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Recurrence Risk in Pediatric Noninfectious Uveitis During Adalimumab Tapering: An International Multicenter Retrospective Study

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Objective. This study aims to assess the risk of noninfectious uveitis (NIU) relapse in pediatric patients undergoing adalimumab (ADA) tapering, evaluating potential predictors of such risk.

Methods. We conducted a multicenter retrospective cohort study involving pediatric patients with NIU who underwent ADA tapering due to inactive uveitis. Cox proportional hazards regression was used to analyze risk factors for NIU recurrence.

Results. The study cohort comprised 114 patients (65 girls; 57%). Most commonly, patients presented with juvenile idiopathic arthritis–associated uveitis (JIA-U) (52 of 114; 46%) or idiopathic uveitis (46 of 114; 40%). At ADA tapering, 46% of patients (53 of 114) experienced NIU recurrence after an overall median time of 30 weeks (interquartile range [IQR] 15–58 weeks) from the start of ADA tapering. Patients without recurrences were observed for a median of 70 weeks (IQR 48–98 weeks). Multivariate Cox regression analysis showed that a slower ADA tapering schedule was associated with a lower recurrence rate during the waning (hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.21–0.74; $P < 0.01$). Subgroup analysis of patients with JIA-U indicated that beginning ADA tapering after at least two years of disease inactivity significantly reduced recurrence risk (HR 0.65, 95% CI 0.43–0.95; $P = 0.05$). Among 59 patients (52%) who discontinued ADA, recurrence rates were similar between fast- and slow-tapering groups (21% vs 33%; $P = 0.6$), but median time to recurrence was shorter with fast tapering (10 weeks vs 37 weeks; $P = 0.05$).

Conclusion. This study highlights the significant clinical impact of ADA tapering on uveitis recurrence risk, recommending a gradual, slow-tapering approach with close monitoring.

INTRODUCTION

Noninfectious pediatric uveitis (NIU) is an inflammatory disorder affecting the uveal tract. It prevails in developed countries, with a childhood prevalence in the United States estimated at 29 per 100,000 persons and a worldwide prevalence of 3 per 10,000 children.[1] The majority of childhood uveitis is chronic anterior uveitis (CAU). Juvenile idiopathic arthritis (JIA), an umbrella term for a group of childhood arthropathies, is the most frequent systemic disorder accompanying

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CAU.[2–4] However, up to 40% of children with CAU never develop JIA.

Persistently active uveitis can result in various complications, including synechiae, glaucoma, cataract, band keratopathy, macular edema, and hypotony.[3,4] Prompt diagnosis and early implementation of steroid-sparing agents may reduce the risk of uveitis-related damage. Current treatment guidelines advocate for the early use of disease-modifying antirheumatic drugs (DMARDs) with methotrexate (MTX) as the first option.[5,6] Adalimumab (ADA), a fully humanized monoclonal antibody against tumor necrosis factor (TNF) α, is frequently administered to pediatric patients with NIU who do not adequately respond to MTX or cannot tolerate it.[7,8] Most patients achieve remission on ADA without experiencing recurrences while on treatment,[7,8] and the number of patients treated with ADA has progressively increased. The possibility of tapering and even withdrawing ADA in pediatric patients experiencing a prolonged period of persistent remission has been suggested.[9] Safety considerations, cost implications, and children's quality of life make this option rather appealing.[10,11]

However, there is a need for further insights about how to discontinue ADA in NIU, as available information is limited and derived from small cohorts.[12–18] This study aims to assess the risk of NIU relapse in pediatric patients undergoing ADA tapering, evaluating potential predictors of such risk.

MATERIALS AND METHODS

We conducted a multicenter retrospective cohort study involving 16 international tertiary centers located in various geographic regions: Europe (4 centers), North Africa (3 centers), the Middle East (2 centers), Asia (3 centers), Central America (1 centers), South America (2 centers), and North America (1 centers). Adherence to the Health Insurance Portability and Accountability Act of 1996 and the principles outlined in the Declaration of Helsinki were ensured. Approval was obtained from the institutional review boards (IRBs) of all authors' centers, following the requirements set forth by each center (approval IRB number of the leading center A-2022-042).

Patients were included based on the following criteria: a diagnosis of NIU before the age of 18 years, treatment with ADA for active NIU, ADA tapering due to persistently inactive uveitis, at least 26 weeks of quiescence, and a negative screening for infectious diseases such as hepatitis B and C, syphilis, and tuberculosis. At the initiation of ADA treatment, active NIU was characterized by at least one of the following: anterior chamber cell grade ≥1, one active inflammatory chorioretinal or retinal vascular lesion, or vitreous haze grade[19] ≥1. Exclusion criteria included incomplete data with loss to follow-up before ADA tapering; the need for weekly ADA to control uveitis, media opacity, or eye conditions hampering the assessment of inflammation activity; ADA tapering not being based on uveitis status; previous use of other biologic DMARDs; and side effects that forced ADA tapering or suspension despite active NIU.

Medical records from the rheumatology and ophthalmology departments from 2012 to 2022 were retrospectively reviewed. Data regarding demographic details (age at NIU onset, sex, race), diagnosis of underlying systemic disease, disease onset and duration, NIU anatomic classification, presenting best corrected visual acuity, clinical characteristics, and history of concomitant therapy other than ADA were collected.

ADA was administered subcutaneously every two weeks, and the dose was determined by the patient's weight (20 mg for patients <30 kg; 40 mg otherwise). Patients were deemed inactive when the anterior chamber cell grade and vitreous haze quality were ≤0.5, in the absence of active inflammatory chorioretinal or retinal vascular lesions or any topical steroid use. Patients with bilateral uveitis should fulfill requirements for inactivity in both eyes to be classified as inactive. In case of persistently inactive uveitis, ADA was tapered progressively by increasing the time between injections (spacing) according to the treating physician's clinical judgment. All enrolled participants began the ADA tapering after 2012. As reported in Table 1, 10 different tapering modalities were identified based on how frequently the interval between ADA injections was increased. For example, the interval between ADA injections could be increased by one week every month (class 1, the fastest tapering modality) or by one week every year (class 10, the slowest tapering modality). Given such wide heterogeneity, patients were subclassified into two groups based on the modality of ADA tapering: "fast tapering" (classes 1–4) and "slow tapering" (classes 5–10) (Table 1). The threshold was determined using a receiver operating characteristic curve analysis based on the Youden index. No change in the tapering class is anticipated. The goal of the taper is to discontinue the medication within two years, based on the treating physician's assessment.

Uveitis recurrence was defined as an increase in anterior chamber cell grade, vitreous haze, or new active inflammatory chorioretinal or retinal lesions compared to the visit when ADA tapering was started, either in one or both eyes during the

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Table 1. Tapering schedules of adalimumab

Tapering class (from fastest to slowest)	Tapering schedule[a]	Patients, n (%)	Patients with recurrences (n = 53), n (%)[b]
Fast tapering			
1	1 week every mo*	1 (1)	1 (100)
2	1 week every 2 mo	2 (2)	1 (50)
3	1 week every 3 mo	50 (44)	27 (54)
4	2 weeks every 4 mo	1 (1)	1 (100)
Slow tapering			
5	1 week every 4 mo	4 (3)	1 (25)
6	1 week every 5 mo	5 (4)	3 (60)
7	4 weeks every 6 mo	1 (1)	0 (0)
8	2 weeks every 6 mo	2 (2)	1 (50)
9	1 week every 6 mo	24 (21)	8 (33)
10	1 week every 12 mo	24 (21)	10 (42)

[a] The interval between adalimumab injections is increased by.
[b] The denominator is the number of patients in each tapering class.
* mo, months.

observation period. The date of NIU recurrence was recorded. The observation period of the study began with the first visit when ADA taper was initiated for the initial patients and ended at the latest visit for the most recently included patient.

This cohort included some patients who had also been enrolled in the Humira in Ocular Inflammations Taper study, in which only 28.4% of recruited patients were below 18 years of age. However, no specific subanalysis was conducted on children, thus preventing the drawing of definite conclusions about the impact of ADA tapering in the pediatric age group.[20]

Statistical analysis and data availability. Continuous variables were described as means ± SDs or medians and interquartile ranges (IQRs), whereas categorical variables were reported as percentages. Variations in continuous variables based on recurrence status were evaluated using the Mann-Whitney nonparametric test. As appropriate, relationships between categorical variables were examined by applying either the chi-square test or Fisher's exact tests.

To assess the incidence of NIU recurrence after the initiation of ADA tapering, Kaplan-Meier survival curves were drawn to plot the time from the beginning of ADA tapering to the first uveitis relapse. Patients without recurrences were censored at their latest follow-up visit. Risk factors for NIU recurrence were analyzed with Cox proportional hazards regression. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed. The assumptions of the proportional hazards model were validated by analyzing Schoenfeld residuals. $P \leq 0.05$ was considered statistically significant. Missing data were imputed using multiple imputation, assuming that the data were missing at random. Analyses were performed with R Studio (version RStudio 2021.09.2+382 for macOS). The data that support the findings of this study are available from the corresponding author (AM) upon reasonable request.

RESULTS

Study cohort and demographics. The study cohort comprised 114 patients (65 girls; 57%) with NIU treated with ADA. Demographic and clinical characteristics of included patients are presented in Table 2. The median age at disease onset was 5.6 years (IQR 3.3–10.2 years). Patients were aged 13 years (IQR 10–15 years) at the start of ADA tapering. White represented the most frequent race (74 of 114 patients; 65%), followed by Asian patients (13 of 114 patients; 10%).

Most commonly, patients presented with juvenile idiopathic arthritis–associated uveitis (JIA-U) (52 of 114; 46%) or idiopathic uveitis (IU) (46 of 114; 40%). Anterior uveitis was documented in half of the patients; panuveitis and intermediate uveitis accounted for 28% of patients (32 of 114) and 18% of patients (21 of 114), respectively. Twenty-two of 114 patients (19%) did not receive any concomitant DMARDs during ADA treatment; concomitant MTX at the beginning of ADA treatment was recorded in 70% of patients (81 of 114). Twenty-one of 114 patients (18%) received a course of systemic glucocorticoids, which was discontinued before ADA tapering began.

The median duration of NIU before the introduction of ADA was 30 weeks (IQR 9–104 weeks); the median duration of disease inactivity before starting the taper was 104 weeks (IQR 52–162 weeks). ADA tapering schedules and the related rates of recurrences are outlined in Table 1.

Recurrence rates and associated risk factors. In our cohort, 46% of patients (53 of 114) experienced NIU recurrence after an overall median time of 30 weeks (IQR 15–58 weeks) from the start of ADA tapering. Patients without recurrences were observed for a median of 70 weeks (IQR 48–98 weeks) since ADA tapering was started. In the whole cohort, the 40th percentile of time to recurrence was 55 weeks (Figure 1).

To manage uveitis relapse, the following treatment strategies were successfully implemented (data available for 44 of 53 patients): 12 patients were treated with topical steroids alone without modification of ADA regimen, 23 patients had changes in ADA frequency or resumed ADA, 4 patients underwent modulation of DMARD therapy, 3 patients received oral steroids, and 2 patients were switched to infliximab. Unfortunately, the time for recapture was not recorded.

In 54 patients, a fast-tapering modality was adopted, whereas physicians opted for a slow tapering of ADA in 60 patients. An association between the tapering schedule and the incidence of uveitis relapse was observed, with 56% of recurrences (30 participants) in case of fast tapering compared to 38% (23 participants) in those undergoing slow tapering ($P = 0.06$). ADA dose reduction over time, categorized into fast- and slow-tapering groups, is presented in Figure 2.

A subanalysis was conducted comparing the fast- and slow-tapering groups, revealing differences in diagnoses, time to initiate

Table 2. Demographic and clinical characteristics of the cohort*

Characteristic	Overall (N = 114)	No recurrences (n = 61 patients)	Recurrences (n = 53 patients)	*P* value
Age at onset, median (IQR), yr	5.6 (3.3–10.2)	6.7 (4.0–10.6)	4.6 (2.4–8.1)	0.02[a]
Age at ADA tapering, median (IQR), yr	13.0 (10.0–15.0)	12.0 (10.0–16.0)	13.0 (9.0–15.0)	0.81[a]
Sex, n (%)				0.85[b]
Female	65 (57)	34 (56)	31 (58)	
Male	49 (43)	27 (44)	22 (42)	
Race and ethnicity, n (%)				0.04[c]
African	7 (6)	5 (8)	2 (3)	
African American	1 (1)	1 (2)	0 (0)	
Arab	4 (4)	1 (2)	3 (6)	
Asian	13 (10)	12 (19)	1 (2)	
White	74 (65)	34 (55)	40 (75)	
Hispanic	9 (8)	6 (10)	3 (6)	
Mixed	2 (2)	1 (2)	1 (2)	
Missing	4 (4)	1 (2)	3 (6)	
Diagnosis, n (%)				0.51[c]
Behçet disease	6 (5)	5 (8)	1 (2)	
Idiopathic uveitis	46 (40)	22 (36)	24 (45)	
Juvenile idiopathic arthritis	52 (46)	28 (46)	24 (45)	
Tubulointerstitial nephritis and uveitis syndrome	4 (4)	3 (5)	1 (2)	
Vogt-Koyanagi-Harada disease	6 (5)	3 (5)	3 (6)	
Uveitis localizations, n (%)				0.98[b]
Anterior	58 (51)	31 (51)	27 (51)	
Other uveitis	56 (49)	30 (49)	26 (49)	
DMARDs on adalimumab, n (%)				0.47[c]
Azathioprine	4 (4)	2 (3)	2 (3)	
Colchicine	2 (2)	2 (3)	0 (0)	
Mycophenolate mofetil	5 (4)	3 (5)	2 (3)	
Methotrexate	79 (68)	38 (62)	41 (77)	
Methotrexate + azathioprine	2 (2)	1 (2)	1 (2)	
None	22 (20)	15 (25)	7 (13)	
Time from diagnosis to adalimumab treatment, median (IQR), mo	7 (2–24)	7 (2–25)	8 (2–15)	0.40[a]
Inactivity before adalimumab tapering, median (IQR), wk	104 (52–164)	102 (52–261)	104 (54–126)	0.72[a]

* ADA, adalimumab; DMARD, disease-modifying antirheumatic drug; IQR, interquartile range.
[a] Mann-Whitney nonparametric test.
[b] Chi-square test.
[c] Fisher's exact tests.

ADA, and inactivity before starting ADA tapering (see Supplemental Table 1). We then focused on the 59 patients (52%) who discontinued ADA during the study observation period (see Supplemental Table 2) after either a slow-tapering (30 patients) or a fast-tapering regimen (29 patients; $P = 0.6$). The rate of JIA was similar between the fast- and slow-tapering groups (31% vs 47%; $P = 0.5$). The incidence of recurrence was also comparable: 6 patients (21%) in the fast-tapering group and 10 patients (33%) in the slow-tapering group experienced uveitis relapse after ADA discontinuation ($P = 0.6$). Notably, the median time to recurrence was shorter in patients who underwent fast tapering: 10 weeks (IQR 8–14 weeks) in the fast-tapering group compared to 37 weeks (IQR 32–48 weeks) in the slow-tapering group ($P = 0.05$).

In our cohort, Kaplan-Meier survival curve for uveitis relapse did not reach the median (Figure 1A). Survival curves for recurrence based on tapering schedule, duration of disease inactivity for the entire cohort and patients with JIA, and JIA versus IU are illustrated in Figures 1B–E. Additionally, the Kaplan-Meier curve depicting patients who discontinued the drug based on tapering schedule is shown in Figure 1F. Initiating ADA tapering after at least two years of disease inactivity did not show any significant benefit in terms of uveitis recurrences for the entire group or for the IU subgroup. However, there was a significant difference when considering only patients with JIA (Figure 1D).

Univariate Cox regression analysis of the whole cohort showed that a slower ADA tapering schedule was linked to a lower recurrence rate (HR 0.49, 95% CI 0.28–0.87; $P = 0.01$). To note, the duration of inactivity before commencing ADA tapering, considered either as a continuous variable or categorized (more or less than two years of disease inactivity), did not impact the risk of recurrences in the whole cohort (Table 3). An increase of one year in age at disease onset was associated with a trend toward a lower risk of recurrence (HR 0.94, 95% CI 0.87–1.01;

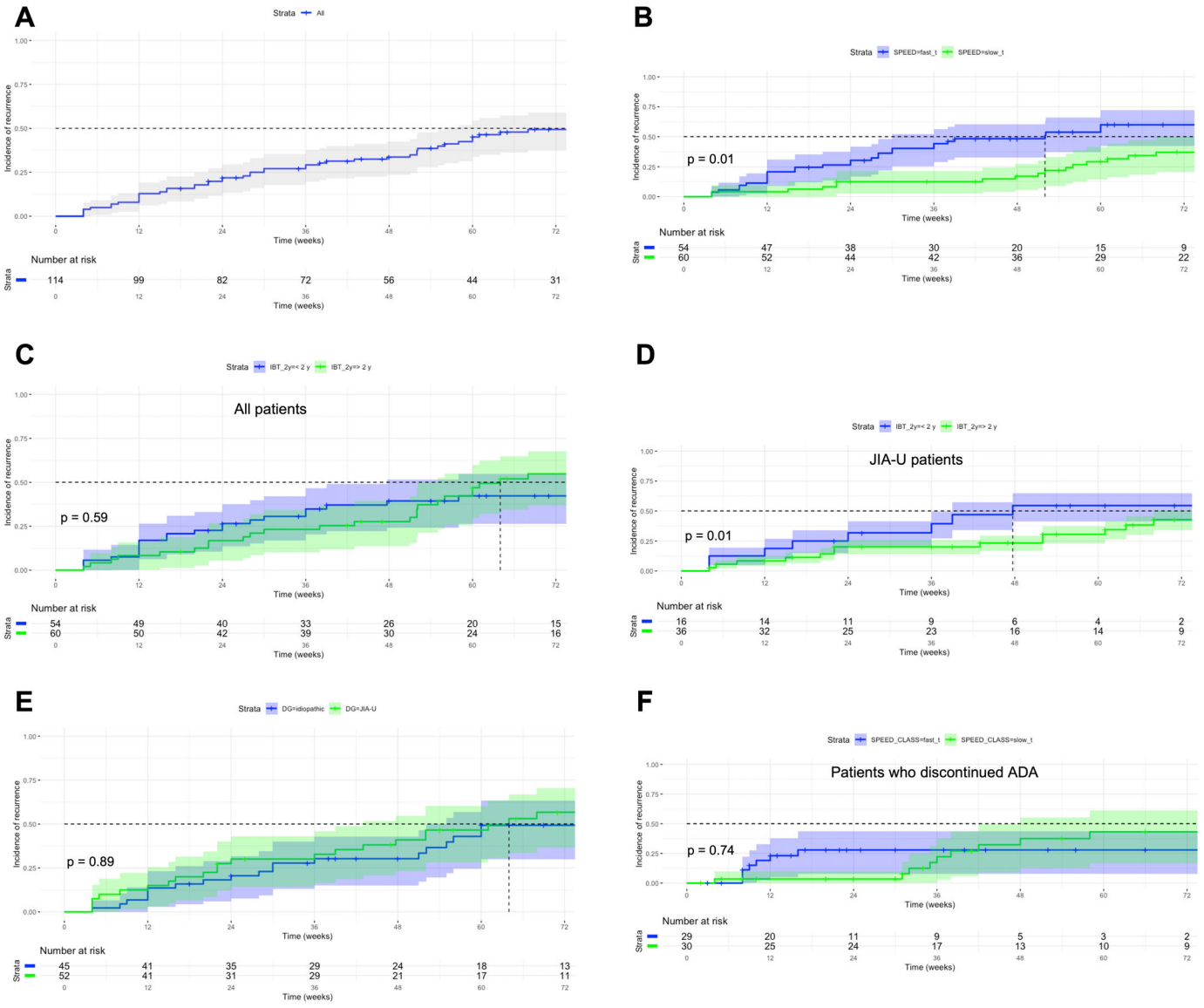

Figure 1. Kaplan-Meier survival curves were analyzed for relapse of (A) the whole cohort, based on (B) speed class, (C) idiopathic versus JIA-U, (D) initiating ADA tapering after at least two years of disease inactivity for the whole cohort, (E) for patients with JIA-U, (F) and speed class restricted to patients who discontinued the drug. The long-rank test is showed. ADA, adalimumab; DG, diagnosis; fast_t, speed classes from 5 to 10 (see Table 1); IBT, inactivity before initiation of adalimumab tapering; JIA-U, juvenile idiopathic arthritis–associated uveitis; slow_t, speed classes from 1 to 4 (see Table 1); SPEED, class of adalimumab tapering according to the speed.

$P = 0.11$). Importantly, in the adjusted model a slower ADA tapering was associated with a 60% lower recurrence risk than a faster tapering (HR 0.40, 95% CI 0.21–0.74; $P < 0.01$) (Figure 3).

Subgroup analysis: patients with JIA-U and IU. When a subgroup analysis of patients with IU and JIA-U was conducted, we found no significant differences in the median follow-up period (50 vs 52 weeks; $P = 0.9$), recurrence rates (51% vs 46%; $P = 0.6$), and time to recurrence (30 vs 30 weeks; $P = 0.7$) between the two groups. However, the JIA group had a longer median duration of inactivity before ADA tapering and a higher rate of slow taper (136 vs 96 weeks, $P < 0.01$; 67% vs 31%, $P < 0.01$, respectively).

When Cox regression analysis was performed for patients with JIA-U, it emerged that a slower ADA tapering schedule reduced the recurrence rate by half (HR 0.50, 95% CI 0.34–0.72; $P < 0.01$). This subgroup analysis indicates that with every one-year increase in age at uveitis onset, the risk of uveitis recurrences decreases by 10% (HR 0.90, 95% CI 0.86–0.94; $P < 0.01$). Furthermore, commencing ADA tapering after at least two years of disease inactivity showed a significant reduction in the risk of recurrence (HR 0.47, 95% CI 0.32–0.69; $P < 0.01$).

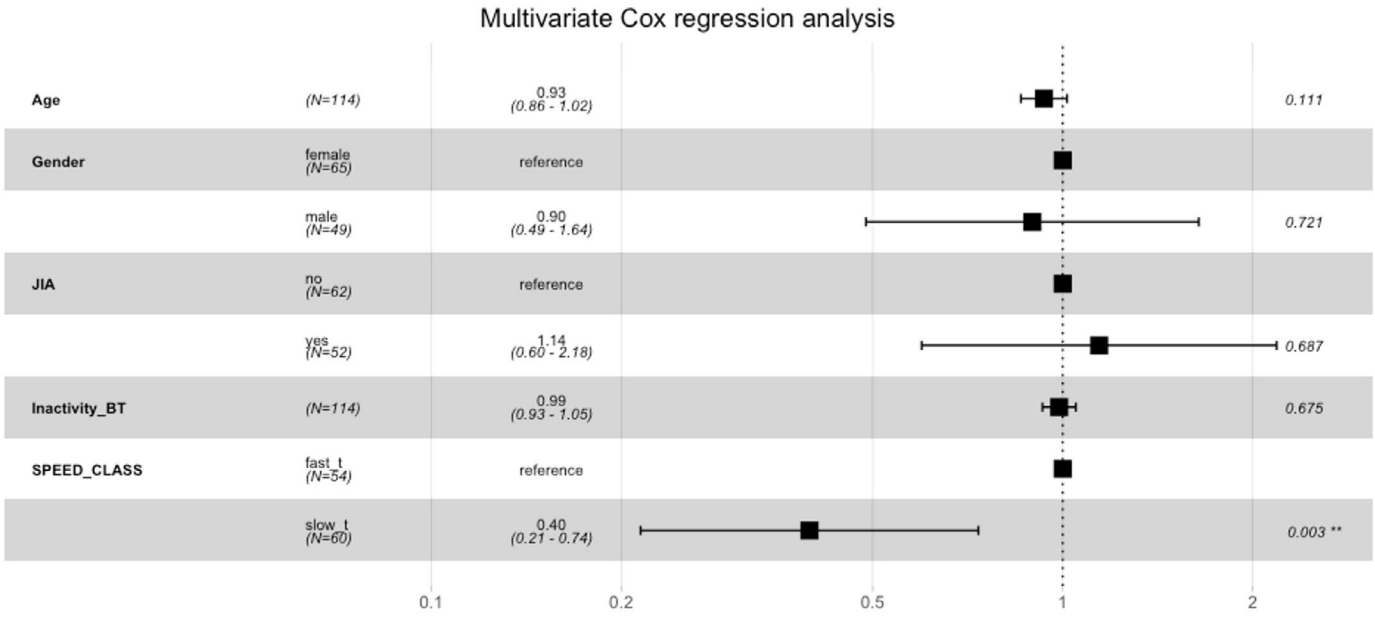

Figure 2. Multivariate Cox regression analysis assessing potential predictors of uveitis recurrence. Age: age at uveitis onset. The hazard ratio for Inactivity_BT reflects the risk associated with a 12-week longer period of disease inactivity before tapering. fast_t, speed classes from 5 to 10 (see Table 1); Inactivity_BT, inactivity before adalimumab tapering; JIA, juvenile idiopathic arthritis; slow_t, speed classes from 1 to 4 (see Table 1); SPEED_CLASS, class of adalimumab tapering according to the speed.

Multivariate Cox regression analysis revealed a reduced risk of recurrences in patients with JIA-U who began tapering ADA after at least two years of disease inactivity (HR 0.65, 95% CI 0.43–0.95, $P = 0.05$) (Supplemental Table 3). There was a lower risk associated with each one-year increase in age at the onset of uveitis (HR 0.92, 95% CI 0.88–0.96; $P < 0.01$). Adjusted analysis pointed out that a slower ADA tapering reduce the risk of uveitis relapse (HR 0.63, 95% CI 0.43–0.93; $P = 0.02$).

Table 3. Univariate Cox regression analysis assessing potential predictors of uveitis recurrence*

Characteristic	Hazard ratio (95% CI)	*P* value
Age at uveitis onset, yr	0.94 (0.87–1.01)	0.11
Age at ADA tapering (for every 10-yr increase), yr	0.79 (0.38–1.67)	0.54
Male sex (reference female)	0.83 (0.48–1.44)	0.51
JIA	1.25 (0.72–2.18)	0.42
Idiopathic uveitis	1.15 (0.66–2.01)	0.65
Anterior uveitis	1.24 (0.71–2.14)	0.45
Methotrexate	2.1 (1.07–4.10)	0.03[a]
Time from diagnosis to adalimumab treatment (for every 12-wk increase)	0.87 (0.72–1.06)	0.16
Inactivity before adalimumab tapering (for every 12-wk increase)	1.02 (0.98–1.05)	0.22
At least 2 yr of inactivity before adalimumab tapering	1.16 (0.67–2.01)	0.60
Slow tapering (reference fast tapering)	0.49 (0.28–0.87)	0.01[a]

* For slow- and fast-tapering schedules, see Table 1. ADA, adalimumab; CI, confidence interval; JIA, juvenile idiopathic arthritis.
[a] $P < 0.05$.

In patients with IU, adjusted Cox regression analysis showed that a slower ADA tapering schedule was associated with an 82% lower risk of recurrence compared to faster tapering (HR 0.18, 95% CI 0.06–0.59; $P < 0.01$). No other significant associations were found in the multivariate analysis of the IU group (Supplemental Table 4).

DISCUSSION

To the best of our knowledge, the present study is the first to investigate the impact of ADA tapering on the risk of uveitis recurrence in a large international cohort of children with NIU who had all been treated with ADA. In particular, approximately half of the patients experienced a recurrence of uveitis at a median time of seven months from the start of ADA tapering.

The rate of uveitis recurrence at ADA tapering we observed falls within the range previously reported in the literature. Indeed, available studies, all retrospective and with a small sample size, reported recurrence rates ranging between 43% and 69% in NIU after stopping immunomodulatory treatment, particularly within the first year after the medication discontinuation.[12–18] Nevertheless, we observed a lower relapse rate after complete ADA discontinuation compared to literature data. Importantly, none of these studies focused on ADA, with the majority assessing the recurrence rate after MTX discontinuation and few studies analyzing the effect of TNF inhibitor (TNFi) withdrawal (mainly infliximab).[12–18] Besides study treatments, the comparison of our results to those emerged in previous studies is also affected

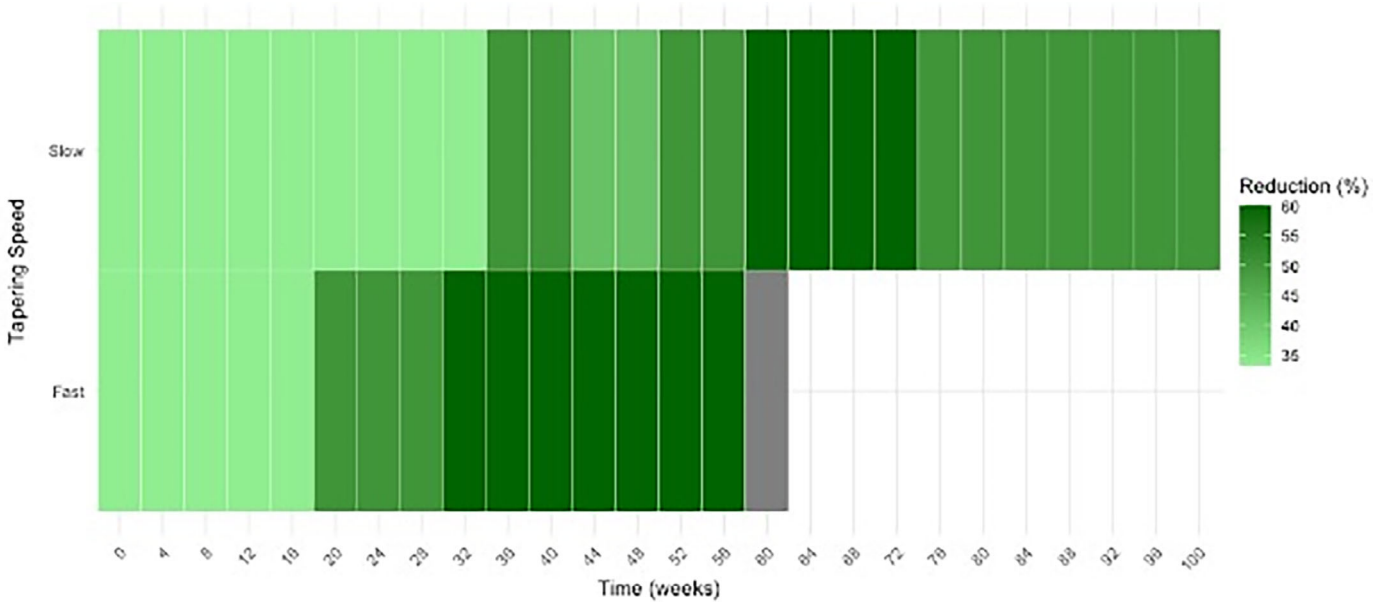

Figure 3. Adalimumab dose reduction over time. Notably, 30 patients in the slow taper group and 29 in the fast-taper group discontinued the drug. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.43165/abstract.

by differences in patients' inclusion criteria and length of follow-up.

We believe that the presented data will impact everyday clinical practice, being the first published evidence about the optimal modality to taper and discontinue ADA in NIU. Indeed, even though the recommendations on JIA-U treatment issued by the American College of Rheumatology suggest tapering DMARDs or TNFi after at least two years of well-controlled disease, there is no clear indication of how to pursue tapering.[6,12] Based merely on clinical experience, it is common practice to progressively increase the time between injections rather than abruptly discontinuing treatment.[17] Most importantly, our data provide clear evidence that the modality of tapering impacts the risk of uveitis relapse: a slow-tapering modality (ie, increasing the time between ADA injections by one week at least every four months, or even with a slower approach) was associated with a 60% reduction of the risk of uveitis after adjusting for several variables.

Importantly, we provide solid evidence to support the practical approach usually adopted in clinical practice to taper ADA after at least two years of disease inactivity, with a reduction of the risk of recurrences by more than one-third in patients with JIA-U. This finding highlights the importance of determining the optimal timing for tapering initiation in JIA-U, emphasizing the need for a more cautious approach in these patients.

A wide heterogeneity in predictors of uveitis recurrence has emerged across available studies. In the largest published cohort assessing uveitis relapse after treatment discontinuation including 94 patients with NIU (23 patients previously treated with ADA), variables associated with a reduced risk of relapse were a shorter time to reach the inactivity status (especially for those receiving a TNFi) and a diagnosis of IU rather than JIA-U.[16] The latter finding might be attributable to the different rates of TNFi use: 56% of patients with IU received TNFi compared to 39% of those with JIA-U. Notably, we found an equal rate of uveitis relapse between patients with JIA-U and IU (45%). Other studies have described several additional predictors of a lower relapse risk of uveitis: earlier onset of treatment, younger age at treatment start, previous use of infliximab rather than ADA, younger age at uveitis onset, use of MTX for more than three years before withdrawal, and two years of inactivity before MTX discontinuation.[12–17] We assessed the impact of age at uveitis onset on recurrence risk and observed a nonsignificant trend toward higher risk in younger patients across the entire cohort. Conversely, when the analysis was restricted to only patients with JIA-U, we found that the risk decreased significantly by 10% with each one-year increase in age at uveitis onset.

In contrast to other studies,[12,20] our analysis of the entire cohort did not find statistically significant evidence that the duration of inactivity before discontinuing ADA treatment affects the risk of uveitis reactivation. Nevertheless, participants who did not experience recurrences had a longer median duration of inactivity before attempting ADA tapering than those who recurred.

The subgroup analysis raises additional points for discussion. Tapering ADA after at least two years of disease inactivity is a significant factor in JIA-U but not in IU. Conversely, when comparing the IU and JIA-U groups, the tapering modality seems to be more important for patients with IU.

About half of the cohort discontinued ADA during the observation period. Among these patients, the rate of recurrences was comparable between fast- and slow-tapering groups. Nevertheless, patients in the slow-tapering group experienced a significantly longer relapse-free period, supporting the beneficial effects of this modality of tapering.

It is worth noting the potential negative impact of uveitis on the success of withdrawing biologic agents in patients with systemic disease. In a recent study involving 220 patients with JIA who discontinued biologic therapy, 54% of participants had to resume treatment after a median time of 4.7 months, and those with a history of uveitis had a more than two-fold higher risk of restarting treatment.[21]

The present study has several limitations that must be acknowledged, *in primis* its retrospective design. Furthermore, the international and multicentric nature of the cohort implies potential differences in the management of NIU among the included centers that, on the other hand, allowed us to compare various modalities of ADA spacing. The participation of tertiary centers could only convey a selection bias as the present cohort might not be representative of the whole spectrum of NIU but only of severe disease. It is important to consider that the tapering modality could affect the frequency of ophthalmologic follow-ups and, consequently, the possibility of detecting a recurrence. Individuals tapering off faster may attend follow-ups more frequently, increasing the likelihood of detecting a uveitis recurrence sooner rather than later. The tapering approach was based on the treating physician's clinical judgment. Some physicians continued treatment at extended intervals, whereas others discontinued therapy earlier.

We understand that the drug exposure time during tapering could be a potential confounding factor, translating into a higher drug exposure. We showed ADA dose reduction over time categorized into fast- and slow-tapering groups in Figure 3. However, the shorter time to recurrence after ADA discontinuation in the fast-tapering group together with the comparable rate of ADA discontinuation across the two groups points toward a true protective effect exerted by the tapering modality.

Despite the aforementioned limitations, this study offers valuable insights into a yet unexplored field. Tapering and discontinuing biologic agents in children with chronic diseases such as NIU represents a key target to limit socioeconomic costs and prevent unnecessary treatment exposition potentially leading to adverse effects, such as infections and malignancies. Although we have a clear understanding of when to initiate biologic agents, determining the optimal time and method for tapering treatment after achieving remission remains uncertain, without any prognostic biomarkers to stratify the risk of recurrence.

Randomized trials conducted in pediatric populations will establish the most effective approach to medication withdrawal. An ongoing trial, the Adalimumab in Juvenile Idiopathic Arthritis–associated Uveitis Stopping Trial (ClinicalTrials.gov identifier NCT03816397), may provide further insights.[22] This approach has raised solid evidence in adult rheumatology: a systematic Cochrane review analyzed 14 clinical trials, not evincing any significant difference in fixed-dose reduction of TNFi compared to the continuation of standard treatments in patients with rheumatoid arthritis. Moreover, disease activity–guided dose tapering of anti-TNF resulted in similar remission and disease activity percentages compared to therapy maintenance. On the other hand, patients who discontinued TNFi without tapering exhibited an increasing trend in disease activity and had minimal radiographic progression.[23]

In conclusion, our multicenter study clearly showed that the modality of ADA tapering exerts a great clinical impact on the risk of uveitis recurrence: it is recommended to taper ADA gradually and with a slow schedule, maintaining a strict follow-up given the high rate of relapse. Our data suggest that slow tapering translates into a longer relapse-free time, both during therapy reduction and after complete drug discontinuation. Importantly, we provide solid evidence to taper ADA after at least two years of disease inactivity in patients with JIA-U.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Marino confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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