Uveitis treatment in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry: response to tumour necrosis factor inhibitors

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Abstract

Objective

Treatment with tumour necrosis factor inhibitors (TNFi) has significantly improved outcomes in uveitis associated with juvenile idiopathic arthritis (JIA-U). This study examines a CARRA Registry cohort of JIA-U patients on TNFi to analyse utilisation patterns and identify factors associated with response.

Methods

This retrospective cohort study used CARRA Registry data for subjects aged 0–25 with JIA-U who had uveitis onset before the age of 19, and ever used TNFi. We collected data about demographics, uveitis courses, and treatment. We defined TNFi response and identified associated characteristics. As appropriate, comparisons between factors were tested using t-test, Chi-square, and Fisher's exact test. Multivariable logistic regression was used to model TNFi response.

Results

Among 871 JIA-U subjects, 616 (70.7%) used TNFi; 558 met inclusion criteria; 418 (74.9%) had successful treatment under TNFi. Among the 140 (25.1%) TNFi non-responders, 117 remained on TNFi and 23 discontinued. Multivariate analysis found significant TNFi success associations with White race (OR=2.08, p=0.005) and non-oligoarticular JIA (OR=1.58, p=0.044).

Conclusion

In this CARRA Registry cohort of patients with JIA-U, a large proportion used a TNFi for uveitis. The percentage successfully treated with TNFi is consistent with the current literature. White race and non-oligoarticular JIA were associated with a successful response to TNFi.

Key words

child, juvenile idiopathic arthritis, tumour necrosis factor inhibitor

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Introduction

Juvenile idiopathic arthritis-associated uveitis (JIA-U) is the most prevalent extra-articular manifestation JIA, affecting about 20% of children with JIA (1).

The presentation of JIA-U is often asymptomatic and associated with a chronic refractory course, leading to visually threatening complications such as cataracts, glaucoma, optic nerve oedema, and irreversible visual loss (2). JIA-U negatively impacts a child's quality of life and function. 3). Early detection and timely intervention are imperative for optimal disease management and preventing permanent visual impairment (3).

Once JIA-U is detected, treatment depends on disease severity and is similar to treatment for non-infectious idiopathic uveitis: initially with topical corticosteroids (CS) extending to various systemic immunomodulatory therapies (IMT). Methotrexate (MTX), a conventional IMT (cIMT), is the most common first-line systemic treatment. However, tumour necrosis factor inhibitors (TNFi) offer an effective steroid-sparing option for patients when MTX falls short (4).

Among TNFi, adalimumab, infliximab, golimumab and certolizumab pegol have also been used successfully with etanercept, the only non-monoclonal antibody TNFi, seeming to be the least beneficial (5-7). The most recent guidelines for JIA-U (published in 2022 by the Multinational Interdisciplinary Working Group for Uveitis in Childhood, MIWGUC) recommend monoclonal antibody TNFi after MTX failure (8).

Despite the transformative impact of TNFi in cIMT-resistant JIA-U, meta-analyses have shown that up to 13-18% of individuals on adalimumab and 28–44% on infliximab do not respond satisfactorily (9).

To characterise the response to TNFi in a large cohort of children with JIA-U, we utilised CARRA Registry data to investigate factors associated with TNFi response

Patients and methods

Study population

This is a cohort study utilising data from the CARRA Registry which includes data retrospectively and prospectively collected beginning in July 2015 (10). Parents/guardians of children and adolescents with rheumatic diseases, including JIA, are approached and consented for inclusion of the patient in the registry at CARRA sites in the US and Canada. For this study, approval was obtained from the University Of Minnesota IRB (FWA00000312). Subjects were included who were enrolled in the CARRA Registry before February 15, 2018 and followed through May 24, 2019. Inclusion criteria for JIA-U cohort are: age 0–25 years; JIA-U; and uveitis onset <19 years.

Data collection

We collected subject demographic data (age, sex, race, and annual household income), uveitis course (anterior chamber cells observed by slit lamp examination, steroid eye drops), and IMT treatment received, including medication initiation and cessation dates. In addition to the International League of Associations for Rheumatology (ILAR)-defined criteria for JIA as collected in the CARRA registry, we created an exploratory category: "spondyloarthropathy" restricted to psoriatic and enthesitis-related arthritis (ERA) subtypes. In this registry, categories for race and ethnicity are not mutually exclusive, and patients could self-identify as more than one race. All subjects who identified as White (alone or with another category) were included in the category "White." Annual household income was analysed as a categorical starting with less than $25,000 category then adding $25,000/year increments for the other categories up to $150,000 after which all incomes were grouped together. Subjects were considered to have used TNFi, if indicated for JIA-U or used after the diagnosis of JIA-U diagnosis. TNFi included etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol. Initial dose/frequency or change over time was not available for bIMT. If more than one TNFi used, we analysed the last oneMTX use was documented as used at any point prior to determining TNFi response.

Uveitis activity at the last visit on TNFi was defined by combining two data

variables: anterior chamber (AC) cells and the use of steroid eye drops. Active uveitis was defined as any AC cells at the last visit on TNFi or no uveitis at the last visit but on ≥3 drops/day. Quiescent uveitis was defined as no AC cells at the last visit on TNFi and not on ≥3 drops/day.

To define TNFi response as success or inadequate, we utilised both uveitis activity and the data field "reason for medication initiation" and "reason for medication discontinuation" (uveitis, arthritis, or other) to be more certain that the TNFi was used for uveitis. We defined "TNFi success" as discontinuing or remaining on TNFi with quiescent uveitis at the end of the study. We defined "TNFi inadequate response" as discontinuing TNFi due to active uveitis, side effects, subject adherence/financial concerns or remaining on TNFi but having active uveitis at the end of the study. For those subjects with "TNFi inadequate response."

For assessment of TNFi response, subjects were excluded for the following missing data regarding TNFi: start and stop dates; reason for start and/or stop; uveitis activity; or steroid eye drops at start and/or stop. Subjects who were excluded were reviewed manually by authors MMR and MAL, first independently and then a second time to reach consensus, to evaluate: 1) appropriateness for inclusion for which subjects must have had documentation of uveitis pre and post TNFi); 2) TNFi response (using a combination of indication for treatment, reason for stopping TNFi, along with previous and subsequent medication use). These patients were included in the TNFi response cohort if adequate data could be abstracted.

Statistical analysis

Descriptive statistics were summarised as means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Comparisons between groups were conducted using t-tests and either Chi-square or Fisher's exact test, as appropriate. A multivariable logistic regression model was fit to model TNFi success adjusting for patient age at uveitis diagnosis, sex, White race status, ANA status, and JIA category (non-oligo *vs*. oligo-arthritis). Sensitivity analyses were performed using more restrictive definitions of race, JIA category, and medication. Mediation analysis using the Baron and Kenny's procedure was conducted to explore mediators of TNFi outcome (11). All analyses were performed using the R statistical software (v. 4.1.0) with a pre-specified significance level of 0.05.

Table I. Comparison of demographics for those who used TNFi and those who did not.

	Used TNFi (n=616)	Did not use TNFi (n=255)	*p*-value
Age at diagnosis (years) mean (SD)	5.74 (3.66) *	5.67 (3.87) †	0.84
Sex			0.287
Female	475 (77.2%)	206 (80.8%)	
Male	140 (22.8%)	49 (19.2%)	
Race	100 (16.3%)	0.479	
Non-White ‡		36 (14.1%)	
White ‡	513 (83.7%)	219 (85.9%)	
JIA type			<0.001 §
Oligoarthritis	305 (49.5%)	165 (64.7%)	
Enthesitis-related arthritis	40 (6.5%)	7 (2.7%)	
Psoriatic arthritis	35 (5.7%)	6 (2.4%)	
Polyarthritis (RF -)	206 (33.4%)	63 (24.7%)	
Polyarthritis (RF +)	12 (1.9%)	0 (0%)	
Systemic arthritis	7 (1.1%)	6 (2.4%)	
Undifferentiated arthritis	11 (1.8%)	8 (3.1%)	
ANA status			0.291
Positive	384 (68.1%)	171 (72.2%)	
Negative	180 (31.9%)	66 (27.8%)	
HLA-B27 status			0.362
Positive	62 (20.3%)	18 (15.8%)	
Negative	243 (79.7%)	96 (84.2%)	
Has spondyloarthropathy			0.002
Yes	75 (12.2%)	13 (5.1%)	
No	541 (87.8%)	242 (94.9%)	

TNFi: tumour necrosis factor inhibitor; JIA: juvenile idiopathic arthritis; RF: rheumatoid factor; ANA: antinuclear antibody. Spondyloarthropathy: psoriatic and enthesitis-related arthritis subtypes grouped. * missing data on 74 subjects; † missing data on 37 subjects; ‡ all subjects who identified as White (alone or with another category); § Fisher's exact test used instead of Chi-Square test.

Results

JIA-U cohort and demographics

A cohort of 7,337 children and adolescents with JIA were included in this analysis, among which 871 (11.87%) were diagnosed with JIA-U with onset of uveitis before age 19 years. The average age at diagnosis was 5.72 years (SD 3.72) in the 760 subjects for whom diagnosis date was available. Most JIA-U subjects were female (78.11%), self-identified as White race (84.33%; missing data for 3), and ANA positive (69.28%; missing data for 70). The most common JIA subtype was oligoarticular (53.96%), followed by rheumatoid factor-negative polyarticular-JIA (30.88%).

TNFi use

Since being diagnosed with JIA-U, 616 of the 871 subjects (70.7%) had received treatment with TNFi. We compared demographic characteristics between subjects who had received TNFi and those who had not (*p*-value) (Table I). There was minimal variance in demographic attributes such as age at diagnosis, race, or ethnicity. However, the distribution of the JIA subtype was significantly different with TNFi use (p=0.001). Specifically, TNFi use was greater amongst those with spondyloarthropathy (p=0.002). Neither the distribution of ANA nor HLA-B27 positivity was statistically different, although HLA-B27 result was only available in only 48%.

TNFi response

We assessed TNFi response in 558/616 subjects due to missing data. The statistical algorithm could not determine

Table II. Demographics by TNFi response.

	TNFi inefficacy (n=140)	TNFi success (n=418)	*p*-value
Age at diagnosis (years) mean (SD)	5.49 (3.64) *	5.8 (3.76) †	0.412
Follow-up from diagnosis (months) mean (SD)	74.6 (55.25)	82.19 (46.72)	0.166
Sex			0.359
Female	113 (80.7%)	319 (76.5%)	
Male 27 (19.3%)	98 (23.5%)		
Race			0.032
Non-White	33 (23.6%)	63 (15.2%)	
White‡	107 (76.4%)	352 (84.8%)	
ANA status			0.403
positive	82 (64.1%)	262 (68.6%)	
negative	46 (35.9%)	120 (31.4%)	
HLA-B27 status			0.371
positive	10 (16.1%)	48 (22.4%)	
negative	52 (83.9%)	166 (77.6%)	
Has spondyloarthropathy			0.017
Yes	9 (6.4%)	61 (14.6%)	
No	131 (93.6%)	357 (85.4%)	
Methotrexate used any time prior to TNFi response§			0.971
Yes	90 (64.3%)	266 (63.6%)	
No	50 (35.7%)	152 (36.4%)	
JIA type			<0.001¶
Oligoarthritis	83 (59.3%)	197 (47.1%)	
Enthesitis-related arthritis	7 (5%)	33 (7.9%)	
Psoriatic arthritis	2 (1.4%)	28 (6.7%)	
Polyarthritis (RF-)	40 (28.6%)	145 (34.7%)	
Polyarthritis (RF+)	1 (0.7%)	8 (1.9%)	
Systemic arthritis	4 (2.9%)	0 (0%)	
Undifferentiated arthritis	3 (2.1%)	7 (1.7%)	
Oligoarthritis status			0.017
Oligoarthritis	83 (59.3%)	197 (47.1%)	
Non-Oligoarthritis	57 (40.7%)	221 (52.9%)	
Last used TNFi at TNFi determination			0.152¶
Adalimumab	84 (60%)	263 (62.9%)	
Certolizumab	0 (0%)	0 (0%)	
Etanercept	17 (12.1%)	69 (16.5%)	
Golimumab	0 (0%)	0 (0%)	
Infliximab	39 (27.9%)	86 (20.6%)	

TNFi: tumour necrosis factor inhibitor; ANA: antinuclear antibody; Spondyloarthropathy: psoriatic and enthesitis-related arthritis subtypes grouped together. JIA: juvenile idiopathic arthritis; RF: rheumatoid factor.

*missing data on 74 subjects; †missing data on 37 subjects; ‡all subjects who identified as White (alone or with another category); §Ever used methotrexate prior to assessment of TNFi response. ¶Fisher's exact test used instead of Chi-Square test.

response in 101 of the 616. Each of these 101 subjects' data underwent manual review for inclusion. Of these, 43 were included in the final 558 subjects. In 418 (74.9%; 95% CI [71.1%, 78.4%]), JIA-U was successfully treated with TNFi; in the other 140 (25.1%) JIA-U response was inadequate

In comparing TNFi success and inadequate response, the distribution of the JIA subtype was significantly different ($p<0.001$) (Table II). TNFi treatment in those with spondyloarthropathy was more often successful. Those identifying as White represented a higher proportion of those successfully treated with TNFi ($p=0.032$). To evaluate whether TNFi response was inadequate because of a shorter treatment time, the duration of the last used TNFi was assessed. TNFi use was of longer duration in the TNFi success than in the TNFi inadequate response group (24.8 months (± SD 19.9) *vs*. 20.2 (± SD 17.4), $p=0.022$). No significant differences were found in sex, age at uveitis diagnosis, or time since uveitis diagnosis. Neither ANA nor HLA-B27 was distributed differently amongst TNFi success or inadequate response groups. Most patients in both groups were treated with ADA as their last TNFi. Neither the distribution of specific TNFi last-used nor the number of prior TNFi used was different between those with TNFi success or inadequate response. Methotrexate had "ever been used" in a similar percentage of both groups.

In a multivariate logistic regression model (Table III), race (White/non-White) and JIA subtype (oligoarticular/non-oligoarticular) were significant factors for TNFi success, with White race and non-oligoarticular JIA as more likely to succeed (OR=2.08, $p=0.005$; OR=1.58, $p=0.044$ respectively). Age at uveitis diagnosis, sex, and ANA status were not significantly associated with TNFi success.

Description of treatments after TNFi inadequate response

Of the 140 subjects who met criteria for inadequate response, 117 (83.6 %) remained on TNFi with active uveitis at the end of the study, while 23 had stopped TNFi (16.4%). The duration of the last-used TNFi was not significantly different between those who remained on TNFi (median [IQR]: 14.5 [9, 27.9] months) and those who stopped TNFi (10 [4.3, 23.8] months) ($p=0.278$).

Of the subjects who stopped TNFi, 13 started on other medications within the year (data not shown).

Sensitivity and mediation analyses

Three sensitivity analyses were conducted: 1. treating race as only-White vs. non-White; 2. removing those with systemic JIA; 3. removing those with "last used TNFi" at determination was etanercept (the only non-monoclonal antibody TNFi). For each sensitivity analysis, the results for the multivariable logistic regression modelling TNFi success were compared to the primary results for changes in effect and statistical significance decision. In both sensitivity analyses (1) and (3) above, the association of non-oligoarticular with success lost statistical significance ($p=0.05$ and 0.051, respectively) (data not shown).

We explored whether household income could mediate the race and TNFi success relationship since race was associated with successful control of uveitis with TNFi ($p=0.024$) and race and in-

Table III. Multivariate logistic regression for successful control of uveitis under TNFi.

	Odds ratio	95% CI for OR	*p*-value
Age at uveitis diagnosis [years]	1.01	(0.95, 1.07)	0.757
Sex: male *vs*. female	1.32	(0.76, 2.28)	0.326
Race: White* *vs*. Non-White	2.08	(1.24, 3.46)	0.005
ANA status: negative *vs*. positive	0.76	(0.48, 1.21)	0.247
Non-oligo JIA *vs*. Oligoarthritis	1.58	(1.01, 2.46)	0.044

ANA: antinuclear antibody; JIA: juvenile idiopathic arthritis.
*All subjects who identified as White (alone or with another category).

come were associated ($p<0.001$) (data not shown). However, when both race and income were included in modelling TNFi success, the impact of race was not weakened by the inclusion of income ($p=0.2$). Under Barron and Kenny's procedure, this suggests that income is not a mediating factor in the relationship between race and TNFi success. As subtype was also statistically associated with treatment response, Chi-square testing was performed to assess co-linearity between race and subtype (oligo *vs*. other) using either the any-White or only White definitions, and there was no association ($p>0.9$) supporting that White race is independently associated with TNFi success in JIA-U.

Discussion

Our analysis of patients with JIA-U within a large multicentre registry underscores the integral role of TNFi in the JIA-U treatment hierarchy with 70% of JIA-U patients receiving TNFi and almost three-quarters achieving a period of steroid-sparing control. The most-used TNFi was adalimumab, with infliximab and etanercept used in similar frequencies.

Population-based studies on the prevalence of TNFi use in JIA-U patients are scarce. An analysis of the previous CARRA Legacy registry from 2010-2013 showed that 56% of 643 JIA-U patients received TNFi, compared to 71% in the current study (12). The lower rate in the earlier study might be due to data collection limitations, as information was only gathered up to the registry enrolment visit. Unlike previous research, our study compares patient-level factors between JIA-U patients treated with and without TNFi. The previous CARRA Legacy registry study identified cataracts and ANA positivity as predictors of TNFi use in a small cohort with idiopathic uveitis. The ANA finding was not replicated in our study, possibly due to differences between JIA-U and idiopathic uveitis. Cataract data were unavailable in our cohort.

Our study shows that adalimumab is this cohort's most frequently used TNFi, paralleling its popularity in clinical practice (13). In line with previous studies and despite its lower efficacy compared to monoclonal antibody TNFi, we found that etanercept continues to be used, suggesting that TNFi choice may be driven by individual patient profiles and clinician preference or experience

Our study analysing uveitis responsiveness to TNFi represents the largest cohort to date. The overall TNFi success rate, 74.9% (95% CI 71.1, 78.5), was higher than that estimated from a recent meta-analysis of 487 children with anterior uveitis, in which 62% had improved anterior chamber inflammation (14). Monotherapy with etanercept, a less effective treatment for uveitis, was more common in that study, likely contributing to the differences between the studies.

In our study, children with non-oligoarticular JIA were 50% more likely to maintain steroid-sparing uveitis control with TNFi treatment compared to those with oligoarticular JIA. In contrast, analysis of the German ICON-JIA cohort demonstrated that children with non-oligo-persistent JIA subtypes had lower odds of maintaining uveitis inactivity for over six months within a 2-year follow-up (when treated with any IMT), compared to those with oligo-persistent JIA, although, this finding was not statistically significant (15). To our knowledge, only one other study has investigated the association between the JIA subtype and response to TNFi. In that multicentre survival analysis of children with uveitis of any cause, children with oligo-JIA had a higher hazard of treatment success than did those with other subtypes (HR 5.93, 95% CI (2.15, 6.26)). The reason for the discordant association of oligo-JIA with TNFi success between this current and the previous study is unclear. It could derive from the much smaller cohort size of the previous study (38 subjects) relative to the present study (616 subjects). However, both studies had similar percentages of subjects with oligo JIA (47% *vs*. 50%) (16). Our findings highlight the potential differential response to TNFi therapy based on the JIA subtype, suggesting a tailored approach may be beneficial in managing JIA-U.

Our findings also reveal a demographic pattern and treatment response indicating a 2-fold higher odds of successful treatment amongst patients who identify as White. Very little work has examined the impact of race on response to therapy in uveitis. A single-centre study of children with uveitis demonstrated that non-Hispanic African American subjects (30% cohort) had worse uveitis outcomes (visual acuity and complications) than White children, even though they had relatively similar exposure to conventional and biologic DMARDs (17). In the multicentre cohort described above, Lerman *et al*. (16), race was not associated with treatment success under TNFi (HR 1.6, 95% CI [0.84, 3.05] (27% non-Caucasian). Our results may differ from the previous cohort because our study had less representation of non-White subjects (18%, compared to 27 %) or possibly because our study only included JIA-U.(16) This demographic finding should prompt further investigations into genetic, environmental, or socioeconomic factors that could influence treatment outcomes.

117 patients remained on TNFi despite inadequate response. We hypothesised that those who remained on TNFi with active disease may have had shorter duration of exposure to TNFi and were awaiting response. To assess this possibility, we evaluated the duration of the last-used TNFi and found that it was not significantly different between those who remained on TNFi (median [IQR]:

14.5 [9, 27.9] months) and those who stopped TNFi (10 [4.3, 23.8] months) (p=0.278) (data not shown). Conversely, it is possible that while response was inadequate providers were still unwilling to give up on TNFi due poor response to previous TNFi type or dose or due to lack of other treatment choices. The number of TNFi used, dose or frequency changes could not be assessed in this study. Data on disease severity or complications were not available. (18) As such, neither the degree of improvement in inflammation nor extent of protection from complications (visual deficits, cataract, glaucoma) could be analysed. The severity of uveitis and presence of pre-exiting complications may have impacted TNFi choice and dosing and this affected response. With this in mind, our study may be underestimating the beneficial effect of TNFi.

Our study encountered limitations, including incomplete data collection/entry, lengthy intervals between evaluations and lack of differentiation between race and ethnicity categories and lack of specificity of chronic or acute uveitis. The retrospective design contributed to gaps in clinical history and medication timelines. Clinical data were entered prospectively but diagnosis, co-morbid conditions, medication start and stop dates and indication for medication use were entered retrospectively for some subjects at enrollment. Because in some cases the eye examination data did not overlap with the historical medication data and diagnosis of JIA-U, TNFi response could not be determined in some subjects. The manual review enabled the inclusion of some additional subjects. In addition, 10% of subjects were excluded from the analysis of TNFi success due to inadequate data to determine if TNFi was discontinued due to arthritis or uveitis activity. Methotrexate use is standard of care in JIA-U, but we could not assess it as an outcome variable due to frequent stop and start dates. As these missing data should not be differential by response subgroup, we do not expect them to contribute to selection bias. A 6-month interval between visits may have missed transient uveitis episodes. The subjects were not identified as having acute *versus* chronic uveitis with the assumption that TNFi given for uveitis would imply a chronic course. Given that acute anterior uveitis is more common in spondyloarthropathy, it is possible that the increased response in that subgroup could be reflected by self-resolving uveitis. In our cohort, race and ethnicity were self-reported and not mutually exclusive so that subjects might fall into multiple categories. We analysed anyone who self-identified as White (which might overlap with Hispanic) *versus* those who did not identify as White. White race was associated with response to TNFi even in a sensitivity analysis in which those who chose multiple categories were excluded

In conclusion, this first analysis of JIA-U in the CARRA cohort identified a large proportion of patients treated successfully with TNFi, as expected. It revealed unanticipated variation in TNFi success based on JIA subtype and race. This study reinforces that TNFi can successfully treat JIA-U and is the standard of care in the hierarchical treatment of JIA-U. While there are consensus-based recommendations for the next steps when TNFi therapy is ineffective, more studies are needed to show the effectiveness of the newer medications beyond TNFi with continued attention to factors that may impact outcomes, such as race, JIA subtype, and ANA status. Given the rarity of JIA-U and subsequent difficulty with performing randomised clinical trials, innovative methodologies to analyse real-world data will be important in establishing effective treatments to improve long-term outcomes and quality of life for this vulnerable population.

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