2013 update of the American College of Rheumatology recommendations for the use of disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs in the treatment of systemic juvenile idiopathic arthritis

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PROJECT OBJECTIVES

The broad objective of this project is to update the 2011 American College of Rheumatology recommendations for the use of disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs in the treatment of systemic juvenile idiopathic arthritis (JIA), in the particular areas outlined below. For the remainder of this protocol and in the updated guidelines, non-biologic DMARDs and biologic DMARDs will be referred to as DMARDs and biologics, respectively.

Specifically we aim to:

1. Update the 2011 ACR recommendations regarding: a) indications for DMARDs and biologics for systemic JIA, and b) switching between DMARDs and biologics for systemic JIA.
2. Incorporate the use of anti-interleukin (IL)-1 and anti-IL-6 therapies into the ACR recommendations for the treatment of systemic JIA. See Table 1 for a comparison of drugs addressed in the 2011 and 2013 recommendations.
3. Modify the treatment recommendations for systemic JIA by defining patients into the following 3 main groups: 1) significant systemic features and no significant arthritis, 2) significant arthritis and no significant systemic features, and 3) significant systemic features and significant arthritis.
4. Address treatment recommendations for macrophage activation syndrome in the 2 groups with significant systemic features.

Table 1. Drugs evaluated for the treatment of systemic JIA

Drug	2011 Recommendations	2013 Recommendations
Anti-IL-1		
Anakinra	X	X
Canakinumab		X
Rilonacept		X
Anti-IL-6		
Tocilizumab		X
Anti-TNF		
Adalimumab	X	X
Certolizumab		X
Etanercept	X	X
Golimumab		X
Infliximab	X	X
Calcineurin inhibitors		
Cyclosporine	X	X
Tacrolimus	X	X
DMARDs		
Hydroxychloroquine	X	X
Leflunomide	X	X
Methotrexate	X	X
Glucocorticoids		
Betamethasone	X	X
Betamethasone 17-	X	X

valerate		
Budesonide	X	X
Dexamethasone	X	X
Dexamethasone isonicotinate	X	X
Fluprednisolone	X	X
Methylprednisolone	X	X
Methylprednisolone hemisuccinate	X	X
Paramethasone	X	X
Prednisolone	X	X
Prednisone	X	X
Triamcinolone	X	X
Triamcinolone acetonide	X	X
Triamcinolone hexacetonide		X
NSAIDs		
Ampyrone	X	X
Antipyrine	X	X
Apazone	X	X
Aspirin	X	X
Celecoxib	X	X
Clonixin	X	X
Diclofenac	X	X
Diflunisal	X	X
Dipyrone	X	X
Epirizole	X	X
Etodolac	X	X
Fenoprofen	X	X

Flurbiprofen	X	X
Ibuprofen	X	X
Indomethacin	X	X
Ketoprofen	X	X
Ketorolac	X	X
Ketorolac tromethamine	X	X
Meclofenamic acid	X	X
Mefenamic acid	X	X
Meloxicam	X	X
Mesalamine	X	X
Naproxen	X	X
Niflumic acid	X	X
Oxyphenbutazone	X	X
Phenylbutazone	X	X
Piroxicam	X	X
Prenazone	X	X
Salicylates	X	X
Sodium salicylate	X	X
Sulfasalazine	X	X
Sulindac	X	X
Suprofen tolmetin	X	X
IVIG	X	X
Other		
Etoposide		X
Lenalidomide		X
Thalidomide	X	X
Rituximab	X	X

BACKGROUND

Juvenile idiopathic arthritis (JIA) is one of the most common rheumatologic conditions of childhood, affecting approximately 1 per 1,000 children.[1] Systemic JIA is a JIA category that accounts for 4-15% of JIA[2,3] and is defined as arthritis in one or more joints of at least six weeks duration in a child younger than 16 years with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days and accompanied by one of more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, and serositis.[4] Exclusions for a diagnosis of systemic JIA according to the ILAR criteria include: psoriasis or a history of psoriasis in a first degree relative; arthritis in an HLA-B27 positive male 6 years or older; ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis, or a history of one of these disorders in a first degree relative; IgM rheumatoid factor positivity on 2 or more occasions at least 3 months apart.[4] Physicians treat systemic JIA to control inflammation and to prevent morbidities such as growth disturbances, contractures, joint destruction, and functional limitations. A subset of children with systemic JIA develop features of macrophage activation syndrome, a life-threatening condition characterized by fever, organomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hemophagocytosis, hepatitis, coagulopathy, low or absent natural killer cell activity, and hyperferritinemia.

The American College of Rheumatology (ACR) recently published recommendations for the treatment of JIA.[5] These recommendations covered indications for the initial and subsequent treatment and safety monitoring of therapeutic agents for all categories of JIA, including systemic JIA. Since these recommendations were published, additional therapeutic agents have become available for use in the systemic category of JIA. The availability of these agents, which are anti-IL-1 and anti-IL-6 drugs, will greatly alter the way in which physicians manage children with systemic JIA.

METHODS

We will utilize the RAND/UCLA appropriateness methodology,[6] as described in detail in the 2011 guidelines, to maintain consistency and to allow for cumulative evidence to inform the recommendations update for the treatment of systemic JIA.[5] The recommendations will be developed by 2 expert panels: 1) the Core Expert Panel (CEP), a non-voting working group of pediatric rheumatologists, and 2) the Task Force Panel (TFP), a voting group of pediatric rheumatologists, an epidemiologist, and a patient-family representative. The CEP is initially responsible for the following: 1) clarification of topics for the update, as necessary; 2) the design and conduct of the systematic review; 3) synthesis of the evidence report based on the systematic review findings; and 4) creation of clinical scenarios. The TFP is responsible for rating the clinical scenarios based upon the evidence report from the CEP according to the RAND/ULCA methodology. Upon completion of the TFP voting, the CEP determines the final recommendations, based primarily on the TFP votes.

Systematic Literature Review

The literature search strategies will be designed by an experienced medical research librarian (Janet Joyce) and the co-PIs, with input from the CEP. It will be peer reviewed

by another medical librarian using Peer Review of Electronic Search Strategies (PRESS).[7]

Criteria for Identification of Studies. We will search the following electronic databases: Ovid MEDLINE® (1946-present), Embase (1974-present), PubMed (mid-1960's to the present, and the Cochrane Library. The grey literature, such as reports by the Agency for Healthcare Research and Quality and health technology assessment agencies, will be searched to identify additional peer-reviewed articles not published in journals identified by the above databases. Conference abstracts will be reviewed, tracked to determine whether the contents of these abstracts were subsequently published as peer-review articles, and included in the final evidence report in order to ensure the completeness of our literature search. Trial registries, such as ClinicalTrials.gov, will be searched to identify ongoing and completed trials, and the literature will be tracked to identify published trial results. In the case of ongoing trials, or completed but not yet published trials, every effort will be made to obtain preliminary data for inclusion in the final evidence report.

Search strategies will be designed using the thesauri for each database, i.e., Medical Subject Headings for OVID Medline, PubMed and Cochrane Library and EMTREE terms for Embase. Text words will also be used in OVID Medline, PubMed, and Embase, and keyword/title/abstract words in the Cochrane Library. The search will include terms to retrieve systemic JIA and specific medication names and classes. One part of the search strategy will be designed to update the results of the 2011 ACR JIA Guidelines related to systemic JIA from October 2009 to the present. Another part will include medications and classes for systemic JIA not covered by the 2011 guidelines, and will cover the periods from the beginning of the respective databases to the present. In addition, the search will cover drug therapies in macrophage activation syndrome in JIA from the beginning of the respective databases to the present. See draft search strategy for OVID Medline, Appendix A.

References and abstracts will be imported into bibliographic management software (Reference Manager) and duplicates removed.

The literature searches will be updated in October 2012, to ensure completeness prior to the face-to-face TFP meeting and final voting on the recommendations.

Criteria for study inclusion/exclusion. The search will be limited to human participants and English language. Studies that do not include participants < 18 years of age will be excluded.

Criteria for data collection and analysis. Articles will be reviewed by designated members of the CEP. Titles and abstracts of identified articles will initially be screened to remove non-systematic review articles, commentaries, studies without patients with systemic JIA, and studies with any of the exclusions noted above. The full text of each remaining article will then be additionally screened by two members of the CEP, who will recommend inclusion or exclusion. Discrepancies between reviewers will be resolved by a third reviewer (SR).

Preparing the evidence report for TFP review. Studies will be organized according to the medication studied. They will be further categorized as randomized controlled trials, non-randomized controlled studies and uncontrolled studies. The quality of randomized

controlled trials will be assessed using the Jadad instrument.[8] The quality of cohort studies will be assessed using the New Castle-Ottawa Quality Assessment Scale.[9]

The data abstracted from each article will include participants (number and diagnosis), medication (including dosage), concurrent medications, inclusion criteria, exclusion criteria, baseline disease measures, and primary and secondary outcomes. The data will be entered by reviewers into an Excel spreadsheet developed by the co-PIs.

Multiple publications from the same trial will be identified, and additional reports from the same trial will only be considered if separate, pre-specified outcomes are reported. The strength of evidence of the included articles will be graded using methods of the University of Oxford Centre for Evidence-Based Medicine, UK. The results of the literature review will be summarized in an evidence report to be distributed to members of the TFP prior to the initial voting in October 2012.

PLANNED APPENDICES

A. Final search strategies for literature review
B. List of relevant medications with their typical maximum tolerated doses

AUTHORSHIP

Authorship of the final guidelines update will be at the discretion of the co-PIs, Drs. Ringold and Weiss, and will be dependent on the efforts made by individuals throughout the guideline development process, using the ICMJE Uniform requirements for manuscripts as guidance. The co-PIs will share co-lead authorship, with the names listed in alphabetical order (Ringold followed by Weiss). The tentative list of authors for the final guidelines update includes all CEP members. TFP members will receive special acknowledgement for their participation in the efforts to develop the final guidelines. The authors of the 2011 JIA guidelines will be listed in the acknowledgement section, if not participating in the current CEP.

CONTRIBUTIONS OF PROJECT LEADERS AND PARTICIPANTS

Project co-PIs

- Protocol development (Drs. Ringold and Weiss)
- Leadership/participation in all CEP activities (Drs. Ringold and Weiss)
- Completion of evidence review (Dr. Ringold)
- Leadership of Task Force Panel, including November 2012 meeting (Dr. Weiss)
- Completion of draft guidelines for publication in *Arthritis Care & Research* (Drs. Ringold and Weiss)
- Work with the ACR to develop and finalize a Clinician's Guide, a practical and easily applicable guideline for use by busy physicians (Drs. Ringold and Weiss)
- Presentation of updated recommendations at the Annual Scientific Meeting of the ACR/ARHP, November 2013 (Drs. Ringold and Weiss)

Core Expert Panel

- Clarification of topics for the update, as necessary
- Design and conduct of the systematic review
- Synthesis of an evidence report based on the systematic review findings
- Creation of clinical scenarios
- Drafting of the final recommendations, based primarily on Task Force Panel voting

Task Force Panel

- Rating the clinical scenarios based upon the evidence report from the CEP and according to the RAND/UCLA appropriateness method
  - 1st round of voting: early October, independently performed
  - 2nd round of voting: at face-to-face consensus meeting following the 2012 Annual Scientific Meeting of the ACR/ARHP

DISCLOSURES

In order for the College to most effectively further its mission and to otherwise maintain its excellent reputation in the medical community and with the public, it is important that confidence in the College's integrity be maintained. The cornerstone of the ACR's Disclosure Policy is disclosure of actual and potential conflicts so that they can be evaluated by the College in order to avoid undue influence of potential conflicts.

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Core Expert Panel	
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Ronald Laxer, MD	4 - Novartis
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Carol Wallace, MD	2 - Genentech; Novartis 4 – Amgen; Pfizer

Disclosure Legend

1. Primary Employment
2. Sources of Personal Income to include speakers bureau, honoraria, royalties, expert witness fees, advisory boards, or any other sources of income (excludes salary from primary employer)
3. Intellectual Property to include copyrights, patents, or licenses
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5. Investments to include medical industry and non-medical industry
6. Organizational Benefit
7. Activities with other organizations
8. Family or Other Relations **-** In accordance with the ACR's disclosure policies, relevant financial or other relationships of members of immediate family should also be disclosed

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Appendix A – Draft Search Strategy, 2013 ACR JIA Guideline Update

Syntax Guide:	
/	At the end of a phrase, searches the phrase as a Medical Subject Heading (MeSH)
Exp	A command; explode a subject heading to include all narrower MeSH
$	Truncation symbol
tw	Textword (from title or abstract)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 Arthritis, Juvenile Rheumatoid/
2 juvenile arthritis.tw.
3 juvenile idiopathic arthritis.tw.
4 juvenile chronic arthritis.tw.
5 (childhood adj2 arthritis).tw.
6 JIA.tw.
7 SJIA.tw.
8 SOJIA.tw. (48)
9 still$ disease.tw.
10 still's disease, adult onset/
11 or/1-10 (10065)
12 exp Antirheumatic Agents/
13 disease modifying anti-rheumatic drug$.tw.
14 DMARD$.tw.
15 Hydroxychloroquine/
16 hydroxychloroquine.tw.
17 leflunomide.tw.
18 rituximab.tw.
19 Methotrexate/
20 methotrexate.tw.
21. Exp Anti-Inflammatory Agents, Non-Steroidal/
22 ((non-steroidal or nonsteroidal) adj (anti-inflammator$ or antiinflammator$)).tw.
23 NSAID$.tw. (16002)
24 (ampyrone or antipyrine$ or apazone or aspirin or clonixin or meloxicam).tw.
25 (diclofenac or diflunisal or dipyrone or epirizole or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen).tw.
26 (ketorolac or ketorolac tromethamine or meclofenamic acid or mefenamic acid or

mesalamine or naproxen or niflumic acid).tw.
27 (oxyphenbutazone or phenylbutazone or piroxicam or prenazone or salicylates).tw.
28 (sodium salicylate or sulfasalazine or sulindac or suprofen or tolmetin).tw.
29 Cyclo-oxygenase 2 inhibit$.tw.
30 cyclooxygenase 2 inhibitors/
31 Cyclooxygenase 2 Inhibit$.tw.
32 COX-2 inhibitor$.tw.
33 celecoxib.tw.
34 Etodolac.tw.
35 exp Glucocorticoids/
36 exp Injections, Intra-Articular/
37 (glucocorticoid$ or betamethasone or betamethasone 17-valerate or budesonide).tw.
38 (dexamethasone or dexamethasone isonicotinate).tw.
39 fluprednisolone.tw.
40 (methylprednisolone or methylprednisolone hemisuccinate).tw.
41 (paramethasone or prednisolone or prednisone or triamcinolone or triamcinolone acetonide).tw.
42 Intraarticular glucocorticoid inject$.tw.
43 intra-articular glucocorticoid inject$.tw.
44 Triamcinolone Acetonide/
45 triamcinolone acetonide.tw.
46 Immunoglobulins, Intravenous/
47 intravenous immunoglobulin$.tw.
48 IVIG.tw.
49 Calcineurin/
50 cyclosporine/
51 tacrolimus/
52 Calcineurin inhibit$.tw.
53 cyclosporine$.tw.
54 tacrolimus.tw.
55 Thalidomide/
56 Thalidomide.tw.
57 Lenalidomide.tw.
58 anakinra.tw.
59 exp Receptors, Tumor Necrosis Factor/
60 Tumor Necrosis Factor-alpha/
61 tumor necrosis factor block$.tw.

62 tumour necrosis factor block$.tw.
63 TNF block$.tw.
64 tumor necrosis factor inhibitor$.tw.
65 tumour necrosis factor inhibitor$.tw.
66 TNF inhibit$.tw.
67 adalimumab.tw.
68 etanercept.tw.
69 infliximab.tw.
70 or/12-69
71 200910*.ed.
72 200911*.ed.
73 200912*.ed.
74 2010*.ed.
75 2011*.ed.
76 2012*.ed.
77 or/71-76
78 11 and 70 and 77
79 exp animals/ not humans.sh.
80 78 not 79
81 limit 80 to english language
82 rilonacept.tw.
83 arcalyst.tw.
84 IL-1 TRAP.tw.
85 Interleukin-1 TRAP.tw.
86 exp Interleukin-1/
87 interleukin 1 antagonist$.tw.
88 interleukin 1 inhibitor$.tw.
89 IL-1 inhibitor$.tw.
90 IL-1 antagonist$.tw.
91 anti-IL-1$.tw.
92 canakinumab.tw.
93 ACZ885.tw.
94 Ilaris.tw.
95 IL-1beta antagonist$.tw.
96 IL-1B antagonist$.tw.
97 interleukin-1B antagonist$.tw.
98 interleukin-1beta antagonist$.tw.

99 tocilizumab.tw.
100 Actemra.tw.
101 Interleukin-6/
102 exp Receptors, Interleukin-6/
103 interleukin-6 antagonist$.tw.
104 interleukin-6 inhibitor$.tw.
105 IL-6 antagonist$.tw.
106 IL-6 inhibitor$.tw.
107 IL-6 receptor inhibitor$.tw.
108 interleukin-6 receptor inhibitor$.tw.
109 anti-IL-6$.tw.
110 golimumab.tw.
111 Simponi.tw.
112 certolizumab.tw.
113 Cimzia.tw.
114 CDP870.tw.
115 Etoposide/
116 etoposide.tw.
117 triamcinolone hexacetonide.tw.
118 or/82-117
119 11 and 118
120 exp animals/ not humans.sh.
121 119 not 120
122 limit 121 to english language
123 Macrophage Activation Syndrome/
124 macrophage activation syndrome.tw.
125 MAS.tw.
126 or/123-125
127 dt.fs.
128 11 and 126 and 127
129 11 and (70 or 118) and 126
130 128 or 129
131 exp animals/ not humans.sh.
132 130 not 131
133 limit 132 to english language
134 81 or 122 or 133