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ORIGINAL ARTICLE

Childhood Arthritis and Rheumatology Research Alliance Consensus Treatment Plans for New-Onset Polyarticular Juvenile Idiopathic Arthritis

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Objective. **There is no standardized approach to the initial treatment of polyarticular juvenile idiopathic arthritis (JIA) among pediatric rheumatologists. Understanding the comparative effectiveness of the diverse therapeutic options available will result in better health outcomes for polyarticular JIA. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed consensus treatment plans (CTPs) for use in clinical practice to facilitate such studies.**

Methods. **A case-based survey was administered to CARRA members to identify the common treatment approaches for new-onset polyarticular JIA. Two face-to-face consensus conferences employed modified nominal group technique to identify treatment strategies, operational case definition, end points, and data elements to be collected. A core workgroup reviewed the relevant literature, refined plans, and developed medication dosing and monitoring recommendations.**

Results. **The initial case-based survey identified significant variability among treatment approaches for new-onset polyarticular JIA. We developed 3 CTPs based on treatment strategies for the first 12 months of therapy, as well as case definitions and clinical and laboratory monitoring schedules. The CTPs include a step-up plan (nonbiologic disease-modifying antirheumatic drug [DMARD] followed by a biologic DMARD), an early combination plan (nonbiologic and biologic DMARD combined within a month of treatment initiation), and a biologic only plan. This approach was approved by 96% of the CARRA JIA Research Committee members attending the 2013 CARRA face-to-face meeting.**

Conclusion. **Three standardized CTPs were developed for new-onset polyarticular JIA. Coupled with data collection at defined intervals, use of these CTPs will enable the study of their comparative effectiveness in an observational setting to optimize initial management of polyarticular JIA.**

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatologic disease, with prevalence estimates ranging from 1–4 per 1,000 children, similar to the prevalence of type 1 diabetes mellitus (1,2). The term JIA describes a clinically heterogeneous group of diseases characterized by arthritis that begins before age 16 years and persists for a minimum of 6 weeks. The majority of

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Significance & Innovations

- There is significant variability in the treatment of new-onset polyarticular forms of juvenile idiopathic arthritis (JIA) among pediatric rheumatologists in the US and Canada.
- The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed consensus treatment plans (CTPs) for new-onset polyarticular JIA.
- These CTPs will facilitate large-scale comparative effectiveness studies through observational registries such as the CARRA Registry.

children with JIA have a polyarticular form of the disease, defined as arthritis in >4 joints during their disease course. For the purposes of consensus treatment plan (CTP) development, polyarticular JIA refers to all JIA with >4 joints involved (cumulatively), excluding children with systemic JIA. This group therefore includes children with rheumatoid factor (RF)–positive and RF-negative polyarticular JIA, extended oligoarticular JIA, and children with enthesitis-related arthritis (ERA), psoriatic, or undifferentiated JIA who have >4 joints involved. Children with polyarticular JIA have a particularly refractory disease course compared to those with fewer joints, with longer periods of active disease that places them at higher risk for joint damage, decreased quality of life, and poorer functional outcomes (3,4). As with all categories of JIA, the objectives of polyarticular JIA treatment are to achieve clinical inactive disease and to prevent long-term morbidities, including growth disturbances, joint contractures and destruction, functional limitations, and blindness or visual impairment from chronic uveitis (5).

A variety of therapies are currently used in the treatment of polyarticular JIA, including both nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDs). Etanercept, adalimumab, tocilizumab, and abatacept are each approved by the Food and Drug Administration (FDA) specifically for polyarticular JIA. However, FDA approval for these drugs is restricted to children who are at least age 2 years (etanercept, tocilizumab), 4 years (adalimumab), or 6 years (abatacept). The initial trials of these medications were designed to obtain regulatory approval, included placebo comparators, and required children to have previously failed additional DMARD therapy (6–8). Subsequent studies have varied in study design and inclusion criteria, making the comparison of medication effectiveness between studies difficult (9). As a result, the comparative effectiveness and safety of these medications is not known, and data are not available regarding the optimal timing of introduction of these medications during the disease course, the optimal combinations of biologic and nonbiologic DMARDs, and the relative effectiveness of these medications among JIA categories. In the absence of these data, there is wide variation in treatment practices among pediatric rheumatologists.

Large, multicenter randomized controlled trials (RCTs) capable of comparing the efficacy of treatment regimens for polyarticular JIA have limited feasibility because of the relatively low prevalence of the disease and the financial and logistical constraints associated with traditional RCTs. Observational studies, and comparative effectiveness research (CER) methodologies, specifically, are likely to be more efficient and feasible to execute in such a patient population. These methodologies are central to generating data regarding the relative effectiveness of the available treatments in order to optimize care for children with polyarticular JIA. A novel approach to conducting CER is to implement CTPs within the setting of an observational patient registry in order to reduce treatment variability and allow for comparisons of effectiveness (10). The Childhood Arthritis and Rheumatology Research Alliance (CARRA), a North American organization of pediatric rheumatologists who have joined together to facilitate research in these diseases, has developed a multicenter registry of pediatric rheumatic diseases, which can be used for this purpose. To date, members of CARRA have collaborated to develop CTPs to facilitate CER in the following diseases: systemic JIA, juvenile dermatomyositis, lupus nephritis, and localized scleroderma (11–15). The objective of this current project was to use consensus methodology to develop CTPs for polyarticular JIA for subsequent implementation within the context of the CARRA Registry.

MATERIALS AND METHODS

The CTPs were developed through a combination of approaches, including surveys of the CARRA membership and face-to-face meetings using modified nominal group techniques (NGTs) to attain consensus. The face-to-face meetings were conducted at CARRA Annual Scientific Meetings held in June 2011, April 2012, and April 2013.

Initial CARRA membership survey. An electronic, case-based survey of the entire CARRA voting membership was conducted in May 2011 to identify the most commonly used treatment approaches for new-onset polyarticular JIA. The survey addressed the treatment of moderate to severe polyarticular JIA (defined as a physician global assessment of 4–7 on a 10-point numerical rating scale, with 10 representing the most severe disease) and included patients with RF-negative polyarticular JIA, RF-positive polyarticular JIA, ERA with or without sacroiliitis, and psoriatic JIA. Subsequently in the consensus

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process, however, a numerical rating of disease activity was not employed to define the patients for whom these plans would be considered. Participants were asked to provide information about which medications they would use as initial therapy and which medications they would use as subsequent therapy, in the case of inadequate response or no response to the initial therapy.

First face-to-face meeting. The June 2011 CARRA Annual Scientific Meeting was used as an initial working consensus meeting to begin the process of refining and converting the survey results described above into CTPs. Data from the Trial of Early Aggressive Therapy in Polyarticular JIA (TREAT) and the Aggressive Combination Drug Therapy in Very Early Polyarticular JIA (ACUTE-JIA), both of which tested tumor necrosis factor α (TNFα) inhibitors as first-line therapy for polyarticular JIA, were also specifically reviewed (16,17). The group was divided into 3 smaller groups and a modified NGT and consensus approach were followed to agree on elements of the operational case definition and general approaches to developing the CTPs.

Role of the core workgroup. A core workgroup of pediatric rheumatologists with specific interest in the treatment of polyarticular JIA was convened following the 2011 CARRA meeting. The polyarticular JIA CTP core workgroup subsequently met regularly via teleconference throughout the process of CTP development. The workgroup was tasked with using the survey data and results of the initial face-to-face meeting to define preliminary aspects of the treatment plans, including the inclusion and exclusion criteria, the definition of primary and secondary outcomes for efficacy and safety, the interval between monitoring radiographs for joint damage, reasonable/feasible patient assessment intervals, and the definition of when patients should be considered discontinued from the CTP. The core workgroup examined the indications, dosing, and safety monitoring for the medications used in treating polyarticular forms of JIA based on considerations from the published literature, including manuscripts from the rheumatoid arthritis literature when relevant. This work led to the development of the initial draft CTPs that were presented to the CARRA JIA research committee at the 2012 CARRA Annual Scientific Meeting (see below). Following the 2012 meeting, the workgroup continued to meet regularly to refine and finalize the CTPs.

Additional face-to-face meetings. At the 2012 CARRA Annual Scientific Meeting, members of the CARRA JIA research committee were divided into 4 groups, each led by members of the core workgroup, to ensure active participation by all members of the committee. Each group was tasked with in-depth review of the preliminary CTPs, case definition, medication dosing and monitoring plans, and the primary and secondary end points. Each group provided feedback to the group at large regarding areas where there was disagreement.

At the 2013 CARRA Annual Scientific Meeting, in a single group setting, members of the CARRA JIA research committee re-reviewed the following aspects of the CTPs: inclusion and exclusion criteria, the definition of primary and secondary outcomes, patient assessment intervals, and the finalized CTP strategies. After discussion, participants were asked to fill out a paper survey indicating whether or not they agreed with the operational case definition, the decision-making method outline in the CTP flow diagrams (patient much improved, physician global assessment $\leq$2, and/or off glucocorticoids), and whether they would be willing to implement the CTPs as outlined. An 80% level of agreement was required for consensus.

RESULTS

The initial CARRA survey was completed by 138 of 230 voting CARRA members (60% response rate). The survey identified substantial variability in the treatment approach for new-onset polyarticular JIA (Table 1). The most common therapies across all polyarticular JIA categories included nonsteroidal antiinflammatory drugs (NSAIDs), methotrexate (oral or subcutaneous), and glucocorticoids. No one indicated use of an interleukin-1 inhibitor or rituximab as an initial therapy for any category of polyarticular JIA. The frequency of using a nonbiologic DMARD alone, biologic DMARD alone, and nonbiologic DMARD and biologic DMARD combination are shown in Table 1. These common strategies are reflected in the final CTPs. NSAIDs, subcutaneous methotrexate, and TNFα inhibitors were the most common therapies that would be added at 3 months for patients with inadequate response across all polyarticular JIA categories. For a polyarticular JIA patient without poor prognostic risk factors (specified as $\geq$1 of the following: positive RF, positive anti–cyclic citrullinated protein, arthritis of the hip or cervical spine, or radiographic damage) and no response at 3 months, 84% of participants indicated that they would use TNFα inhibitors. While TNFα inhibitors were the most commonly used class of biologic agents for polyarticular JIA patients at any time point, 57% of physicians indicated a willingness to use other classes of biologic agents as the initial biologic treatment.

Seventy-two CARRA members participated in the JIA research committee during the face-to-face consensus meeting in June 2011. Using a modified NGT, $>$80% consensus was reached on the following items: 1) inclusion of all categories (except systemic JIA) of treatment-naive JIA presenting prior to patient's 19th birthday with arthritis for at least 6 weeks affecting $\geq$5 joints; 2) CTPs defined as treatment "strategies," consisting of varying the timing of introduction of general categories of medications (nonbiologic and biologic DMARDs); 3) prior treatment with NSAIDs and/or intraarticular glucocorticoids was allowed; and 4) prior treatment with any biologic or nonbiologic DMARD (including methotrexate, leflunomide, and sulfasalazine) would not be allowed. The inclusion of all categories of JIA with polyarticular involvement was based on review of the 2011 American College of Rheumatology (ACR) JIA Treatment Recommendations that similarly grouped these JIA categories (18). Results from the initial CARRA survey (Table 1) indicated that initial therapy

Table 1. Initial therapy preferences for polyarticular JIA: results from provider survey (n = 138)*

	Polyarticular JIA ILAR category					
	Typical polyarticular JIA, no risk factors†	Polyarticular JIA, with risk factors†	ERA, no sacroiliitis	ERA, with sacroiliitis	PsA	Oligoarticular, extended‡
Intraarticular glucocorticoid injections	31 (24)	34 (27)	21 (17)	25 (21)	23 (19)	30 (25)
Glucocorticoids						
IV pulse	3 (2)	7 (6)	2 (2)	5 (4)	4 (3)	§
Oral, <0.5 mg/kg/day	38 (30)	45 (36)	28 (23)	27 (23)	22 (18)	
Oral, >0.5 mg/kg/day	10 (8)	24 (19)	5 (4)	10 (8)	5 (4)	
IL-6 inhibitor	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	§
Methotrexate (any route)¶	103 (81)	119 (88)	74 (54)	66 (49)	97 (71)	104 (89)
Oral	56 (44)	57 (46)	40 (32)	29 (24)	50 (42)	
Subcutaneous	54 (43)	69 (55)	39 (32)	44 (37)	54 (45)	
NSAIDs	103 (81)	85 (68)	100 (81)	85 (71)	98 (82)	53 (45)
Sulfasalazine	0 (0)	2 (2)	30 (24)	19 (16)	3 (3)	3 (3)
T cell costimulation inhibitor	2 (2)	2 (2)	0 (0)	1 (1)	0 (0)	§
TNFα inhibitor	13 (10)	65 (52)	23 (19)	68 (57)	20 (17)	71(62)
Treatment strategies						
Nonbiologic DMARD alone	103 (81)	56 (41)	76 (56)	38 (28)	80 (59)	46 (34)
Biologic DMARD alone	2 (1)	2 (1)	7 (5)	31 (23)	3 (2)	13 (10)
Nonbiologic DMARD and biologic DMARD	12 (9)	63 (46)	16 (12)	38 (28)	17 (13)	58 (43)

* Values are the number (percentage). Medication options were not mutually exclusive. JIA = juvenile idiopathic arthritis; ILAR = International League of Associations for Rheumatology; ERA = enthesitis-related arthritis; PsA = psoriatic arthritis; IV = intravenous; IL-6 = interleukin-6; NSAIDs = nonsteroidal antiinflammatory drugs; TNF = tumor necrosis factor; DMARD = disease-modifying antirheumatic drug.
† Risk factors: rheumatoid factor positivity, anti–cyclic citrullinated protein positivity, arthritis of the hip or cervical spine, and radiographic damage.
‡ First visit that the oligoarticular JIA patient extends disease to involve >4 joints.
§ Medication not presented as an option.
¶ Choice of oral and subcutaneous route of methotrexate not mutually exclusive.

tended to be similar for JIA patients with polyarticular involvement regardless of the specific International League of Associations for Rheumatology (ILAR) category to which they belonged. Consensus was not initially obtained on the following issues, but was reached in subsequent consensus meetings: 1) CTP duration, 2) duration of biologic DMARD use prior to assessment of response, 3) no allowance for prior oral glucocorticoid treatment before starting CTP, 4) dosing of adjunct glucocorticoid with the CTP, 5) inclusion of annual radiographs as a secondary outcome, and 6) inclusion of patients with uveitis. The polyarticular JIA core workgroup conducted conference calls throughout the year to discuss and refine findings from the survey and face-to-face meeting. The core workgroup also examined in depth the indications, dosing, and safety monitoring for the following medications: glucocorticoids (systemic and intraarticular), nonbiologic DMARDs (leflunomide, methotrexate, and sulfasalazine), and biologic DMARDs (abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab) (see Supplementary Appendix A, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22259/abstract).

Based on these findings the following strategies were developed to be used as CTPs: step-up plan (nonbiologic DMARD followed by a biologic DMARD if inadequate response in 3–6 months, similar to the ACR JIA Treatment Recommendations (18); early combination plan (nonbiologic and biologic DMARD within a month of treatment initiation, similar to ACUTE-JIA TNF arm and TREAT-JIA most intensive treatment arm (16,17); and biologic only plan (biologic DMARD started without initiation of nonbiologic DMARD). These approaches were aligned with the most common treatment timing strategies employed by pediatric rheumatologists in the initial treatment survey.

Fifty-eight CARRA members participated in the JIA research committee workgroup at the second face-to-face consensus meeting in April 2012. After small group breakout sessions and subsequent discussion, 80% consensus was achieved on the following items: operational case definition (including age <19 years at onset of symptoms and inclusion of patients with uveitis), data collection time points, disease activity measures to be collected, and the medication dosing and monitoring guidelines. Consensus was not reached on whether the primary end point should be a pediatric ACR90 or inactive disease at 6 or 12 months. The polyarticular JIA core workgroup continued to meet following the face-to-face meeting and discussed the end points to be used and continued to refine the CTPs.

Seventy-two CARRA members participated in the third JIA research committee face-to-face meeting for this project in April 2013. The final operational case definition, CTP flow diagrams, assessment intervals, and primary and secondary end points were presented and discussed, fol-

Table 2. Operational case definition of polyarticular JIA*

Patient should be/have:
Age <19 years at baseline (if age ≥18 years, agrees to be followed for at least 1 year)
Arthritis (ACR definition)†
Present in 1 joint for at least 6 weeks
>5 active joints at baseline
Patients may have:
Any of the following:
RF-positive polyarticular JIA
RF-negative polyarticular JIA
Extended oligoarticular JIA
Psoriatic JIA
Enthesitis-related JIA
Undifferentiated JIA
Psoriasis
Sacroiliitis
Uveitis
Enthesitis
Past or current treatment with:
NSAIDs
Intraarticular, topical, and intraocular steroids
Hydroxychloroquine
Patient should NOT have:
Systemic JIA
Treatment with any medications for JIA aside from those listed above, including systemic glucocorticoids
Known inflammatory bowel disease
Known celiac disease
Known trisomy 21
History of or current malignancy
Concomitant serious active/recurrent chronic bacterial, fungal, or viral infection
Significant organ system disorder limiting use of treatments for polyarticular JIA
Live vaccine within a month prior to baseline

* The operational case definition is not meant to represent diagnostic or International League of Associations for Rheumatology Classification Criteria for polyarticular juvenile idiopathic arthritis (JIA). ACR = American College of Rheumatology; RF = rheumatoid factor; NSAIDs = nonsteroidal antiinflammatory drugs.
† Swelling within a joint, or limited range of motion with joint pain or tenderness, is observed by a physician, and is not due to primarily mechanical disorders or to other identifiable causes.

lowed by voting. Seventy-seven percent of respondents agreed with the operational case definition (Table 2). Ninety-six percent consensus was reached regarding the decision-making method outlined in the CTP flow diagrams (patient much improved, physician global assessment ≤2, and/or off glucocorticoids), and 96% of respondents voted they would be willing to implement the CTPs as currently outlined. Intraarticular glucocorticoid injections are permitted prior to starting on a CTP, as long as there are still at least 5 active joints at the baseline visit. Systemic glucocorticoids that are intended as treatment for arthritis are not permitted in the month prior to starting on a CTP. The final CTP flow diagrams are shown in Figures 1, 2, and 3. All strategies suggest treatment modifications at 3–4-month interval assessments in the following circumstances: the patient is not much better, physician global assessment is ≥2, and/or the patient is still on glucocorticoids. Duration of the CTPs is for 12 months after treatment initiation. All 3 CTPs allow concomitant initiation of systemic glucocorticoids. It is recommended that the treating physician discontinue systemic glucocorticoids by 3 months, if possible. Suggested glucocorticoid tapering regimens are shown in Supplementary Appendix B (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22259/abstract). The step-up strategy allows for an increase in nonbiologic DMARD dose, initiation of an alternate nonbiologic DMARD, or initiation of a biologic DMARD at 3 months if there is inadequate response. In the early combination strategy, patients are started on both a nonbiologic DMARD and a biologic DMARD within the first month. The nonbiologic DMARD and/or the biologic DMARD can be changed at 3 months if there is an inadequate response. The biologic DMARD only strategy allows for an alternate biologic DMARD at 3 months and/or initiation of a nonbiologic DMARD at 6 months if there is inadequate response. A standardized clinical assessment schedule and clinical data collection are shown in Table 3. If medication changes are required and are clinically indicated at interim visits, additional data collection is suggested.

DISCUSSION

This article documents the development of standardized, consensus-derived treatment plans for polyarticular forms of JIA. CTPs have been developed and are being piloted for systemic JIA (11). These plans focus on evaluating the importance of timing of initiation of various therapeutic classes of medication rather than use of specific medications in polyarticular JIA, and address issues that remain unresolved despite recent RCTs (16,17). Clinical trials have been conducted successfully to compare the effectiveness of different treatment strategies rather than specific medications for rheumatoid arthritis (19,20). The CTPs include recommendations on medication dosing and monitoring, and tapering of glucocorticoids along with a recommended schedule of visits and monitoring parameters. These plans are not intended to be identical to each individual clinician's usual practices, but are intended to represent the general and most common approaches to the treatment of polyarticular JIA by pediatric rheumatologists across North America, and are endorsed by consensus formation among CARRA members. Three different CTPs were developed: the step-up plan, the early combination plan, and the biologic only plan (Figures 1, 2, and 3). These plans are intended for guidance to reduce variation in care. It is anticipated that the fidelity with which clinicians will follow them will be according to their clinical judgment of the patient's progress. Data regarding adherence to the CTPs will be necessary in order to understand whether there are aspects of the protocols that require modification in order to be feasible in the setting of routine clinical care.

The intent of all CARRA CTPs is to reduce variation in treatments, which together with prospective data collection in a large number of patients will facilitate comparative research of medication effectiveness, safety, and tol-

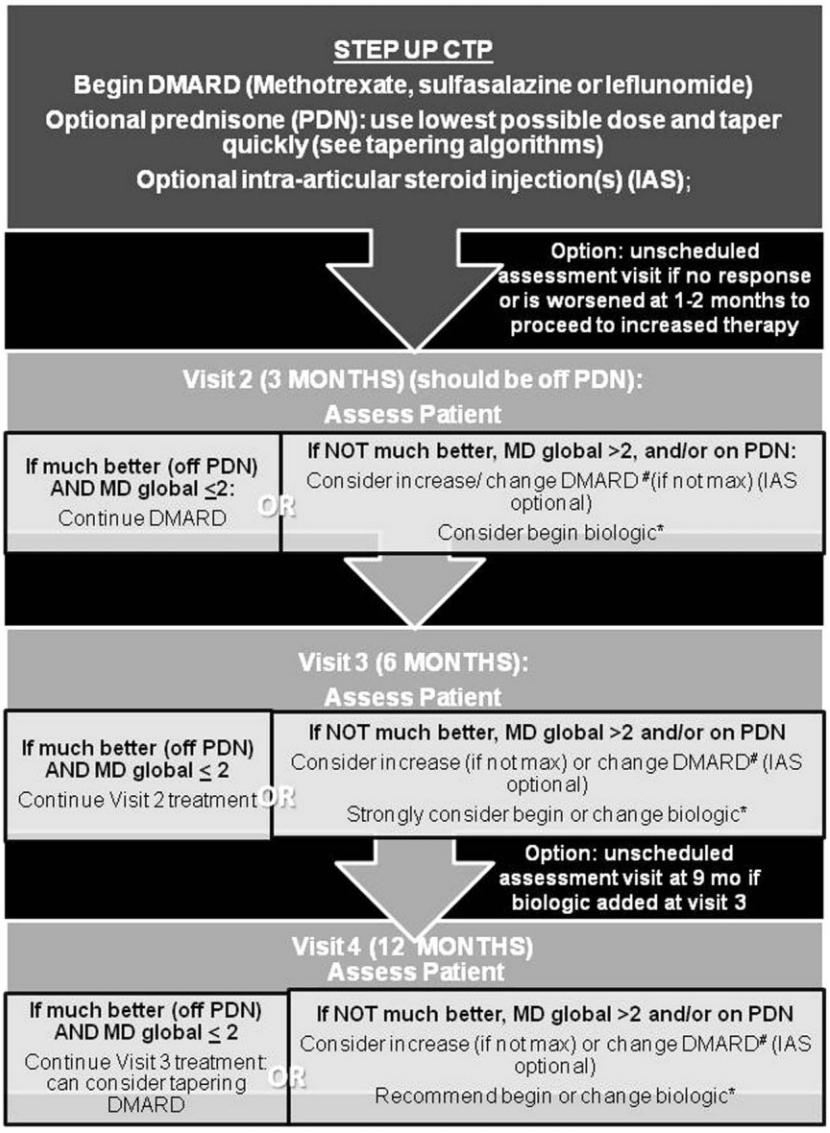

Figure 1. Step-up consensus treatment plan (CTP). # = nonbiologic disease-modifying antirheumatic drug (DMARD): methotrexate, sulfasalazine, or leflunomide; * = biologic DMARD: any inhibitor of tumor necrosis factor, T cell costimulation, interleukin-6, or B cell; MD = physician.

erability in clinical practice in an observational setting like the CARRA Registry. The CARRA Registry is the largest prospective pediatric rheumatic diseases registry in the world, with more than 9,000 patients enrolled in 62 of the more than 100 CARRA sites across North America as of November 2013. By building additional data fields into the basic disease information collected by the Registry, information resulting from the use of the CTPs can be used to learn about the effectiveness of these treatment approaches. Generating knowledge from this approach requires analytic methods to reduce bias and confounding by indication, which may include regression with adjustment for known confounders, propensity scores, and instrumental variable approaches. Given the current variability in treatment patterns evidenced by our surveys, each CTP is expected to be used in patients with differing characteristics and disease activity. As new evidence and knowledge from the use of the CTPs become available, the CTPs will be updated and revised in an iterative fashion.

There was some disagreement at the third face-to-face meeting (2013) about the inclusion of patients with inflammatory arthritis and onset of disease at age >16 years as they would not strictly fulfill the ILAR age criteria (21). Despite this, 77% of participants agreed with the operational case definition including this criterion, and 96% agreed that they would use the CTPs as presented. Additionally, in the 2 previous CARRA consensus meetings, >80% agreement (consensus) had been achieved that the CTPs could be used in patients up to their 19th birthday, as long as the patient agreed to be followed for at least a year. This is a reflection of pediatric rheumatology treatment practices that generally sees new patients up until at least age 18 years rather than based on the ILAR criteria. Lastly, the operational case definition being used for the

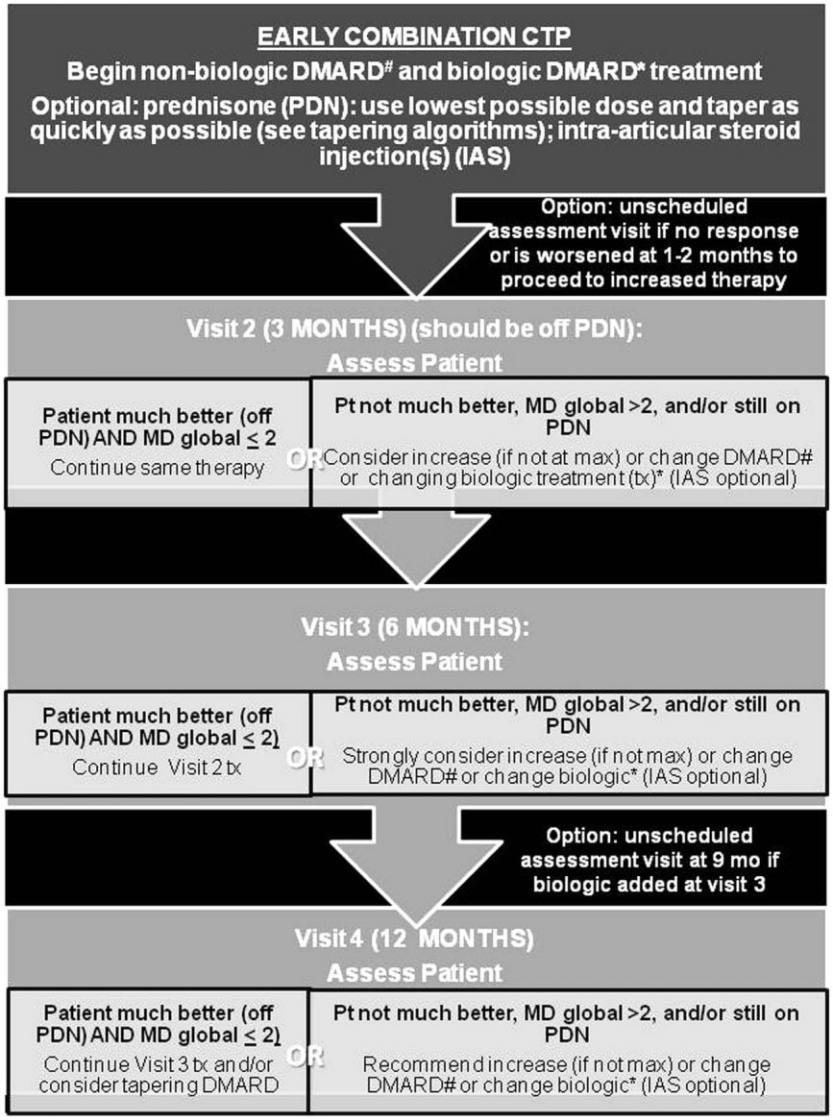

Figure 2. Early combination consensus treat plan (CTP). # = nonbiologic disease-modifying antirheumatic drug (DMARD): methotrexate, sulfasalazine, or leflunomide; ∗ = biologic DMARD: any inhibitor of tumor necrosis factor, T cell costimulation, interleukin-6, or B cell; MD = physician; pt = patient.

CARRA systemic JIA CTPs has the same age criterion (11). There was also discussion regarding the inclusion of children with concomitant inflammatory bowel disease, celiac disease, and trisomy 21. Children with inflammatory bowel disease were ultimately excluded because the majority of participants felt that bowel disease activity would be the primary driver of treatment decisions. Patients with celiac disease were excluded since dietary changes may affect their musculoskeletal symptoms, and children with trisomy 21 were excluded because of concerns over sensitivity to medications (such as methotrexate) and the need for individually tailored therapy (22–25).

The end points were also a topic of discussion; there was general agreement that the primary end point should be a meaningful and robust outcome. There was discussion about whether it should be a pediatric ACR90 score or inactive disease, and whether this should be at 6 or 12 months. Ultimately, it was decided that the pediatric ACR90 score at 12 months was a very robust, meaningful, and achievable outcome. If there are not significantly different outcomes between the strategies at 12 months, then the costs and relative risks of additional months of medication exposure on one strategy versus the others will need to be closely considered. The use of radiographic outcome measures was also a subject of debate because it would not be feasible to have radiographs read in a standardized fashion centrally and the low likelihood that significant radiographic changes would be seen 1 year from treatment initiation. However, ultimately it was decided that radiographic changes were an important and objective outcome and that most pediatric rheumatologists could agree to obtain radiographs of at least 1 involved joint at baseline and on a yearly basis.

The CTPs differ from the 2011 ACR JIA treatment rec-

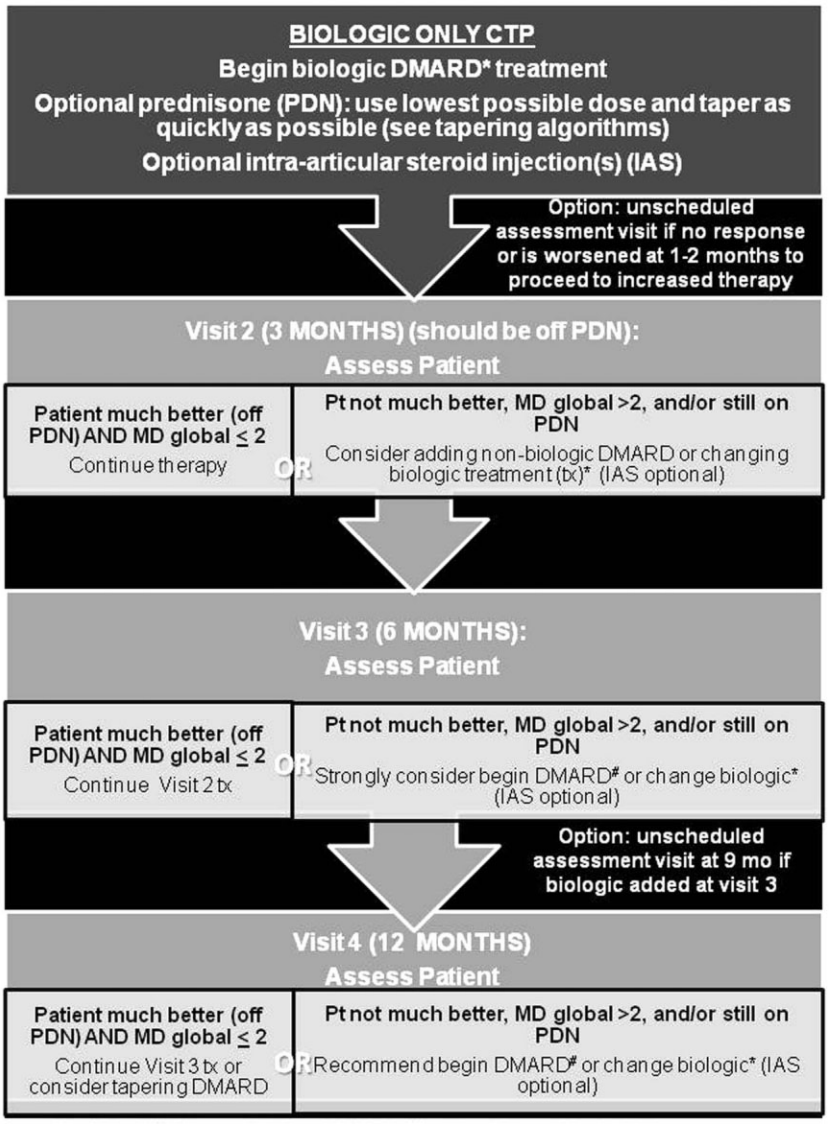

Figure 3. Biologic only consensus treat plan (CTP). ∗ = biologic disease-modifying antirheumatic drug (DMARD): any inhibitor of tumor necrosis factor, T cell costimulation, interleukin-6, or B cell; # = nonbiologic DMARD: methotrexate, sulfasalazine, or leflunomide; MD = physician; pt = patient.

ommendations in a number of ways. The CTPs are based upon consensus opinion, whereas the recommendations are based on a different process, i.e., the Research and Development (RAND)/University of California, Los Angeles (UCLA) Appropriateness Method (18). The RAND/UCLA method is primarily evidence-based with some accounting for expert opinion and specifically does not force consensus. The 2011 ACR recommendations consider both poor prognostic features and disease activity levels, outline the currently recommended evidence-based treatments, and are intended for use in JIA patients with polyarticular involvement at any time during their disease course. In contrast, the polyarticular JIA CTPs are developed by consensus, reflect treatment strategies that are in current use by pediatric rheumatologists, and are intended to be initiated in treatment-naive recent-onset polyarticular JIA patients. The ACR treatment recommendations for polyarticular JIA are most similar to the step-up CTP, but the CTPs additionally acknowledge that other treatment pathways commonly used by physicians to treat polyarticular JIA need to be evaluated (early combination strategy and biologic only strategy). It is anticipated that data collected from patients treated using CTPs will ultimately help inform future updates of the ACR JIA treatment recommendations.

Lastly, there is an effort under way to develop consensus guidelines for treatment and care of pediatric rheumatic diseases in European countries called SHARE (Single Hub and Access Point for Pediatric Rheumatology in Europe), which will differ from both the ACR JIA treatment recommendations and the CTPs (26). SHARE does not aim to reflect current treatment practices among pediatric rheumatologists, but are minimum recommended standards of care based on consensus among pediatric rheumatology

Table 3. Routine assessment schedule and clinical data collection*

Variables	Assessments	
	Baseline	Followup visits (every 3–4 months)
Demographics		
Month/year of birth	X	
Sex	X	
Race and ethnicity	X	
Date of symptom onset	X	
Physician assigned ILAR JIA category	X	
Clinical variables		
ESR and/or CRP	X	X
Number of joints with LROM	X	X
Number of joints with swelling	X	X
Physician global assessment of disease activity	X	X
Patient/parent global assessment of disease activity	X	X
C-HAQ	X	X
Morning stiffness (<15 or ≥15 minutes)	X	X
Uveitis		
Present in the 3 months prior to visit	X	X
Topical steroid therapy	X	X
Quality of life measure	X	X
Medication exposures		
Pre-CTP intraarticular glucocorticoid injections	X	
Pre-CTP NSAIDs	X	
Pre-CTP hydroxycholoroquine	X	
CTP-related exposures		
Intraarticular glucocorticoid injections	X	X
Topical or ophthalmic glucocorticoids	X	X
Systemic glucocorticoids	X	X
Adverse events		
Serious adverse events	X	X
Important medical events	X	X
Medication side effects	X	X
Reasons for changing treatment	X	X
Radiograph of involved joint (wrist/hand preferred)	X	X

* Assessment intervals: baseline, visit 2 (3–4 months), visit 3 (3–4 months after visit 2), visit 4 (12 months); optional visits: between visit 3 and 4 (if treatment is changed at visit 3), other unscheduled visits when there is change in treatment, and recommend continued data collection on a yearly basis for purpose of comparative effectiveness studies. ILAR = International League of Associations for Rheumatology; JIA = juvenile idiopathic arthritis; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; LROM = limited range of motion; C-HAQ = Childhood Health Assessment Questionnaire; CTP = consensus treatment plan; NSAIDs = nonsteroidal antiinflammatory drugs.

expert panels rather than the widespread network-wide consensus process as was used to develop the CTPs.

Limitations of the CTPs include that they do not go beyond the initial 12 months, and do not address medication tapering aside from glucocorticoids. New immunomodulatory agents will need to be incorporated as they become available. The decision-making process outlined in the CTPs may need to be adjusted, as ideally this would incorporate continuous measures of disease activity such as the Juvenile Arthritis Disease Activity Score once meaningful cut points for decision making are validated (27). Additionally, the CTPs are based upon the practice and opinions of the CARRA physicians who participated in the consensus process and may not reflect the current practice patterns outside of the North American CARRA membership, particularly in countries where there is less availability of biologic agents. These CTPs are meant for use in routine clinical care, and the ease of use of these CTPs and decision-making processes should be tested and improved upon through a piloting process prior to widespread dissemination.

Three CTPs for treatment-naive polyarticular JIA were developed with the goal of reducing variation in care and to ultimately facilitate evaluation of the comparative effectiveness of treatment selection and the timing of treatment introduction. These plans were acceptable to the majority of CARRA members. Widespread use of these CTPs in clinical practice, along with standardized assessments and data collection, may allow the study of comparative effectiveness of these strategies and will ultimately guide improved and evidence-based decision making for children and adolescents with new-onset polyarticular JIA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Kimura had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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