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ORIGINAL ARTICLE

Consensus Treatment Plans for New-Onset Systemic Juvenile Idiopathic Arthritis

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Objective. **There is wide variation in therapeutic approaches to systemic juvenile idiopathic arthritis (JIA) among North American rheumatologists. Understanding the comparative effectiveness of the diverse therapeutic options available for treatment of systemic JIA can result in better health outcomes. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed consensus treatment plans and standardized assessment schedules for use in clinical practice to facilitate such studies.**

Methods. **Case-based surveys were administered to CARRA members to identify prevailing treatments for new-onset systemic JIA. A 2-day consensus conference in April 2010 employed modified nominal group technique to formulate preliminary treatment plans and determine important data elements for collection. Followup surveys were employed to refine the plans and assess clinical acceptability.**

Results. **The initial case-based survey identified significant variability among current treatment approaches for new-onset systemic JIA, underscoring the utility of standardized plans to evaluate comparative effectiveness. We developed 4 consensus treatment plans for the first 9 months of therapy, as well as case definitions and clinical and laboratory monitoring schedules. The 4 treatment regimens included glucocorticoids only, or therapy with methotrexate, anakinra, or tocilizumab, with or without glucocorticoids. This approach was approved by >78% of the CARRA membership.**

Conclusion. **Four standardized treatment plans were developed for new-onset systemic JIA. Coupled with data collection at defined intervals, use of these treatment plans will create the opportunity to evaluate comparative effectiveness in an observational setting to optimize initial management of systemic JIA.**

INTRODUCTION

Systemic juvenile idiopathic arthritis (JIA) is a rare and complex inflammatory disease of childhood associated with significant morbidity. Systemic JIA is characterized by arthritis accompanied by high spiking fevers, plus a variety of additional features such as a typical rash, generalized lymphadenopathy, hepatosplenomegaly, and se-

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Significance & Innovations

- Use of standardized treatment protocols has radically improved outcomes of treatment for childhood malignancies. There is wide variation in treatment of children with systemic juvenile idiopathic arthritis (JIA) with no clear superior approach. Reducing variation and standardizing treatment plans coupled with data collection will enable relevant comparisons of treatments for systemic JIA in clinical practice.
- The Childhood Arthritis and Rheumatology Research Alliance (CARRA) is a clinical research network of more than 300 pediatric rheumatologists at 92 centers in North America. With funding from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, CARRA has developed, with a combination of literature review, surveys, and consensus meetings, 4 standardized initial treatment approaches for systemic JIA.
- The treatment plans are not meant to be guidelines, but it is anticipated that with widespread adoption these plans can serve as a benchmark against which new therapies/approaches can be compared.

than $10,000) from Genentech. Dr. Schikler owns stock and/or holds stock options in Novartis, Biogen, and Immunogen. Dr. Ilowite has received consultant fees, speaking fees, and/or honoraria (less than $10,000 each) from Genentech and Abbott Immunology, serves on the advisory board for Genentech and on the Data Safety and Monitoring Board for Novartis and Janssen, and has received drug and placebo from Regeneron for use in an NIH-sponsored clinical trial. Dr. Wallace owns stock and/or holds stock options in Eli Lilly, has received consultant fees, speaking fees, and/or honoraria (less than $10,000) from Genentech, and has received grants from Amgen, Pfizer, and Bristol Myers Squibb.

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Additional Consensus Meeting Attendees: Patient Representatives Vincent Del Gaizo and Anne Murphy, and CARRA Members Ciaran Duffy, Norman T. Ilowite, Daniel Lovell, Elizabeth Mellins, Michael Rapoff, and Susan Thompson.

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rositis. There is considerable variation in the therapeutic approaches to new-onset systemic JIA, in part due to a heterogeneous and somewhat unpredictable disease course, differences in physician practices, and, until recently, a lack of clinical trial data (1–3) and evidence-based guidelines (4) targeting this population.

Systemic JIA accounts for 5–15% of patients diagnosed with some form of JIA in North American and European populations. It accounts for a disproportionate share of the morbidity in childhood arthritis, including poor growth, severe joint destruction causing physical disability and necessitating joint replacement surgery (5), and JIA-related deaths (6). The disease course is variable, with approximately 11–42% of patients following a monocyclic course of variable length. The majority of affected children have a chronic and unrelenting course, while a smaller fraction (7–34%) follow a polycyclic course punctuated by flares and remission of arthritis, with or without systemic features (6–9). Deaths occur more frequently in children with systemic JIA than other categories, mostly due to overwhelming infection (historically associated with chronic glucocorticoid treatment), macrophage activation syndrome (MAS), and amyloidosis (mainly outside North America) (6,10,11). Correlates of poor prognosis include continued active systemic disease 6 months after diagnosis (as manifested by fever, requirement for systemic glucocorticoids, or thrombocytosis) (10), aggressive polyarthritis (12), and cervical spine involvement (13).

Systemic glucocorticoids and nonsteroidal antiinflammatory drugs (NSAIDs) have been the mainstays of treatment for many years, but glucocorticoids, which must often be given for years in this disease, are associated with many side effects (14). For treatment of the articular disease, methotrexate and sometimes tumor necrosis factor α (TNFα) inhibitors (such as etanercept and infliximab) have been used with limited success (15,16). However, these treatments have in some settings been supplanted by the use of an anti–interleukin-1 (anti–IL-1) therapy, anakinra, which has been reported to result in dramatic improvement in both the systemic and articular disease in some patients with systemic JIA (9,17). Anakinra has been approved by the Food and Drug Administration (FDA) for treatment of adult rheumatoid arthritis, but its use for systemic JIA is currently "off-label." An anti–IL-6 therapy (tocilizumab) recently became the first treatment approved by the FDA for systemic JIA (April 15, 2011) and has also been demonstrated to be of remarkable benefit (3). Additional anti–IL-1 therapies (such as canakinumab and rilonacept) are currently in clinical trials in systemic JIA.

With these new options for treatment, there is an urgent need for research to determine their relative effectiveness, safety, and tolerability in systemic JIA. Comparative effectiveness studies in an observational setting may be used to examine which treatments are effective in routine care and help guide decision making about which treatment may be most appropriate for an individual patient (18). Systemic JIA, being a relatively uncommon severe disease with widely diverging therapeutic approaches, is particularly suited for comparative effectiveness research. To be able to carry out meaningful comparisons between therapeutic agents in an observational setting, however, requires stan-

dardization of treatment regimens and outcome measures. In this present effort, we therefore aimed to develop consensus-derived standardized treatment plans for this disease as part of improving patient outcomes in systemic JIA, a scientific priority of the Childhood Arthritis and Rheumatology Research Alliance (CARRA). CARRA is a North American organization whose research mission is to prevent, treat, and cure rheumatic diseases in children through fostering and conducting high-quality research. Our aim was to generate treatment plans and data collection recommendations similar to current clinical practice. This would increase the likelihood of their use by practicing pediatric rheumatologists and lead to standardization of care for many systemic JIA patients, in order to reduce unwarranted variation in care and increase the ability to make meaningful comparisons of the relative effectiveness of treatments. In addition, these treatment plans may guide practicing clinicians and serve as a discussion tool for patients and families. Although these plans may differ from the usual practice of some physicians, the intent was to develop plans that most physicians would feel comfortable using despite modest differences from their usual practice. In addition, use of these plans is not meant to replicate a clinical trial protocol, i.e., they are not meant to be proscriptive; physicians should use a consensus treatment plan (CTP) if they feel it is appropriate for a given patient, and the treating physician may diverge from any CTP when it is in the best interest of the patient to do so.

MATERIALS AND METHODS

The CARRA systemic JIA core work group (EMD, YK, TB, PAN, KO, SP, RS, and MLS), consisting of board-certified pediatric rheumatologists with special interest and expertise in systemic JIA, met once or twice monthly from October 2009 to March 2011 to review published evidence, formulate clinical scenarios and an operational case definition describing characteristics of patients intended for the treatment plans, construct surveys, analyze responses, organize and run a consensus meeting, and finalize resultant treatment plans.

Preconsensus meeting survey. A case-based online survey was administered to CARRA members in the JIA disease-specific work group to identify prevailing therapeutic approaches to treatment of new-onset systemic JIA according to 4 clinical scenarios that represented varying severity of disease activity (mild, moderate, moderate-high, and high). Survey respondents reported first-, second-, and also third-line treatment choices for patients with inadequate responses to the prior regimen. Discrete options as well as free-text items were included. Respondents also provided input on formulation of characteristics of the patients to be treated, such as the minimum duration of fever before a diagnosis of systemic JIA would be considered probable. Responses were analyzed and served as the basis for a 2-day consensus conference, which convened in April 2010 during the CARRA Annual Scientific Meeting. A sample of questions and response options is shown in Supplementary Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Consensus meeting. Pediatric rheumatologists, fellows in training, researchers, and lay members (who were parents of children with JIA) attended the systemic JIA consensus treatment plan meeting along with 3 facilitators. The setting was the CARRA Annual Scientific Meeting. Voting participants were CARRA members in clinical practice who treated patients with JIA and were members of the CARRA JIA disease-specific committee. Since clinicians will be the ones to use the CTPs, and given their experience and position as stakeholders in the process, their participation was valued. After a presentation of the overall meeting goals and objectives, preconference survey data, and an overview of consensus methodology, participants divided into 3 self-selected work groups to determine the details of: 1) a glucocorticoid treatment plan, 2) a disease-modifying antirheumatic drug (DMARD) treatment plan, and 3) assessment details. Within each work group extensive input was sought from all meeting attendees through structured small group interactions. Specific questions were posed for discussion, and an 80% level of agreement for each question was required to achieve consensus. After completion of each group's panel of questions, work group participants reconvened as a larger group for presentation of the progress of each work group. Topics were then presented for discussion with the larger group to obtain more widespread consensus. If the larger group did not show clear agreement (by show of hands), then there was additional discussion and a more formal voting process occurred. After the meeting, questions for which consensus answers were not achieved were brought back to the CARRA systemic JIA core work group for further analysis, discussion, and decision making. Additionally, the preliminary treatment plans created at the meeting were further refined by this core work group. A subsequent presentation of the revised treatment plans was then presented to the entire CARRA membership for review and response by an online survey.

Postconsensus meeting survey. The online survey of the entire CARRA membership described above was conducted in December 2010 to assess the acceptability and feasibility of use of the revised treatment plans derived from the April 2010 consensus meeting. The thematic content of the questions included: 1) a review for acceptability of the proposed operational case definition for systemic JIA, 2) specification of the details of the 3 treatment plans developed during the consensus meeting (glucocorticoid plan, methotrexate plan, anti–IL-1 anakinra plan), 3) whether an anti–IL-6 treatment plan should be added, 4) willingness to use one of the presented plans on newly diagnosed systemic JIA patients, and 5) estimation of the number of patients that might be treated with each plan yearly. A sample of survey questions is shown in Supplementary Appendix B (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). Based on these survey results, the CARRA systemic JIA core work group further refined the

treatment plans and monitoring schedules presented herein.

RESULTS

The preconsensus meeting case-based survey was completed by 63 of 137 members of the CARRA JIA disease-specific work group (response rate 46%, which was expected based on completion rates of other CARRA membership surveys and given the complexity of the survey).

The survey identified considerable variability in current therapeutic approaches to new-onset systemic JIA, confirming the suitability of systemic JIA as a target for comparative effectiveness research. For example, the initial treatment choices among the respondents for the systemic JIA patients described in the cases included anti–IL-1, anti–IL-6, and anti-TNF agents, calcineurin inhibitors, methotrexate (oral and injectable), intravenous (IV) methylprednisolone pulse(s), NSAIDs, and prednisone (low, middle, or high dose), depending on the severity of the patient. Several distinct treatment preferences emerged. In summary, NSAIDs were used widely across the disease severity spectrum as part of initial treatment, then trending down as disease activity increased (85.7% for mild cases down to 39.7% for high disease activity). Use of methotrexate (37.9–43.3%) was stable across the disease activity spectrum. As disease activity increased, so did use of methylprednisolone pulses and anti–IL-1. Failure to respond to the above resulted in use of anti–IL-6, and to a lesser extent, calcineurin inhibitors and anti-TNF agents (Supplementary Appendix C, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). The new-onset systemic JIA operational case definition that a patient should meet prior to initiating any of the standard treatment plans was also addressed. A total of 74.1% of respondents thought that a minimum of 2-week duration of fever should be required. The majority (87.9%) found it acceptable to initiate a treatment for systemic JIA in the absence of arthritis, based on fever and other systemic features such as characteristic rash, serositis, and adenopathy, provided that infection and malignancy had been adequately excluded.

Forty-three CARRA members attended the face-to-face consensus meeting in April 2010, as did 2 nonvoting lay parent members and 3 facilitators. The glucocorticoid treatment plan group generated a preliminary draft treatment approach that offered a choice of either high-dosage (2 mg/kg/daily) or low-dosage (0.5 mg/kg/daily) oral prednisone, with methylprednisolone pulses and/or intraarticular injections as needed. The goal was to discontinue glucocorticoids by 6 months, with defined tapering schedules to proceed as tolerated. The DMARD treatment plan group generated preliminary methotrexate- and anakinra-based plans, each of which could be used with the glucocorticoid plan if needed. The assessment details group developed schedules of proposed visit intervals, laboratory and clinical assessments, and data collection items (19).

Table 1. Operational case definition of new-onset systemic JIA*

Patient should be/have
1. Age 6 months to 18 years
2. Fever for at least 2 weeks†
3. Arthritis in ≥1 joints (6 weeks' duration not required)‡
4. At least 1 of the following:
   a. Evanescent erythematous rash
   b. Generalized lymphadenopathy
   c. Hepatomegaly or splenomegaly
   d. Pericarditis, pleuritis, and/or peritonitis

Patient should not have
1. Infection, including concomitant active or recurrent chronic bacterial, fungal, or viral infection at presentation, nor underlying infection that may mimic initial presentation of systemic JIA§
2. Malignancy§
3. Positive screening test for TB without documented past treatment
4. Prior treatment for systemic JIA other than NSAIDs or short-term steroids¶
5. Immunization with live virus vaccines within the 4 weeks prior to enrollment

* The above is not meant to represent diagnostic nor classification criteria for systemic JIA. The differences between this operational case definition and the International League of Associations for Rheumatology (ILAR) criteria are: 1) ILAR specifies that the duration of quotidian fever has to be 3 days (the total duration of fever is 2 weeks for both the ILAR criteria and the operational case definition) and 2) ILAR specifies 6 weeks' duration of arthritis. Listed as exclusions in the ILAR definition are psoriasis, rheumatoid factor positivity, arthritis in HLA–B27–positive male after age 6 years, family history of ankylosing spondylitis, irritable bowel disease with sacroiliitis, acute anterior uveitis, and reactive arthritis. JIA = juvenile idiopathic arthritis; TB = tuberculosis; NSAIDs = nonsteroidal antiinflammatory drugs.
† Daily fever is not required, but patient must at some point exhibit a quotidian fever pattern, defined as fever that rises to ≥39°C at least once a day and returns to ≤37°C between fever peaks.
‡ Swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness, is observed by a physician, and is not due to primarily mechanical disorders or to other identifiable causes.
§ Infections, malignancy, and other diagnoses that can present with similar symptoms to systemic JIA should be excluded before initiating treatment plans for new-onset systemic JIA in order to avoid unintended adverse effects of the treatment plans if used for other diagnoses.
¶ Prior treatment with steroids should not exceed 2 weeks of oral steroids and/or 3 pulses of methylprednisolone. Prior treatment with intravenous immunoglobulin for possible Kawasaki disease is allowed. Duration of NSAIDs is without restriction.

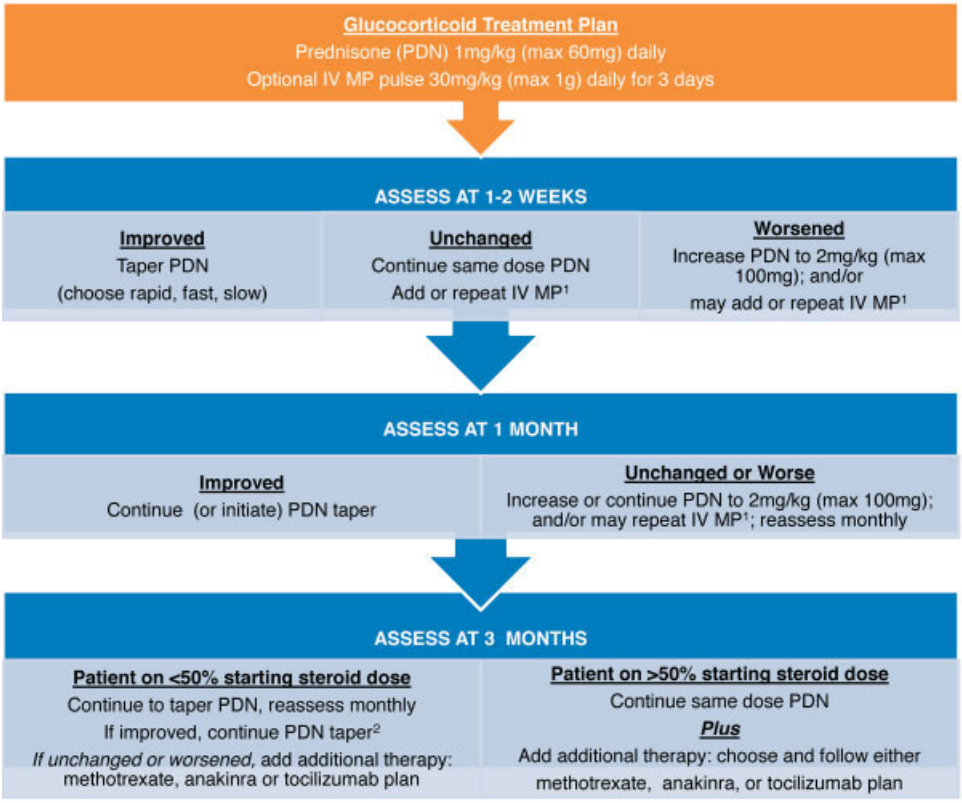

Figure 1. Glucocorticoid treatment plan. [1] = intravenous methylprednisolone (IV MP) pulses are 1 dosage weekly; [2] = patients who started with rapid taper may be off prednisone.

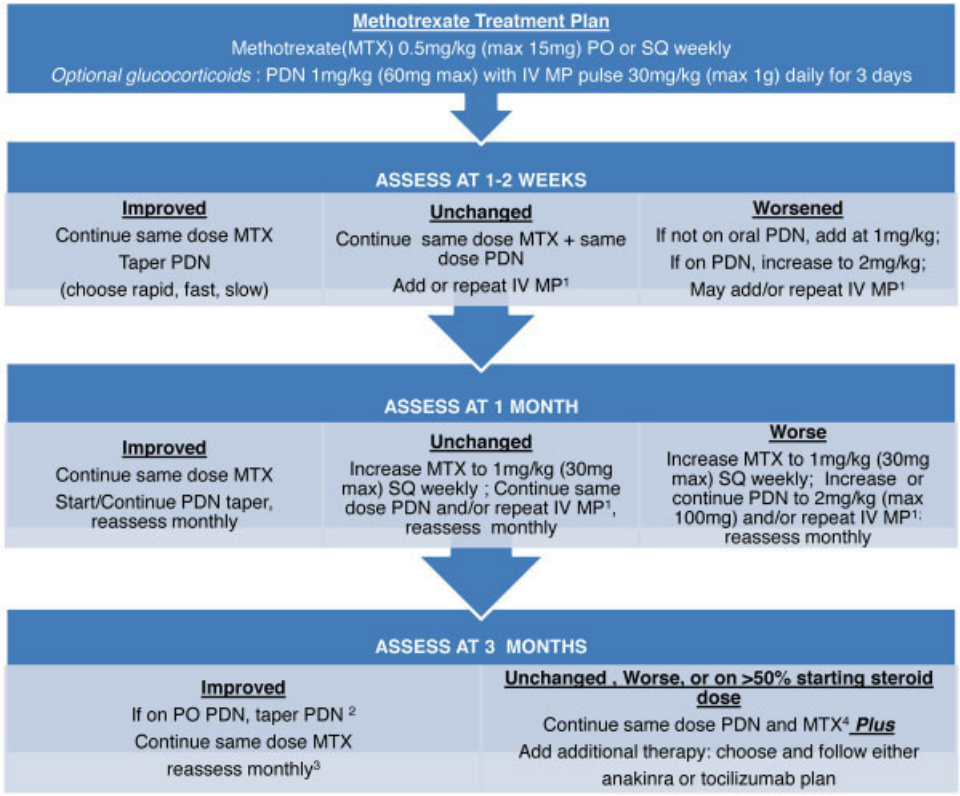

Figure 2. Methotrexate treatment plan. [1] = intravenous (IV) methylprednisolone (MP) pulses are 1 dosage weekly; [2] = patients who started with rapid taper may be off prednisone (PDN); [3] = if condition worsens, follow "Unchanged, Worse" pathway; [4] = if patient is intolerant of methotrexate, discontinue and add additional therapy; PO = by mouth; SQ = subcutaneous.

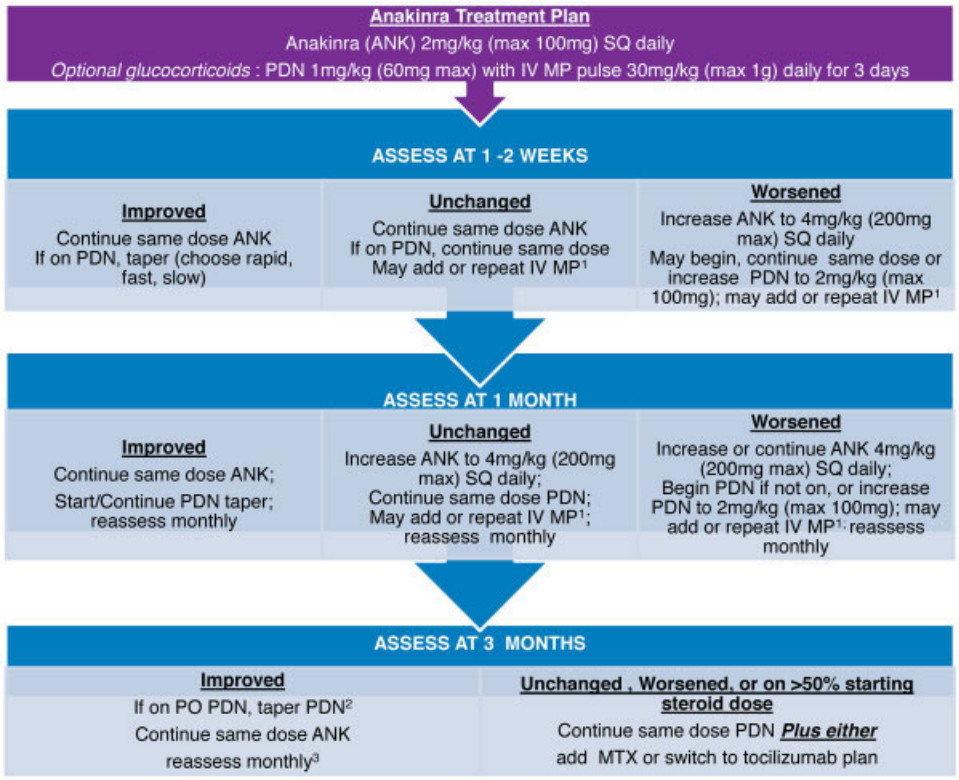

Figure 3. Anakinra treatment plan. [1] = intravenous (IV) methylprednisolone (MP) pulses are 1 dosage weekly; [2] = patients who started with rapid taper may be off prednisone (PDN); [3] = if condition worsens, or patient is intolerant of anakinra, follow "Unchanged, Worse" pathway; SQ = subcutaneous; PO = by mouth; MTX = methotrexate.

After refinement of the operational case definition and treatment plans by the systemic JIA core work group, a survey of the entire CARRA membership was conducted in December 2010 to assess their acceptability and feasibility. Most respondents found the proposed adjustments made by the core work group to be acceptable, specifically, the glucocorticoid plan and patient characteristics to be included in the operational case definition (now requiring at least 1 joint with arthritis observed by a physician to be present) (Table 1). There was a 63% response rate (133 of 211 surveyed), of which 92.6% expressed willingness to follow glucocorticoid, methotrexate, or anti–IL-1 treatment plans as outlined. Eighty-two percent concurred that an anti–IL-6–based treatment plan should also be offered. Consensus was reached at the 78–85% level for all topics posed (acceptability of patient characteristics, specific details of presented treatment plans, and ability to use plans). Respondents were also asked to rank the 4 CTPs in terms of likelihood of use, with 1 being most likely and 4 being least likely, and there was a relatively even distribution of ratings among the CTPs: glucocorticoids (mean rating 2.48), methotrexate (mean rating 2.05), anakinra (mean rating 2.0), and tocilizumab (mean rating 3.26; note that tocilizumab had not yet received FDA approval for systemic JIA at the time of the survey). The survey may be found in Supplementary Appendix B (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

These standardized CTPs evolved iteratively through meetings of the systemic JIA core work group to the final treatment plans shown in Figures 1–4, which include the addition of a fourth plan (anti–IL-6 [tocilizumab]). Supplementary Appendix D (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658) presents the plans in written form. The glucocorticoid-only plan was simplified without provision for maintenance IV methylprednisolone pulses, and glucocorticoid tapering guidelines were developed (rapid, fast, and slow) with a stated target to be at 50% of the initial dose by 3 months and discontinue by 6 months or earlier (Supplementary Appendix E, available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). The methotrexate and 2 biologic DMARD plans allow for the addition of glucocorticoids with dosing according to the glucocorticoid-only plan. NSAIDs may be added to any treatment plan. All CTPs follow a routine assessment schedule (Table 2) and suggest switching treatment plans in any of the following circumstances: 1) inadequate response, 2) inability to wean glucocorticoids by at least 50% of the starting dose by 3 months, or 3) disease worsening in the first 3 months. Suggested assessment intervals correspond with decision points in the treatment plans. Duration of CTPs cover the initial 9 months of treatment in order to capture at least 6 months of treatment with a second-line agent if a treatment switch is made at 3

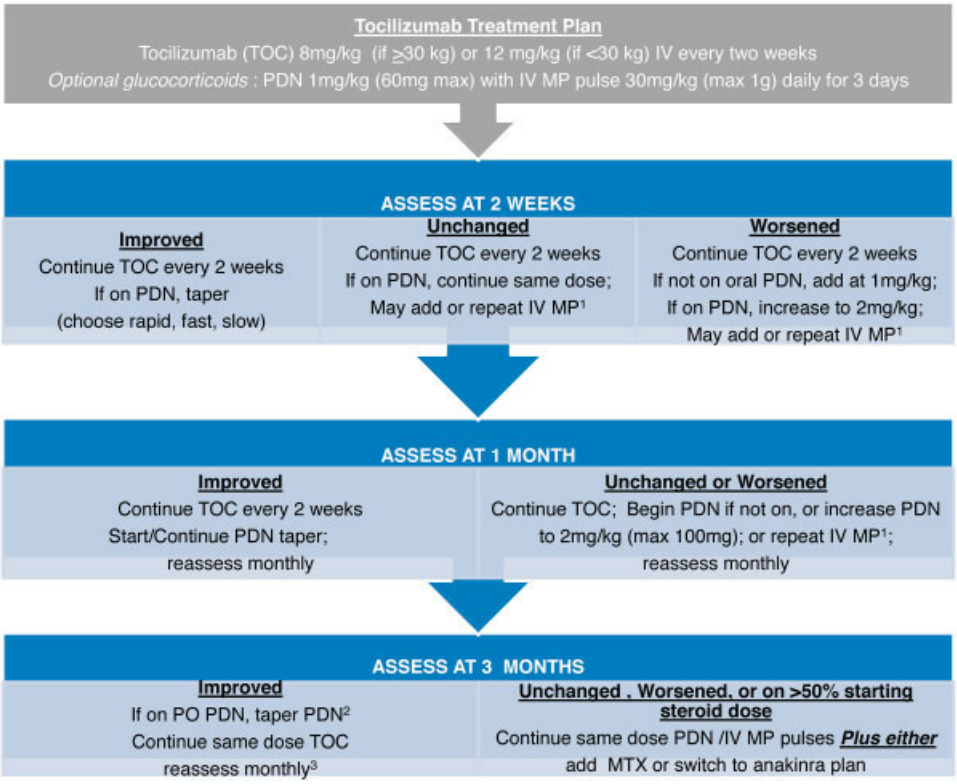

Figure 4. Tocilizumab treatment plan. [1] = intravenous (IV) methylprednisolone (MP) pulses are 1 dosage weekly; [2] = patients who started with rapid taper may be off prednisone (PDN); [3] = if condition worsens, or patient is intolerant of tocilizumab, follow "Unchanged, Worse" pathway; PO = by mouth; MTX = methotrexate.

months. Since the decision to continue with a treatment, add or increase glucocorticoids, or change to a different treatment is dependent on physician judgment, components of evaluation and determination of disease status (worsened, unchanged, or improved) were also included. These components include joint count, systemic features, and suggested minimum laboratory evaluations (Table 2).

DISCUSSION

This is the first effort in pediatric rheumatology to develop consensus-derived standardized treatment plans for the initial 9 months of treatment of new-onset systemic JIA. These plans include recommendations on medication dosing 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 do represent the general and most common approaches to treatment of systemic JIA by pediatric rheumatologists across North America.

Four different CTPs were developed: glucocorticoid only, methotrexate, and 2 biologic DMARD-based plans, anakinra or tocilizumab, any of which can be used with the glucocorticoid treatment plan if necessary. These plans are intended for use by clinicians according to their clinical judgment and experience. The intent of these standardized treatment approaches 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 tolerability in clinical practice. The opportunity to generate knowledge from this approach requires analytical methods to reduce bias, including confounding by indication. Given the current variability in treatment patterns evidenced by our surveys, we expect that each of the different plans will be adopted, thus resulting in patients with differing characteristics and levels of disease activity being treated with each plan. This variation in care can be used advantageously to identify the best clinical situations in which these treatment plans should be used. It is anticipated that as new evidence and therapeutic agents become available, the treatment plans will be updated and revised in an iterative fashion.

There were a number of important challenges in deriving these CTPs. These included the acknowledged heterogeneity of disease presentations and disease courses, as well as the heterogeneity of existing opinions regarding treatment, often based on personal experience and observation. While the project would ideally have created only a few standardized treatment plans to reduce the complexity of comparison, the anticipated availability of IL-6 blockade could not be ignored as a likely effective treatment option. As a consequence, medications less com-

Table 2. Suggested minimum data collection and assessment intervals to be used with treatment plans*

Proposed variables†	Assessment intervals	
	Baseline visit	Followup visits
History		
Demographics		
Date of birth	X	
Sex	X	
Race and ethnicity	X	
Date(s) of symptom onset		
Fever	X	
Rash	X	
Joint symptoms	X	
Pre-enrollment treatment history for systemic JIA	X	
Current medications and doses	X	X
Comorbid diagnoses	X	
Fever of systemic JIA in the past week	X	X
Rash of systemic JIA in the past week	X	X
Duration of morning stiffness	X	X
Serositis in the past week	X	X
Patient has MAS (impression of treating physician)	X	X
Patient-reported outcomes and global assessments		
Pain	X	X
Health-related quality of life	X	X
Physical function	X	X
Parent/patient global assessment of disease activity	X	X
Physician global assessment of disease activity	X	X
Physical examination		
Height, weight, body mass index (kg/m^2)	X	X
Rash	X	X
Active joint count	X	X
Lymphadenopathy	X	X
Hepatomegaly	X	X
Splenomegaly	X	X
Serositis	X	X
Laboratory findings		
CBC (WBCs, hemoglobin, platelet count)	X	X
C-reactive protein	X	X
Erythrocyte sedimentation rate	X	X
Ferritin	X	X
LDH	X	X
Treatment plan–related items		
Serious adverse events or important medical event		X
If plan discontinued, rationale		X
Number of intravenous steroid pulses, if any		X
Uveitis status at last eye examination		X

* Data are collected at baseline and at followup visits: 1–2 weeks and 1, 2, 6, and 9 months. Data collection is encouraged at changes in treatment (even if it does not occur at a scheduled time point). Monthly phone followup is recommended. Any additional visits in between these time points are at the discretion of the physician and data may or may not be collected. JIA = juvenile idiopathic arthritis; MAS = macrophage activation syndrome; CBC = complete blood cell count; WBCs = white blood cells; LDH = lactate dehydrogenase.
† Not included in the table are malignancy and infection evaluation, and screen for tuberculosis at baseline (and then annually).

monly used in systemic JIA, such as TNF antagonists and calcineurin inhibitors, were not included in the treatment plans.

Additionally, the first American College of Rheumatology (ACR) recommendations for the treatment of JIA were published in April 2011 (4). There are notable differences between the CTPs and these recommendations, which were developed using different methodologies and sought to address different questions. One significant difference was the exclusion of tocilizumab from the ACR recommendations because it was not commercially available at the time the recommendations were being formulated (3,4). Another difference is that the guidelines consider the treatment of systemic features and the treatment of arthritis in systemic JIA completely separately. In contrast, the consensus decision was that these clinical aspects could not practically be separated because systemic and arthritic features usually coexist in new-onset systemic JIA pa-

tients. In addition, while TNF inhibitors (20) and abatacept (21) are included in the ACR recommendations for the treatment of the arthritis features of systemic JIA, these treatments are not included in the CTPs, again for similar reasons. Lastly, the CTPs offer more specificity with regard to suggested medication dosing, evaluations, and anticipated time to treatment responses. A significant strength of the plans is that they were derived with the input of a larger and broader group of pediatric rheumatology clinicians.

There was extensive discussion about the development of the operational definition of patients who could be treated with the plans. It is recognized that many patients with systemic JIA in the early stages of disease do not strictly fulfill International League of Associations for Rheumatology (ILAR) criteria, yet need treatment (22). Indeed, the Yamaguchi et al criteria for adult Still's disease does not include arthritis as a criterion (23,24). In order to capture as many patients with systemic JIA as possible while avoiding inclusion of patients with self-limited febrile illnesses or alternative diagnoses, it was ultimately decided to require at least 2 weeks of fevers, at least 1 joint with physician-documented arthritis, and at least 1 other feature compatible with the ILAR criteria for systemic JIA. It must be emphasized that care must be taken to exclude other diagnoses such as infection, malignancy, or a different autoinflammatory condition prior to using these plans, since there is no foolproof diagnostic test for systemic JIA, and these illnesses can be mistaken for systemic JIA. It is essential that these plans should be used only when the practitioner is extremely confident of the diagnosis of systemic JIA. Additionally, these plans are not meant to be proscriptive in either the choice of treatment plan or when the treatment plan should be initiated. Only the treating physician can decide whether one of the plans is appropriate for any given patient at any point in the disease course.

Other discussion points included the scope of the diagnostic evaluation, which is not specified in the treatment plans. Systemic JIA is by necessity a diagnosis of exclusion, for which no specific tests are diagnostic. Given that not all patients with suspected systemic JIA will require a bone marrow aspiration, a positron emission tomography scan, or other specific testing, the extent of exclusionary evaluation must be left to the judgment of the treating physician. Another area of considerable debate included specifics of the dosing of methotrexate, anakinra, and glucocorticoids (the initial dosing, rapidity of dose escalation, and routes of administration of these medications).

Limitations include that the proposed CTPs do not go beyond the initial 9 months and do not address medication tapering aside from glucocorticoids. New anti–IL-1 agents will need to be incorporated as part of the anti–IL-1 plan as they become available, along with modifications to account for any pharmacokinetic differences. Since the CTPs are meant for use in routine clinical practice, the proposed variables and timing of data collection should be similar to the standard of care, yet able to effectively capture relevant health outcomes. Lastly, the CTPs do not address the treatment or diagnosis of MAS, an important complication of systemic JIA, because there are currently no clinically useful standard definitions that are applicable to every patient. The treating physician must therefore be aware of the signs of possible MAS, which can cause rapid deterioration and even death in systemic JIA patients if not recognized and treated promptly. Signs and symptoms of MAS may include persistent fever, marked hyperferritinemia, inappropriate cytopenias (platelets, erythrocytes, and/or leukocytes), evidence of liver injury (e.g., elevated liver enzymes), liver dysfunction (e.g., coagulopathy, synthetic blockage, and elevated triglycerides), and central nervous system dysfunction (25). Note that these are not the only signs and symptoms of MAS, and not all symptoms may be present in any individual patient with MAS.

In conclusion, 4 standardized CTPs for new-onset systemic JIA were developed with the goal of reducing variation in care and to ultimately facilitate evaluation of the comparative effectiveness of these treatments. These plans were found to be acceptable to the majority of survey respondents who are members of CARRA. Coupled with standardized data collection at routine intervals, widespread use of these CTPs offers the potential to serve as the basis for rigorous study of comparative effectiveness of the regimens as used in clinical practice and to ultimately guide increased evidence-based decision making for treatment of systemic 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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