Authors' Response to Public Comments on the Project Plan for the ACR Juvenile Idiopathic Arthritis Guideline

October 2017

We greatly appreciate the thoughtful comments from members of the pediatric rheumatology community regarding the proposed ACR juvenile idiopathic arthritis treatment recommendations. The questions and our responses are summarized as follows:

1. "Did you consider including the BASDAI and BASFI as outcome measures for axial arthritis?"
   These outcomes were considered, but they were not initially included as they have not been validated in children and adolescents. However, based on this comment and further discussion, we have added them as disease activity outcome measures for the questions related to treatment of enthesitis and sacroiliitis.

2. "Did you consider including intra-ocular steroid as a treatment for uveitis?"
   Intra-ocular glucocorticoids are currently addressed in Question 9 of the uveitis questions as posted (In JIA children with chronic active uveitis, irrespective of use of topical or systemic therapy, should giving intraocular steroid injections versus not giving intraocular steroid injections be recommended?)

3. A comment was made regarding whether hydroxychloroquine monotherapy was considered.
   Hydroxychloroquine is currently considered in these guidelines as part of triple DMARD therapy. Hydroxychloroquine monotherapy was not considered within the scope of these questions as hydroxycholoroquine has been shown not to be superior to placebo in the treatment of JIA (Brewer EJ, et al. NEJM 1986:15;314(20):1269-76).

4. A comment was made regarding whether the treatment of patients with < 5 joints who had failed multiple therapies would be addressed.
   We agree this is an important group of patients to address. Their treatment will be considered in a future update on oligoarthritis.

5. How were the participating "experts" and other members chosen? By whom and with what criteria? What was the process?
   The participants were selected in accordance with ACR policy and conflict of interest guidelines (please see attached).

6. "Sacroiliitis, by any means, is rare in children and adolescents. Inflammatory back pain (IBP) is also rare before 18 years old. Despite specificity and PP values are high, its sensitivity is very low. . . . active SI and/or IBP are detectable in 15% of patients with jSpA, ERA, and related entities before the age of 16 and seldom occur as a unique manifestation; most patients have arthritis and or enthesitis.
   The estimates of the prevalence of sacroiliitis / inflammatory back pain are variable across published cohorts. While these new recommendations could be applied to patients with isolated sacroiliitis or enthesitis, it is anticipated that patients with a combination of sacroiliitis and peripheral arthritis would be treated primarily according

to the sacroiliitis recommendations, but with consideration of the updated polyarthritis recommendations (if 5 or more joints involved) or the previously published oligoarthritis recommendations (Beukelman T, et al. Arthritis Care Res. 2011:63[4]:465-482) (if fewer than 5 joints involved), particularly in the setting of refractory peripheral arthritis. The enthesitis guidelines are intended for patients with predominantly enthesitis, including those with isolated or refractory enthesitis.

7. ”The extrapolation of poly and oligo JIA recommendations to ERA would be certainly inappropriate since there is no evidence at all that MTX, HXCL, and leflunomide produce some benefit in these children; such circumstance would delay the onset of TNFi and other biologics for at least three months. Sulfasalazine has a marginal effect.

   The treatment of children with peripheral spondyloarthritis is of significant research interest. The decision to include these patients in the polyarthritis group of the current recommendations was based on discussions with the Core Workgroup and Expert Panel. It was agreed that there is lack of evidence at this time to support the conclusions stated by the commenter above. We also agree that additional research is needed for this group of patients. This may be readdressed as additional data become available and classification criteria are refined.

8. “The definitions that include clinical exam findings rely on unreliable signs of both sacroiliitis and enthesitis. These definitions are certainly practical and likely correspond to many studies that investigated treatment and outcomes of these conditions, but they are nonetheless problematic. Levels of evidence and recommendations should consider the definitions of sacroiliitis and enthesitis that studies used. “

   The definitions of sacroiliitis and enthesitis were chosen to be practical and appropriate for use in routine clinical care, the setting where these recommendations are intended. These definitions are also similarly used in clinical trials. Although they lack sensitivity and specificity, as do other definitions, this should not affect the level of evidence for the studies.

9. “Was there consideration of evaluating evidence and making recommendations for weaning therapy for polyarthritis and sacroiliitis?”

   The topics of tapering and discontinuation of medications for patients with JIA and inactive disease were considered and candidate PICO questions were developed. However given the need to restrict the scope of the current projects, these questions were put on hold for future JIA treatment recommendation efforts.

10. “. . . there should be international participation in this project (both to the task force and voting panel), including ACR international members. I think that more than two experts (as in 2013) from various parts of the world should be added.”

    We agree that there are international experts who could contribute greatly to the development of JIA guidelines. The input of international experts is eagerly considered through public comment on the project plan and scope, and their published work is included in the literature review. However, because ACR guidelines are primarily written for the U.S. audience and consider the health care system and therapies that are available in the U.S., the ACR generally populates its guideline development teams with members from the U.S. Exceptions may be made if there is a non-U.S. expert whose

knowledge and/or experience is so unique that it cannot otherwise be conveyed in the development team's work without that person's presence, but this is not common.

11. "Summary efficacy/safety data from the major registries (Germany, Pharmachild/PRINTO, CARRA, UK), if possible, should be made available to the task force/voting panel. The registries have come a long way since the 2011 recommendations and add important info that should be considered in the decision process."

    Published data from these Registries were included in the literature review and have been included wherever relevant. Unpublished data or data summaries were not included.

12. ". . . some of the questions, like NSAID use, were settled in the 2011 recommendations.

    Prior recommendations were generated using Rand methodology. The goals of this project were to update existing recommendations using GRADE methodology, which included assessing evidence for medications previously included, while also incorporating medications not addressed in the prior recommendations.

13. "The treatment of polyarthritis is not complete without specifically addressing TMJ arthritis (which has caused much controversy). The question should include IA steroids vs. systemic therapy (DMARD +/- biologics) and how many maximum injections."

    We agree that the topic of treatment of TMJ arthritis is very important. This topic was included in the initial scoping and candidate PICO questions were generated. However, given the large number of questions required to address the current scenarios, the decision was made to consider TMJ arthritis in the next update.

14. A comment was made regarding the need to reassess frequency of laboratory monitoring for patients on methotrexate, in particular whether liver function testing is needed as often as 3 months given some animal models suggesting rare significant liver toxicity even with very high doses of methotrexate.

    We agree that updates to medication monitoring recommendations are of ongoing importance. This topic was considered as part of the initial scoping but was subsequently excluded given the large volume of questions generated. It is anticipated that this topic will be addressed in future updates.