Editorial

Is Minimal Clinically Important Difference Relevant for the Interpretation of Clinical Trials in Pediatric Rheumatic Diseases?

It is increasingly recognized that a complete assessment of patients with rheumatic diseases should include not only disease related measures such as activity, damage, and laboratory markers of inflammation, but also the evaluation of quality of life (QOL), or the associated constructs of health related QOL (HRQOL) and disability[1]. In recent decades many authors have developed instruments to measure these 3 concepts in children to provide needed specific instruments to take into account disease and physical/mental age-related issues related to growth and development.

The most widely used tools to assess HRQOL are the Child Health Questionnaire (CHQ)[2], the Pediatric Quality of Life Inventory Scale (PedsQL)[3], and for disability the Childhood Health Assessment Questionnaire (CHAQ)[4]. These 3 tools are multidimensional (they include assessment of physical and psychosocial well-being), can be completed by the children or parents, are fully validated for different pediatric conditions, and are available in several languages[5]. The main disadvantages are their complexity, length, and difficult scoring systems, which sometimes makes their use problematic in the everyday clinical setting.

In this issue of *The Journal*, Gong, *et al* report further psychometric properties of the Quality of My Life questionnaire (QoML); a one-dimensional tool, the QoML uses 2 visual analog scales to evaluate global QOLand HRQOL[6,7]. The most striking characteristic of the QoML is its simplicity: respondents "determine for themselves which aspect of life (or health) should receive the most weight in determining their own QOL or HRQOL." This simplicity, and the lack of direct statistical comparison with classic multidimensional tools, are the reasons why the QoML has not yet found a place in the quality of life research field.

THE CONCEPT OF RESPONSIVENESS AND MINIMALCLINICALLY IMPORTANT DIFFERENCE

One of the key concepts for the validation of a tool is the evaluation of responsiveness, defined as the ability of a measure to detect change over time.

While calculation methods for responsiveness are well defined[8], it is not clear how to quantify the importance of such change. Directly related to responsiveness is the concept of minimal clinically important difference (MCID), initially defined as "the smallest (absolute) difference in score which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management"[9]. Therefore differences in scores smaller than the MCID are considered not important independent of their statistical significance.

Recently the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group proposed 3 key features to define responsiveness[10,11]: the setting of the study, either at a group level (average change) or an individual level (smallest detectable change in an individual); the way in which groups are structured for comparison (e.g., changes within or between groups over time, etc.); and the type of change (in increasing order of importance) from minimum potentially detectable change to the observed change/difference measured in a given population deemed to be an important difference/change from the perspective of the patient, researcher, payer, or society.

Few studies are available to evaluate MCID in children. Gong, *et al* report the MCID for the QoML, with an approach that mirrors previous work by the same group on the Childhood Health Assessment Questionnaire[12]. With an elegant method, the authors invited parents and children with juvenile idiopathic arthritis (JIA) to think about an hypothetical clinical scenario with a drug that improves or worsens the disease "just enough to make a difference."[7] The median MCID for improvement is equal to 7 mm (7% change over the total possible score) for the QOL scale and 11 mm (11%) for the HRQOL scale, while the corresponding values for worsening were somewhat greater (–33 mm and –38 mm, respectively). As recognized by the authors it can be argued that their innovative use of hypothetical scenarios to discern MCID is also a major limitation that ham-

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pers the transferability of their work in the research field as discussed below.

Similar work has been done on the CHAQ, for which the same group proposes a median MCID for improvement equal to –0.13 (–4.3%), and for worsening, 0.75 (25%). Similar results were reported by Brunner, *et al*[13] in a data-driven study with comparable patients.

THE CONCEPT OF MCID IN PEDIATRIC RHEUMATOLOGY CLINICALTRIALS

If there is no doubt that evaluation of MCID is a fundamental step in psychometric evaluation of a new tool, then it would also seem important to carefully evaluate the setting of the study and the type of change/difference measured.

With regard to setting, Gong, *et al* used a convenience sample of 131 patients with inflammatory arthritis in which up to 22 (17%) were non-JIA (i.e., reactive arthritis, etc.). The joint count and inflammatory markers were not reported, but the majority of patients had mild or no disability, with a median Steinbrocker class I, mean parent-reported CHAQ of 0.36, and an almost normal parent-reported QOL and HRQOL (mean 84.2 and 83.7, respectively). A sample with similar baseline characteristics has been reported by Brunner, *et al*[13] and can be considered as the current standard population for most tertiary pediatric rheumatology centers with access to biologic therapies. Indeed, it has been reported from a very large unselected population with JIA that up to 24% (780/3310) have no disability (CHAQ equal to zero)[14]. The problem with this kind of sample is that the baseline values for QOL/HRQOL or disability are so close to normal that the expectation for further improvement is minimal and the related MCID is small. Similarly, the reverse holds for worsening, where there is greater potential for deterioration, making the MCID relatively bigger. Moreover, the well known ceiling effect of the CHAQ (i.e., tendency of scores to cluster at the end of the scale) makes the scale intrinsically less sensitive to change in milder levels of disability, decreasing its ability to detect improvement in function for those patients who are close to or at the ceiling.

A different situation is likely encountered in clinical trials, where only patients with a minimum threshold of disease activity/severity (i.e., at least 5 active joints) are enrolled. While there are no data for the QoML scale, abundant information for the CHAQ shows that the median CHAQ was 1.4 in a trial with etanercept[15] and 1.3 in a trial with methotrexate (MTX)[16], and that only 3% and 6% of patients, respectively, had a score of zero at baseline. The same considerations hold true for juvenile dermatomyositis, with just 6% (16/290) of patients having no disability[17].

Regarding types of MCID, the OMERACT group are considering the merits of the American College of Rheumatology 20% improvement criteria (ACR20) as a method to discern important difference/change in rheumatoid arthritis (RA)[18]; similar definitions exist in pediatric rheumatology, like the ACR pediatric 30% criteria for JIA[19], as well as for other diseases[17,20]. These definitions were developed with a data-driven approach that took into account both physician and parent judgment of response to therapy, and all contain a domain that is aimed to evaluate HRQOL and/or disability. The definitions require a certain minimal degree of improvement (20% for RA, 30% for JIA, etc.) in the core set variables (joint measures, disability, HRQOL, etc.) that can be considered as the MCID to evaluate drug efficacy. If we return to the example of pediatric trials in JIA, it can be observed that the median absolute improvement for the CHAQ in etanercept trial was 0.5 and for the MTX trial 0.34, which are much higher than the reported MCID in the convenience samples presented above. This difference becomes even more striking when compared with change calculated only in the subgroups of patients who responded to MTX therapy according to ACR pediatric 30%, 50%, and 70% levels of improvement, with an absolute change for the CHAQ ranging from –0.5 to –0.71.

CONCLUSION

The development of new, more user-friendly questionnaires to evaluate QOL and HRQOL is surely needed, but the relevance of new findings should be compared with that of other already validated tools.

While the MCID concept is important for the psychometric validation of a tool, its clinical meaning must be carefully evaluated in the setting of the study and cannot be transferred immediately for the evaluation of more complex situations such as response to therapy in a clinical trial. The existing validated definition of improvement used to define response to therapy in pediatric rheumatic diseases remains the main outcome to prove the efficacy of drug therapies.

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