anti-TNF-α, JIA patients with pOligo showed a lower probability to flare compared to eOligo and Poly JIA subtypes (Mantel-Cox $\chi^2 = 31.9$ $p<0.001$). In addition, we performed a subgroup analysis limited just to JIA children who flared after treatment discontinuation due to arthritis flare (n=117). After that 19 subjects who flared only with uveitis were excluded from the analysis, the same statistical results have been obtained. Cox regression analysis, at mean of the above-reported covariates, showed that JIA children with uveitis history and then flared only with arthritis (Mantel-Cox $\chi^2 = 20.39$, $p=0.009$), and JIA children who did not lengthen the interval of anti TNF administration (Mantel-Cox $\chi^2=26.82$, $p=0.001$) had a higher probability to relapse after treatment discontinuation.

Discussion

In order to properly customise JIA treatment, identification of timing and modality of drug withdrawal in JIA children is one of the current main focuses of research in paediatric rheumatology. Prolonged treatment is associated with cost, potential side effects and stress for the patients and their family. However, there is little understanding in which context medication may be safely with-

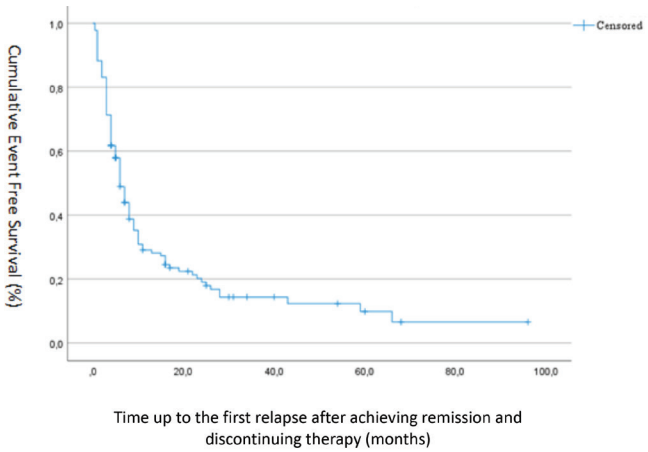

Fig. 1. Survival functions from Kaplan-Meier curve, showing the time up to the first relapse after discontinuing therapy among enrolled patients.

drawn, avoiding subsequently relapse and damages. Thus, identifying children who are candidates for stopping systemic therapy is critical to improve the clinical outcomes of patients.

In this study, we reported one of the largest cohorts of JIA children who stopped the first course of anti-TNF due to persistent inactivity on therapy. However, to overcome the heterogeneity of a JIA population including all the different JIA subtypes, the inclusion criteria to enrol JIA children made our population a quite homogenous population to be analysed. Therefore, the inferred conclusions may be overall generalised to other similar JIA population. In this homogenous cohort, four clinical risk factors for relapse have been identified: uveitis, age at onset, JIA type and, eventually, slower weaning of the drug.

According to the literature data, our study confirmed that most of the JIA children, roughly 80% in our study, relapsed within 12 months after stopping treatment.

However, in our cohort the proportion of patients who relapsed is higher compared to the other cohorts reported by Kearsley-Fleet *et al*. (55%) (8), Aquilani *et al*. (60%) (7), Gerss *et al*. (60%) (20), but similar to Iglesias *et al*. (82%) (21) and Klotsche *et al*. (77%) (22). A longer period of observation after drug withdrawal, and the characteristics of the selected population, with a high proportion of JIA associated uveitis, may possibly explain differences among our cohort and the ones with a lower rate of relapse. Other possible explanations for the higher rate of relapse in our cohort is the longer period of observation after drug withdrawal and the characteristics of included population that showed a high proportion of JIA associated uveitis and/or patients who stop therapy after the first course of biologic therapy. However, the inclusion criteria of our study were built, in order to have a more homogeneous group, we included only patients with oligoarticular and polyarticular JIA treated with the first anti-TNF. Our findings result in accordance with a recent systemic review that displayed that 60–83% of patients relapsed in the first 12 months (6, 7, 14, 23, 24). Nonetheless a selections bias may also be advocated, we defined strict inclusion criteria in order to judge and analyse a homogeneous JIA group: our data can therefore be considered representative for oligoarticular and polyarticular JIA children treated with the first course of anti-TNF-α.

According to our data, it seems that the time of relapse is driven by the duration of tapering rather than the modality of tapering, although lengthening the interval of administration may have an action in delaying the disease flare. This result is in agreement with a study performed in a small cohort of patients treated with etanercept who withdrawn the treatment due to persistent inactivity (25), although the majority of the available studies did not show significant differences between tapering *versus* abrupt drug discontinuation (7, 25, 26). The difference might be explained by the homogeneity of our cohort, including only oligo and poly JIA, and the longer follow-up compared to previous studies. Therefore, longer time to stop the drug withdrawal by lengthening the interval of administration might help in increasing the honeymoon of being free off therapy.

Additionally, our results about tapering therapy are in accordance with adult experience in rheumatoid arthritis, where a gradual discontinuation led to a reduced risk of flare (27) and also with Prince *et al*., who evaluated such protective role in a smaller cohort (14). However, other studies conducted in smaller cohorts than ours, did not find a significant protective action of drug weaning (7, 26). It cannot be excluded that this finding is merely due to the fact that lengthening the interval of administration was the most representative discontinuation strategy across the four paediatric rheumatology units of this study, although our statical approaches were adjusted by the sample size.

Conversely, no significant differences have been detected between JIA patients who relapsed keeping concomitant therapy versus those who discontinued it. Published data about this issue are quite controversial: Simonini *et al*. found a protective effect of methotrexate (4) for relapse, while Chang *et al*. found that patients who continued methotrexate while stopping anti-TNF flared more than who stopped methotrexate and continued anti-TNF (10).

Of note, we reported that a significant proportion of patients with JIA and uveitis relapsed after drug withdrawal. According to our cohort, uveitis results as independent predictors of relapse after drug withdrawal. Unfortunately, only few studies investigated this specific risk factor and a recent study by a Russian group highlighted uveitis as a risk factors for flare, even if it is not clear if on or off therapy (28). Nevertheless, several studies investigated risk of relapse in JIA associated uveitis and idiopathic chronic uveitis and they highlighted that rapid anti-TNF responders had more favourable outcomes than the others and lower risk of flare in children with longer inactive disease on therapy (5, 29).

According to Lovel *et al*. and Garcia-Fernandez, a younger age at JIA onset seems to be a higher risk of flare after drug withdrawal (13, 30), which might

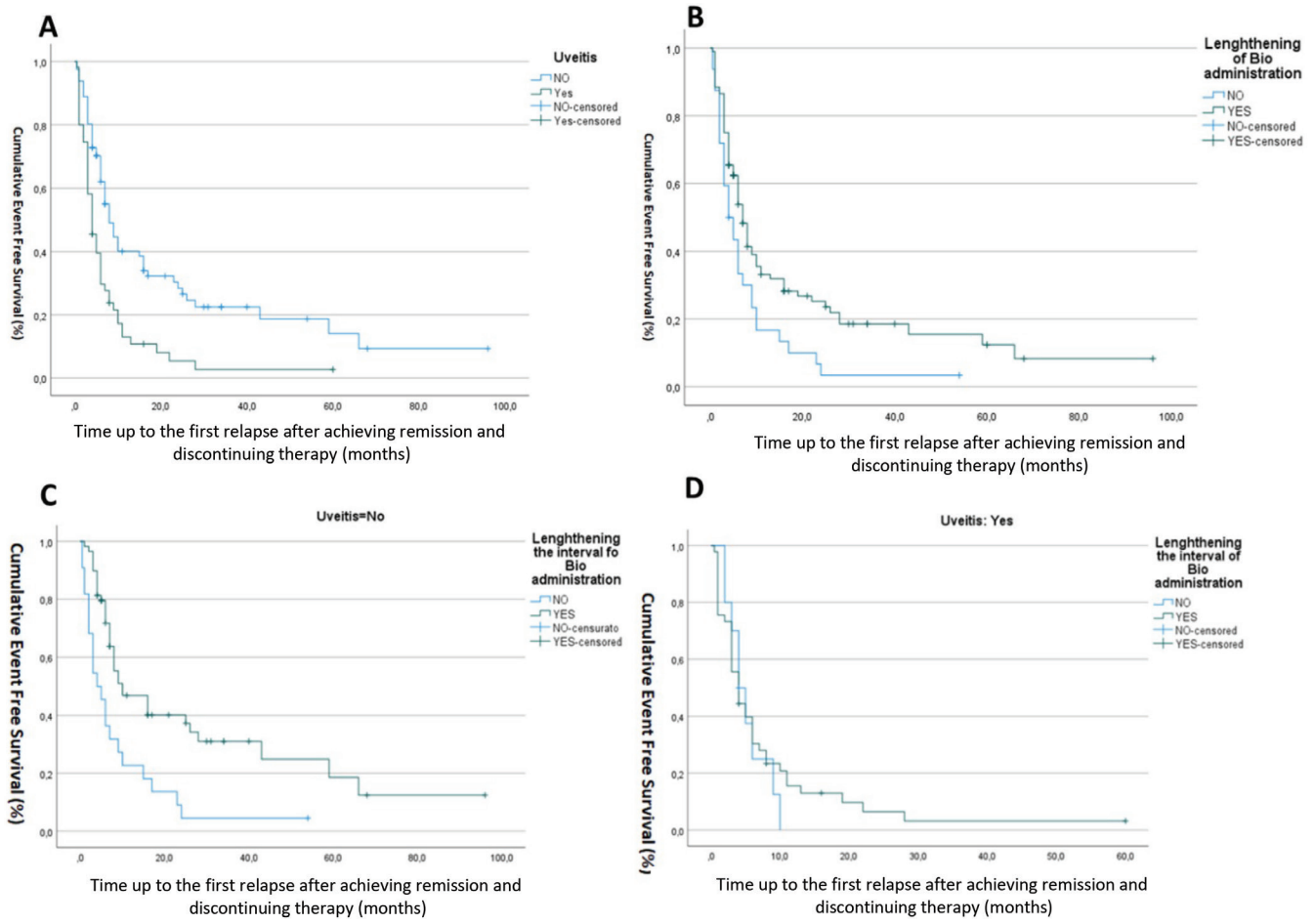

Fig. 2. A: Survival functions from Kaplan-Meier curves, showing difference in the time up to the first relapse after discontinuing therapy according to the history of uveitis (log rank χ^2=16.4 p<0.0001).
B: Survival functions from Kaplan-Meier curves, showing difference in the time up to the first relapse after discontinuing therapy according to the drug discontinuation modality (lengthening the interval of administration) (log rank χ^2=6.95 p<0.008).
C-**D**: Survival functions from Kaplan-Meier curves, showing difference in the time up to the first relapse after discontinuing therapy according to uveitis history and drug discontinuation modality (lengthening the interval of administration) (log rank χ^2=8.97 p<0.003).

suggest a more aggressive course of the disease with an early onset.

Surprisingly, our study and that by Garcia-Fernandez *et al*. are the only ones that have highlighted female sex as a risk factor for relapse out of therapy (30), while the others did not find a significant difference, with only one exception in which female sex had a protective action (7, 10, 11, 14, 16, 21, 25). ANA positivity seems to be one of the most common reported risk factors for relapse after drug withdrawal, in accordance also with our study, although in the studies that reported this specific predictor, no specific attention was given to uveitis history (2, 7, 11, 31). Since ANA positivity is highly represented in JIA with uveitis and JIA females, ANA autoantibody might not be an independent risk factor, but a risk factor associated to female gender and history of uveitis.

Several risk factors have been identified for relapse after drug withdrawal such as female sex, age at diagnosis, uveitis history, ANA positivity, presence of comorbidity, age at biologic initiation, the time intercourse between diagnosis and biologic initiation, the duration of weaning and the modality of stop therapy. However, after specific statistical corrections, several of these factors are not confirmed as independent risk factors for relapse in our cohorts.

We tried to investigate whether there was a difference in relapse out of therapy between the two most common anti-TNF used in JIA, but we were not able to identify a specific difference between adalimumab and etanercept even though the group of patients with uveitis were more likely to be treated with the former.

JIA patients with shorter duration of disease when anti-TNF treatment was started had a lower proportion of relapse. This is not surprising, considering the recent results of two studies, which showed better outcomes in children that received an early combined treatment with biologics, rather than the common step-up approach with disease modifying anti-rheumatic drugs (DMARDs) (32, 33). Unfortunately, neither of these two studies investigated whether there was a relationship with the risk of relapse when the drugs were stopped. However, it is important to underline that disease duration at the time anti-TNF treatment was started has not been confirmed in the analysis to identify independent risk predictors.

Additionally, we were not able to identify a specific duration of biologic treatment or duration of inactivity on treatment that distinguish patients who relapse from who maintain inactivity off therapy. Contradictory results come from the literature about this topic. In a recent work, it was reported that patients with JIA who received biologics (including etanercept, adalimumab, infliximab, anakinra, rituximab, and abatacept) for more than 2 years after achieving inactive disease had a higher probability of maintaining such inactivity off therapy (4). However, Su *et al*. and Lovell *et al* . highlighted the opposite, describing a higher proportion of patients with a longer period in clinical inactivity on therapy in the relapse group (13, 16). Additionally, Aquilani *et al*. showed in their cohort that even though the patients received etanercept for more than 2 years, up to 85% relapsed after drug withdrawal 7. Similar contrasting data are available about the time to achieve clinical inactivity on therapy (16, 22, 31).

Moreover, the results of a protective action of the category pOligo compared to polyarticular JIA and extended oligoarticular JIA for an earlier relapse might suggest a similar disease course of these two last JIA subtypes as recently proposed by the new classification of JIA (34).

Unfortunately, because of the retrospective nature of our study, we were not able to analysis specific novel biomarkers, we have just been able to conclude that common inflammatory indexes (ESR and CRP) at the time of biologic starting did not differ between patients who maintained inactivity and those who instead relapsed.

Intriguingly a recent study published by the Childhood Arthritis and Rheumatology Research Alliance Registry evaluated the disease recapture rates after medication discontinuation and flare. They showed across all the different subtypes of JIA a rate of 47–69%, with increased odds for patients treated with a biologic drug of successful recapture (24).

Apparently, we were not able to identify a specific duration of therapy with biologic as well as duration of remission on therapy to identify patients at higher risk of relapse; because of the low number of patients who received a short duration of therapy (5 patients with less than 12 months and others 6 with less than 18 months), we were not able to stratify the analysis.

Several caveats need to be discussed before drawing our conclusion. Firstly, the retrospective nature of this study might have led to missing data about the disease activity, and additional specific inflammatory biomarkers at the disease onset and at the time of biologic initiations. However, we were able to assess standard inflammatory biomarkers as ESR and common CRP, that are available in most of the laboratory. None of these were useful tool in predicting relapse after drug withdrawal. Additionally, another study limitation that we should consider is the sample chosen, only oligoarticular and polyarticular JIA, that did not allow us to make generalisation for all different subtypes of JIA, but only to these two subtypes, which, however, are the most represented subtypes of JIA. Additionally, a study limited to children who stopped treatment may be biased because it is not able to capture patients who flare during the tapering. Another aspect that we need to consider is that patients treated with biologics have a more aggressive disease and therefore flares are highly expected. Finally, we were not able to evaluate the recapture rates after flare. Moreover, we included 19 patients who relapsed for uveitis in isolation, but JIA is a systemic disease that includes arthritis as well as uveitis. However, when we corrected the regression analyses, excluding children who flared only with uveitis, the results did not change.

In conclusion, our study showed that up to 80% of patients treated with the first course of anti-TNF relapse after drug withdrawal. Uveitis, younger age at disease onset, duration of tapering, and pOligo JIA seem to be independent risk factors for relapse. Such a high proportion of patients relapsing after drug withdrawal, and the protective role of lengthening the time under treatment are key elements to properly discuss with the family the trade-off of discontinuing/keeping treatment, balancing risks, and benefits of the choice. Future studies combining clinical features and potentially helpful serum biomarkers might help us identify patients who can successfully stop systemic therapy and thus improve the clinical care of JIA children.

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