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Implementation study of the CARRA Uveitis Consensus Treatment Plans: feasibility for clinical practice and applicability for research

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Abstract

Background Chronic anterior uveitis (CAU) carries a significant risk for eye complications and vision loss. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) introduced consensus treatment plans (CTPs) to standardize treatment for CAU and facilitate future comparative effectiveness studies. Two CTPs were developed to address: 1) initiation of methotrexate (MTX) in patients with CAU naïve to steroid-sparing therapy, and 2) initiation of a TNF inhibitor (TNFi) in patients with severe uveitis or uveitis refractory to MTX. We evaluated implementation of the uveitis CTPs using existing CARRA Registry infrastructure and assessed feasibility of the CTPs for comparative effectiveness research.

Methods This prospective observational cohort study was conducted at nine pilot sites between February 2020 and August 2022. Patients with JIA-associated CAU (JIA-U) were treated according to either the MTX or TNFi CTP. Uveitis activity and medication use were recorded at 0, 3, and 6 months. We assessed patient enrollment rates, CTP arm selection, uveitis control, and quality of data collection. We also evaluated CTP arm selection in a retrospective cohort of similar JIA-U patients enrolled in the CARRA Registry during the same study period.

Results Seventeen patients were included in the pilot cohort. Eight were treated with the MTX CTP (4 oral MTX, 4 subcutaneous MTX), and 9 with the TNFi CTP (9 received standard-dose adalimumab, none selected high-dose adalimumab or infliximab). Uveitis was controlled in 13 of 17 patients by 6 months. Query of the CARRA-wide Registry identified 42 patients with JIA-U who were treated according to the MTX or TNFi CTPs. Among these, 26 were treated with MTX (8 oral, 18 subcutaneous) and 16 with TNFi (12 standard dose adalimumab, 2 high dose adalimumab, and 2 infliximab).

Conclusion Both the MTX and TNFi uveitis CTPs can practically be implemented in clinical settings and are currently being utilized across Registry sites. However, in patients starting TNFi therapy, all pilot study participants and most

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patients across the CARRA Registry were treated with a standard dose of adalimumab. This consensus on the treatment approach underscores its broad acceptance but also limits the applicability of the uveitis TNFi CTP for comparative effectiveness research.

Keywords Uveitis, Juvenile idiopathic arthritis, Consensus treatment plan, Methotrexate, Adalimumab, Infliximab, Comparative effectiveness

Introduction

Chronic anterior uveitis (CAU) is an inflammatory eye disease often associated with ocular complications and vision loss if not treated promptly and effectively [1]. Limited clinical trial data in pediatric CAU has led to significant variability in treatment approaches among pediatric rheumatologists [2]. The relative rarity of pediatric rheumatic diseases such as CAU makes it challenging to conduct comparative effectiveness studies. In response to this challenge, the Childhood Arthritis and Rheumatology Research Alliance (CARRA), a network of 74 sites across North America, has developed consensus treatment plans (CTPs) for multiple childhood rheumatic conditions. These CTPs were created through a collaborative effort between pediatric rheumatologists, other pediatric subspecialists, researchers, and patient representatives. The CTPs, which typically offer 2 or 3 treatment options, have the dual purpose of establishing expert consensus on best care approaches and minimizing variability in treatment practices in order to enable future comparative effectiveness studies [3]. Therefore, most existing CTPs also define intervals and outcomes for disease assessment. Many CARRA CTPs also center assessments around existing data collection points within the CARRA Registry, leveraging an established longitudinal data repository of prospective data collected from over 13,000 children with rheumatic disease [4].

Although CTPs can help guide treatment options, experience with applying CTPs for comparative effectiveness research has yielded mixed results. Pilot studies evaluating the implementation of the scleroderma, lupus nephritis, and systemic juvenile idiopathic arthritis CTPs showed that selecting a treatment arm was primarily driven by provider or institutional preference with minimal dependence on individual patient factors [5–7]. While pseudorandomization by treatment provider is a benefit of CTPs, as it allows for outcomes assessment without having to adjust for confounding by indication, lack of individual variation can potentially lead to inadequate diversity in treatment arm selection. As an example, almost all providers in the lupus nephritis CTP pilot chose mycophenolate mofetil as maintenance therapy [5]. Medical insurance challenges, local drug availability, and cost may also limit treatment selections. Lack of treatment diversity can ideally be mitigated with increased participation from patients, providers, and more diverse sites. Additional challenges encountered in the application of the CTPs for comparative effectiveness analysis included enrollment difficulties, data gaps, and the need for disease-specific data variables beyond those captured in the CARRA Registry [5, 6, 8]. Examples of these variables include disease-specific patient-reported outcomes, disease-specific activity scores, and additional time points not captured through usual CARRA Registry procedures [9]. In these cases, data was required to be housed separately in parallel databases unique to each CTP study, and additional Institutional Review Board and informed consent protocols may have been necessary. These logistical and funding considerations may limit the utility of CTPs as comparative effectiveness tools.

In 2019, the CARRA uveitis workgroup developed two different CTPs for systemic therapy for patients with recently diagnosed CAU and uncontrolled CAU activity [10]. These CTPs address two possible scenarios: 1) initiating methotrexate (MTX) in patients with new CAU who are naïve to steroid-sparing therapy, and 2) introducing TNF inhibitor (TNFi) therapy in active CAU patients who are refractory to MTX, or in new CAU patients whose disease is severe. The MTX and TNFi CTPs each offer multiple treatment options/arms for their respective scenarios (Fig. 1). Although the uveitis CTPs were developed for both idiopathic and JIA-associated CAU, the CARRA Registry currently includes only patients with JIA-associated uveitis (JIA-U). The design of the uveitis CTPs aims to facilitate future studies by utilizing only data gathered through existing CARRA Registry infrastructure. We conducted a prospective pilot study at select CARRA sites to evaluate the feasibility of uveitis CTPs for comparative effectiveness research within the Registry by assessing data collection rates and treatment arm selection. We further performed a retrospective assessment of how JIA-U treatment practices across the CARRA Registry align with the published uveitis CTPs, comparing passive collection of data within the Registry to our prospective study.

Methods

Patient cohort

For the prospective study, patients with JIA-associated CAU (JIA-U) were prospectively enrolled in the CARRA

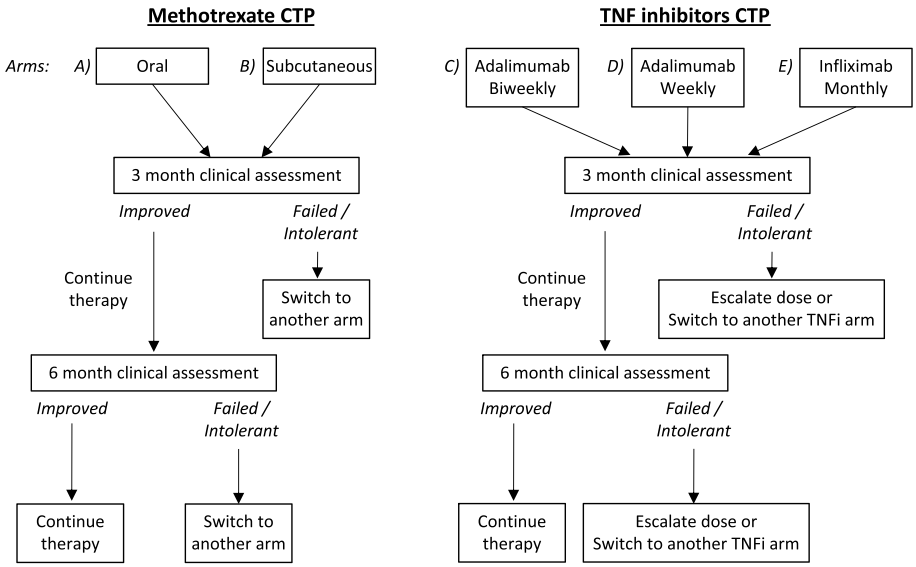

Fig. 1 Outline of uveitis consensus treatment plan algorithm. Flowchart depicting CTP algorithms. Dosing for methotrexate (MTX) is 0.5–1 mg/kg/week (maximum 30 mg). Adalimumab dosing is based on weight: 10 mg for 10 kg to < 15 kg, 20 mg for 15 kg to < 30 kg; 40 mg for > / = 30 kg. Dose escalation of adalimumab consists of doubling the biweekly dose if on 10 mg of 20 mg. Infliximab dosing starts at 6–10 mg/kg, with a recommended loading regimen of infusions at 0 and 2 weeks, followed by every 4 weeks thereafter. Dose escalation of infliximab is permitted up to maximum dose of 20 mg/kg

Registry at the pilot sites. Patients with JIA previously enrolled in the Registry who developed new JIA-U were also included in the analysis. The CARRA Registry collects data from patients with JIA-U but does not collect data from patients with other forms of CAU, including acute anterior uveitis, infectious uveitis, panuveitis, intermediate uveitis, posterior uveitis, retinal vasculitis, or uveitis associated with a systemic disease other than JIA. Our study cohort included patients 18 years old or younger with uncontrolled JIA-U who fit one of the two CTP scenarios described above. Patients with biologic therapy exposure within the 3 months prior to the study, contraindications to either MTX or TNFi therapy, pregnancy, or history of malignancy were excluded from this pilot study.

Prospective patients were assigned to a treatment arm within the CTPs through shared decision-making. Patients with newly diagnosed JIA-U and naïve to steroid-sparing therapy were managed according to the MTX CTP, with options of oral or subcutaneous (SQ) MTX (Fig. 1). Patients with ongoing uveitis activity despite MTX, or those who were intolerant of MTX, were managed according to the TNFi CTP, with options of standard-dose adalimumab, high-dose adalimumab, or infliximab (Fig. 1). Patients with severe uveitis, as assessed by the treating provider, were also considered eligible for the TNFi CTP even if they were MTX-naïve. Per the CTPs, the recommended dose for (MTX) is 0.5–1 mg/kg/week (maximum 30 mg) [10]. Standard adalimumab dose is based on weight: 10 mg for 10 kg to < 15 kg, 20 mg for 15 kg to < 30 kg; 40 mg for > / = 30 kg. Dose escalation of adalimumab consists of doubling the biweekly dose if on 10 mg of 20 mg. Infliximab dosing starts at 6–10 mg/kg, with a recommended loading regimen of infusions at 0 and 2 weeks, followed by every 4 weeks thereafter. Dose escalation of infliximab is permitted up to maximum dose of 20 mg/kg. Of note, the rate of infliximab infusion administration was not addressed in the original CTPs and the CARRA Registry only collects information on dose, not rate, of medication. As the CTPs were designed to utilize data gathered through existing CARRA Registry mechanisms, and the assignment was by patient and physician preference, no additional study consent was required beyond written consent to participate in CARRA Registry studies. Patients were enrolled from February 2020 through August 2022.

We also conducted a retrospective review of patients who were enrolled in the CARRA Registry and treated using one of the CARRA CAU CTPs (retrospective arm). They were identified based on the response to the data entry question, "Is the subject being treated according to CARRA CTP for uveitis?" at a Registry visit during the February 2020 and August 2022 enrollment period. Patients in this retrospective cohort were included in the study if their uveitis diagnosis date was within one year

preceding the visit, as these patients were thought to be less likely to be restarting a medication due to flare and more likely to fit the inclusion criteria for the prospective cohort.

Pilot site selection

We selected 9 pilot sites within the CARRA registry with established rheumatology and ophthalmology interdepartmental relationships to participate in this prospective cohort study: Boston Children's Hospital, Children's Hospital of Philadelphia, Children's Mercy Kansas City, Cincinnati Children's Hospital Medical Center, Connecticut Children's Medical Center, Duke Children's Hospital & Health Center, Nationwide Children's Hospital, Seattle Children's Hospital, and University of Utah Clinics at Primary Children's Hospital.

Data collection

Date of uveitis diagnosis, date of uveitis CTP selection, chosen CTP treatment arm, ophthalmologic examinations and other clinical and patient-reported outcome measures were collected using standardized CARRA Registry Case Report Forms (CRFs) at 0 and 6 months per the standard Registry protocol for both the prospective and retrospective cohorts. An additional 3-month study visit with data collection was performed in the prospective cohort at pilot sites to follow CTP guidelines recommending interval evaluation at 3 months.

Following completion of the enrollment period, a REDCap questionnaire was used for data validation for the prospective pilot study cohort (Supplemental Data 1). This data was collected from internal chart reviews conducted by individual site investigators and compared to data collected directly from the CARRA Registry. For retrospective analysis of the CARRA-wide cohort, only Registry data was utilized.

At the end of the study, principal investigators at each site completed a survey regarding the feasibility of enrolling JIA-U patients in the Registry and barriers to implementing the CTPs (Supplemental Data 2), including logistical, financial, and administrative challenges.

Outcomes

Our primary outcome was to determine whether the uveitis CTPs could be effectively integrated into the CARRA Registry, indicating their suitability for future utilization in comparative effectiveness research. We assessed integration by quantifying prospective enrollment rates, assessing the quality of data collection, and evaluating barriers to enrollment into the Registry.

Our secondary outcomes evaluated the variability in treatment arm selection and control of uveitis disease activity in patients treated according to the uveitis CTPs throughout the CARRA Registry.

Definitions

Uncontrolled CAU was defined as any of the following [10]: 1) ongoing CAU activity with 1 + grade or higher anterior chamber cells (a least 6–15 cells per 1 mm x 1 mm slit beam field) based on the Standardization of Uveitis Nomenclature (SUN) criteria [11] despite the use of topical steroids or if they were unable to adhere to or tolerate topical steroids, 2) worsening CAU activity while using topical steroids, 3) recurrent uveitis with taper of topical steroids to 2 drops a day or less, 4) development of new ocular complications attributable to inflammation or treatment during topical steroid therapy. Controlled CAU was defined as not requiring systemic steroids and using less than or equal to 2 drops per day of topical ophthalmic steroids with less than or equal to 0.5 + grade anterior chamber cells (1–5 cells per 1 mm x 1 mm slit beam field) by SUN criteria [11]. Patients with adequately controlled CAU also could not have any new ocular complications within the last 3 months. The study was not powered for and did not intend to focus on uveitis outcome comparisons.

Statistical analysis

We examined the enrollment and distribution of subjects among various treatment arms across participating sites in the CTP pilot study. Differences in patient demographics, including median age, sex, and JIA subtype, were determined by t-test, chi-squared analysis, and Fisher's exact test, respectively. Statistical significance in variability in the utilization of the CTP treatment arms among pilot sites compared to the CARRA registry was determined by a Fisher's exact test. Barriers to implementing the CTPs, including logistical, financial, and administrative challenges, were qualitatively assessed through descriptive analysis.

Results

CTP enrollment and implementation at pilot sites

At the end of the study period, 39 patients from pilot sites were recorded in the Registry as being treated according to a uveitis CTP (Fig. 2). Of these, only 17 (44%) were verified through REDCap data verification surveys as prospective patients initiating steroid-sparing therapy, as per our intended target population criteria (Fig. 2). The remaining patients were excluded because they were not naïve to steroid-sparing therapy. Examples include patients who had started MTX or TNFi before the enrollment period and patients who were re-starting medications after prior discontinuation and subsequent flare.

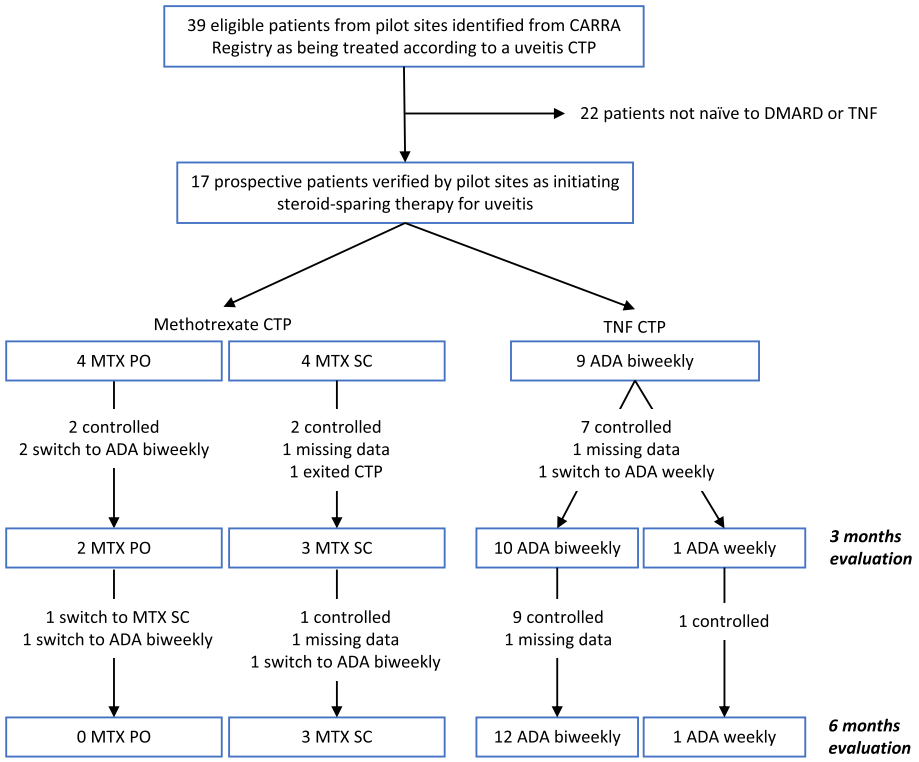

Fig. 2 Treatment arm selection of patients enrolled in CTP at pilot sites. Flowchart illustrating eligible patients identified from the CARRA Registry, prospective patients included in the study, their treatment arms, follow-ups and results at 3 and 6 months. MTX, methotrexate; ADA, adalimumab; PO, oral; SC, subcutaneous

Quality of prospective data collection

Data captured by the CARRA Registry for prospectively enrolled patients was less complete than the data reported by site investigators in the follow-up REDCap verification survey. At the 3-month follow-up, the CARRA Registry captured data from 9 of 17 (53%) prospectively enrolled patients from pilot sites, while REDCap verification by site investigators reported data from 15 (88%) of these patients ($p=0.02$, chi-square test). At the 6-month follow-up, data from 12 of 16 (75%) prospectively enrolled patients was captured by the Registry, while 14 (88%) of these patients had data reported in the REDCap verification survey ($p=0.36$, chi-square test).

Barriers to implementation at pilot sites

Surveys of the pilot site investigators reported several barriers to patient enrollment (Supplemental data 2). Five of 9 (56%) site investigators reported fewer JIA-U patients than expected during the study period; 4 of 9 (44%) reported having inadequate research coordinator support to identify and register eligible patients, and 3 of 9 (33%) reported that the COVID-19 pandemic was an obstacle due to in-person restrictions in both clinical and research settings. One investigator reported that ophthalmology dictated the follow-up schedule, creating difficulty with adherence to the CTP visit schedule. Otherwise, there were no reported difficulties with adherence to CTPs or Registry data collection.

Variability in treatment arm selection

Among the 17 verified patients in the prospective pilot cohort, 8 were entered in the MTX CTP (4 received oral MTX, 4 received SQ MTX, $p=1.0$, two-tailed exact binomial test against stochastic distribution) and 9 were entered in the TNFi CTP (all participants were started on adalimumab biweekly, $p=0.0001$, two-tailed exact binomial test against stochastic distribution) (Table 1 and Fig. 2). There were no significant differences between JIA subtypes, age of JIA diagnosis or age of CTP enrollment between the arms of the MTX CTP (data not shown). Further, there were no significant differences in baseline eye exam, vision, ocular complications or topical steroid drops usage between the arms of the MTX CTP at the time of entry (Supplemental Table 1). The recommended methotrexate dosing per the uveitis CTP is 0.5–1 mg/kg/week (maximum 30 mg), with a preference for doses closer to 1 mg/kg [10]. There was

Table 1 Demographics of patients treated according to uveitis CTPs

	Prospectively enrolled at Pilot Sites (*n* = 17)	Retrospective review of CARRA Registry (*n* = 42)	*p*-value
Median age at enrollment (years)	5.00	5.63	0.24[α]
Sex, female (%)	0.82	0.69	0.30[β]
JIA category (n)			0.02[δ]
- systemic	0	3	
- oligo	12	23	
- RF neg poly	0	9	
- RF pos poly	0	0	
- Psoriatic	2	2	
- ERA	3	1	
- Undifferentiated	0	4	
MTX CTP (n)			0.41[δ]
- oral MTX	4	8	
- SQ MTX	4	18	
TNFi CTP (n)			0.37[δ]
- standard dose adalimumab	9	12	
- high dose adalimumab	0	2	
- infliximab	0	2	

[α] t-test

[β] chi-square test

[δ] Fisher's exact test

no significant difference between average oral (0.72 mg/kg/week) and SQ MTX dosing (0.65 mg/kg/week, p = 0.70, two-tailed t-test). By 3 months, one patient exited the MTX CTP due to nonadherence to the treatment plan (Fig. 2). Two patients started in the MTX CTP had switched to the TNFi CTP (selecting standard-dose adalimumab), and 1 patient receiving standard-dose adalimumab in the TNFi CTP had switched to high-dose adalimumab by 3 months. At 6 months, 1 patient in the MTX CTP had switched from oral to SQ MTX, while 2 patients in the MTX CTP had switched to the TNFi CTP (selecting standard-dose adalimumab) (Fig. 2). After 6 months, none of the patients who started on oral MTX remained on this therapy, and 50% (4 of 8) of the original 8 patients enrolled in the MTX CTP had switched to a TNFi CTP.

Uveitis disease control

At the 3-month follow-up, CAU was controlled in 4 of 7 (57%) patients enrolled in the MTX CTP at pilot sites, while CAU was controlled in 7 of 8 (88%) patients in the TNFi CTP (Fig. 2). Of the patients who did not achieve disease control on the MTX CTP, 2 were receiving oral MTX, and 1 was receiving SQ MTX. At the 6-month follow-up, 75% of patients in the MTX CTP, all of whom were receiving SQ MTX at that point, and 100% of patients on TNFi CTP had achieved CAU control (Fig. 2).

CTP use across all CARRA Registry sites; retrospective analysis

We compared CTP treatment arm selection by patients prospectively enrolled at our pilot sites to those retrospectively collected in the CARRA-wide Registry. We queried the CARRA Registry for the same CRF question described above ("Is the subject being treated according to CARRA Consensus Treatment Plan (CTP) for uveitis?") and found that during the same enrollment period, across all sites, 170 patients were designated as receiving therapy per the uveitis CTP. Among these, 42 patients across 22 sites were listed as having uveitis onset within 1 year of the study period, and were thus considered to represent a comparable group to our prospective pilot study cohort, although we could not confirm whether medications were prescribed for CAU or JIA (Table 1). Of these 42 patients, 10 were also among the 17 patients in the prospective pilot cohort (Fig. 2). The remaining 7 patients from the prospective cohort were not captured in the retrospective CARRA-wide Registry query because they were either missing data on date of uveitis onset or had an onset date > 1 year prior to the date of study period. Patients with an earlier uveitis diagnosis may still have been eligible for the CTP at pilot sites due to uveitis flare, however. An example of a patient included in the pilot cohort but not in the retrospective data capture is a child with uveitis for > 1 year maintained on MTX, but starting TNFi due to

uveitis flare. This patient would be entering the TNFi CTP. Within the retrospective CARRA-wide cohort, 26 patients were treated per the MTX CTP and 16 were treated per the TNFi CTP, compared to 8 in the MTX CTP and 9 in the TNFi CTP at pilot sites ($p=0.39$, Fisher's exact test, Table 1). Providers across the Registry prescribed subcutaneous MTX more often as compared to the pilot sites, although this difference was not statistically significant (69% vs 50%, $p=0.41$, Fisher's exact test). Within the retrospective Registry cohort, there was also a trend towards presence of AC cells on ocular exam in patients receiving subcutaneous MTX (75% vs 40%, $p=0.29$, Fisher's exact test); however, there were too many missing data to determine whether this was significant or representative (Supplemental Table 2). A statistically greater proportion of patients within the retrospective cohort that were treated with TNFi received standard dose adalimumab (12 of 16, $p=0.0019$, two-tailed exact binomial test against stochastic distribution) compared to high dose adalimumab ($n=2$), and infliximab infusions ($n=2$) (Table 1). This preference for standard dose adalimumab was comparable to the pilot sites ($p=0.37$).

The age and sex demographics of the patients utilizing the uveitis CTPs CARRA-wide were similar to those in the pilot study (Table 1). However, there was a better representation of different JIA categories in the CARRA-wide retrospective cohort ($p=0.02$). While the majority (70%) of the prospective JIA-U patients enrolled at the pilot sites had oligoarticular JIA, with a few psoriatic and enthesitis-related arthritis patients, the retrospective CARRA-wide cohort included a wider breadth of patients with systemic JIA, RF-negative polyarticular JIA, psoriatic arthritis, and undifferentiated arthritis (Table 1).

Discussion

This is the first comprehensive assessment of the uveitis CTPs applied prospectively at 9 pilot sites within the CARRA Registry network. As CTP treatment arm selection and CAU activity outcomes could be assessed from data collected exclusively through the existing CARRA Registry protocol, implementation of the uveitis CTPs for comparative effectiveness studies is theoretically achievable with minimal external effort or funding. We conducted here a prospective, real-world assessment of the uveitis CTPs in practice. We found that while patients were treated per the uveitis CTPs at both pilot and non-pilot sites throughout the Registry, there were challenges related to patient enrollment and data collection at the designated follow-up time points.

Prospective patient enrollment fell short of our initial enrollment goal. The most common barrier reported was finding fewer eligible patients with JIA-U than expected. Factors that may have contributed to fewer eligible patients include fewer patients seeking care or following routine ophthalmology screening recommendations during the pandemic [12, 13], fewer JIA patients developing uveitis with earlier/more aggressive systemic therapy for arthritis [14–17], and a perceived shift from etanercept to adalimumab as the initial TNFi of choice for JIA [18]. Expansion of the inclusion criteria to all CAU, as intended by the original uveitis CTPs, could potentially improve enrollment; however, the current CARRA Registry is limited to CAU patients with JIA. Other barriers that may have affected patient enrollment included inadequate staffing to identify and register patients and logistical barriers due to COVID-19 pandemic restrictions in in-person clinical and research visits.

The CARRA Registry standard protocol for data collection includes time points for data entry at 0 and 6 months. We included an additional study visit at 3 months as an unscheduled visit recommended by the uveitis CTPs, but found that, even among pilot sites, this additional data entry into the Registry was missed in almost half of the cohort. For most of these patients, data was available in the patient record and later captured through the REDCap data verification survey. Similar challenges with data collection have been reported with other CTP pilot studies [6]. The rate of data capture in the Registry was much higher at the 6-month follow-up (75% of data was captured at 6 months vs. 53% at 3 months), speaking to the feasibility of using existing Registry infrastructure for CTP implementation if comparing 6 month outcomes. Our experience suggests that deviations from existing CARRA Registry protocols are difficult to enforce and may not be practical for comparative effectiveness studies that rely on additional data collection time points.

We also found that more clarity was needed around the original intention of the uveitis CTPs. Even among the pilot sites, multiple patients receiving MTX or TNFi therapy as continuing, rather than initial, therapy for uveitis were marked as being treated per CTP. This was mirrored throughout the CARRA Registry, as most of the patients recorded as receiving treatment according to the uveitis CTPs were receiving continuing therapy rather than initial therapy. We considered whether data from these patients could still be utilized for comparative effectiveness research; however, data from patients continuing therapy would not yield insight into how best to capture uncontrolled CAU. Alternatively, we considered whether data from patients continuing therapy could be utilized to compare flare rates. However, current Registry data collection does not specify whether medications are initiated for uveitis or arthritis activity. This limitation makes retrospective analysis of uveitis CTP implementation challenging. Interpretation of medication efficacy would be further confounded by the heterogeneous nature of the Registry population, which includes patients with

longstanding and refractory disease and those who have previously trialed multiple medication regimens. Notably, the original uveitis CTPs permit patients with "severe uveitis" to enter the TNFi CTP without having failed MTX first. This exception was included due to the tacit acknowledgement that insurance companies often base decisions on guidelines such as the CTPs, and the authors were concerned that the lack of an exception for severe disease could present a barrier to care. However, severe uveitis was not defined in that study and the inclusion of these patients in future CTP studies could represent a complicating factor for interpretation of outcomes. Future comparative effectiveness studies using the Registry will necessitate revision of the uveitis CTP utilization question to ensure that only patients meeting refined specific target population criteria are included, as well as clarification on whether medications were initiated specifically for uveitis activity.

Unexpectedly, all nine patients who enrolled in the TNFi CTP at pilot sites received the same treatment (standard dose, biweekly adalimumab), with none receiving high-dose adalimumab or infliximab. While our pilot cohort was relatively small, analysis of CARRA-wide treatment practices also revealed a strong preference for biweekly adalimumab, with 75% of patients in the TNFi CTP enrolled in this arm. This contrasts with previous findings from CARRA's Legacy registry, which showed much greater variability in TNFi usage [2]. Insurance regulations may in part drive this, as adalimumab is currently the only biologic medication approved by the Food and Drug Administration for pediatric uveitis. Since the CTPs were initially developed, the American College of Rheumatology/Arthritis Foundation and the Canadian Rheumatology Association have released uveitis treatment guidelines that did not specify a preference for a particular TNFi [19, 20]. However, there now appears to be a greater consensus amongst the community, as demonstrated by the Multinational Interdisciplinary Working Group for Uveitis in Childhood, who recently unanimously recommended adalimumab over infliximab for patients with CAU refractory to MTX [21]. Such strong consensus presents limits for future comparative effectiveness studies using the TNFi CTP to address the question of initial therapy. Future iterations of the CTP may need to address questions with less consensus, such as medication selection after TNFi failure.

Although this study was not intended to address the question of efficacy, it is important to note that outcomes in our small cohort were generally favorable. Among the 17 patients prospectively registered in the study, at least 13 had achieved CAU control within the first six months. Of the remaining four, one case remained uncontrolled, two had missing data, and one patient exited the CTP before 6 months. Detecting subtle differences in treatment efficacy between treatment arms will require a substantially larger sample size. This observation aligns with the original presumption of clinical equipoise upon which the CTP design was based but also suggests additional challenges to the utility of CTPs in the context of comparative effectiveness research.

Conclusion

We show that it is feasible to implement and collect data on the treatment algorithms outlined in the uveitis CTPs and assess outcomes through the CARRA Registry. However, our pilot study revealed inadequate data completion particularly at the 3-month follow-up time point and highlighted that the TNF inhibitor CTP in its current state was not useful for.

research, as all patients were treated according to the same treatment arm. Notably, the ubiquitous use of standard-dose adalimumab as the primary choice for TNFi therapy aligns with new recommendations from international working groups dedicated to uveitis treatment in children [21] and further illustrates how CARRA CTPs have served as treatment guidelines for the pediatric rheumatology community. Our findings underscore the need for a practical evaluation of CTPs in real-world settings as the lag between CTP development and implementation, with interval standardization of care, can ultimately make it more difficult to conduct comparative effectiveness studies.

Abbreviations

CARRA	Childhood Arthritis and Rheumatology Research Alliance
CAU	Chronic anterior uveitis
CTP	Consensus treatment plan
JIA	Juvenile idiopathic arthritis
JIA-U	Juvenile idiopathic arthritis-associated uveitis
MTX	Methotrexate
SQ	Subcutaneous
TNFi	Tumor necrosis alpha inhibitor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12969-024-01022-x.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

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Authors' contributions
MSL, FBS developed the study and methodology. MSL, MHC, and FBS analyzed the data and drafted the manuscript. MAL, SAH, and AMC provided critical revisions for the manuscript. All the authors have read and approved the final manuscript.
This study utilized data collected in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. The views expressed are the authors' and do not necessarily represent the view of CARRA.

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Availability of data and materials
The data described in this study are available from Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of CARRA.

Declarations

Ethics approval and consent to participate
This study has been exempted from review by the Institutional Review Board at Boston Children's Hospital.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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