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Correspondence:
Namasivayam Ambalavanan
Division of Neonatology, Department of Pediatrics
525 New Hillman Bldg, 619 - South 19th St.
University of Alabama at Birmingham
35233 Birmingham, AL - USA
Tel.: +1 (205) 934.4680
Fax: +1 (205) 934.3100
E-mail: ambal@uab.edu

Childhood quality of life in the changing landscape of pediatric rheumatology

Andreas Reiff*

The last decade has seen dramatic changes in the treatment of children with rheumatic disease. With the introduction of biologic agents into adult and pediatric autoimmunity comes an increasing understanding that patients with these disorders can experience improvement in their quality of life (QOL).

Prior to their introduction, the therapeutic armamentarium was not only limited in its extent and toxicity but also by its efficacy. On the other hand, the available tools assessing outcome were narrowly focused, literally applied from the adult literature, untested and mainly failed to assess the true impact of a therapeutic approach, which ultimately remains the only relevant one, QOL.

See related article on page 308

The article by Klatchoian et al.[1] from São Paulo, Brazil, which this editorial is dedicated to, examines the validity of a QOL score in a Brazilian population of children with systemic lupus (SLE) and juvenile arthritis (JA).

In the latter population, it has finally been recognized that these diseases can persist into adulthood causing disability, pain, and physical dysfunction.[2,3] Although it was once thought that children with JA outgrow their disease, long-term remission is infrequent, with remission rates (defined as drug-free and asymptomatic for ≥ 2 years) varying greatly among disease subtypes.[4,5] A recent retrospective analysis of 392 patients 8 years of age and older found that the probabilities of remission 10 years after onset were 37, 47, 23, and 6% for patients with systemic-onset, oligoarticular, rheumatoid factor (RF)-negative polyarticular, and RF-positive polyarticular JA, respectively.[4]

A review of several studies in 984 children with JA over a mean of 20.5 years concluded that, at a mean age of 30 years, 47% of these patients still had active arthritis, 46% reported difficulties in daily living, and 22% had undergone JA-related

* MD. Head, Division of Rheumatology, Keck School of Medicine, University of Southern California (USC), Los Angeles, CA, USA. Children's Hospital Los Angeles, Los Angeles, CA, USA.

The author is member of Scientific Advisory Board at Abbott Laboratories, Pfizer, Merck, Novartis, Promotional SpeakersBureau - Amgen Inc., Wyeth Pharmaceuticals, Abbott.

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surgery.[2] A long-term follow-up study of 246 adults with long-standing JA showed that more than 1/3 of patients had severe functional limitation[5] and 1/3 of patients experienced severe pain.[6] Children with JA experience impairment in health-related QOL (HRQOL) compared to their healthy peers, as measured by decrements in the domains of physical and psychosocial well-being.[7] Chronic arthritis also negatively impacts emotional, social and school functioning.[4,5,8,9] Adult patients who had childhood-onset arthritis have been shown to have high rates of anxiety and depressive illness,[5] and have a higher mortality rate compared to the general population.[10]

Similar data have been reported in children with SLE. In this condition, improved treatments have led to increased life expectancy, but children and adolescents with SLE are now facing considerable morbidity due to the sequelae of disease activity, side effects of medications, comorbid conditions and delays in academic achievements.[11-15] Lacks & White[16] found that at least some degree of long-term and often permanent organ dysfunction from either SLE or its treatment was seen in 88% of the sampled patients. These complications included hypertension (41%), growth retardation (38%), chronic pulmonary impairment (31%), ocular abnormalities (31%), permanent renal damage (25%), neuropsychiatric symptoms (22%), musculoskeletal damage (9%) and gonadal impairment (3%). Thus, the management of patients with juvenile-onset SLE is now aimed not only at preventing death, but also at providing QOL for children adapting to the physical and psychological consequences of a severe chronic illness.

So how can we neglect the assessment of QOL under these circumstances?

Preliminary evidence from trials mainly with anti-tumor necrosis factor (TNF), anti-IL-1 and anti-IL-6 agents in arthritis and anti-B cell therapies in SLE, seems to suggest that patient outcomes and consequently QOL are about to change. Multiple trials over the past 10 years not only demonstrated unprecedented efficacy and safety but also, for the first time, introduced tools that assessed a comprehensive treatment outcome for arthritis and SLE including functional and pain scores.

The more recently introduced arthritis tool, known as the ACR Pediatric 30 (ACR Pedi 30), was developed in 1997 to standardize the definition of a clinical response and improvement in trials involving patients with JA.[17] These preestablished and validated definitions of response now also enable comparisons of antiarthritis therapies across studies. Trials published after the development of the ACR Pedi 30 have generally used these criteria to evaluate the efficacy of JA therapies. The ACR Pedi 30 is achieved when there is an improvement in at least three variables by at least 30% and worsening in not more than one variable by more than 30%:

- Physician global assessment of disease activity;
- Parent/patient assessment of overall well-being;
- Functional ability (disability index of the Childhood Health Assessment Questionnaire - CHAQ);
- Number of joints with active arthritis;
- Number of joints with limited range of motion;
- C-reactive protein or erythrocyte sedimentation rate.

However, achieving only a 30% improvement can no longer be considered a meaningful degree of progress, since in many clinical trials patients receiving placebo often achieve this level. The ACR Pedi 50, 70, 90, and 100 implying 50, 70, 90, and 100% improvement, respectively, are more meaningful parameters to evaluate true improvement and have to become the true benchmark of successful clinical treatment.

Similar to the ACR Pedi 30 in arthritis, standardized methods to assess morbidity, although less focused on QOL such as the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (the SLICC/ACR Damage Index or SDI), have been recently used and validated for children and adolescents with SLE.[18,19]

In this changing landscape of revising treatment paradigms and increasing need for the development and utilization of pediatric HRQOL tools, falls the study by Klatchoian et al.,[1] which attempts to comprehensively assess patient health and well-being and demonstrates the initial feasibility, reliability and validity of the Brazilian Portuguese version of the Pediatric Quality of Life Inventory (PedsQL™) version 4.0, Generic Core Scales for interviewer-administration in a sample of mostly poor children with rheumatic diseases in São Paulo, Brazil. Multidimensional HRQOL tools have been increasingly acknowledged as an essential health outcome measure in pediatric medicine.

The study is based on the original American PedsQL™ 4.0[20] which has been cross-culturally validated in a growing number of countries, including Australia,[21] Germany,[22] United Kingdom,[23] Norway,[24] Finland[25] and Japan.[26] Using a Brazilian Portuguese translation of the PedsQL™ 4.0, the authors compared 240 healthy children and adolescents from São Paulo City and 105 children with chronic JA and SLE. However, different from the original studies of Varni et al.,[27,28] which were self-administered, the authors opted to read the PedsQL™ (interviewer-administration) for all groups and parent/caregivers due to the low socioeconomic status and high rate of illiteracy in their patient population.[1]

They could confirm that the QOL in children with rheumatic diseases was significantly lower throughout all dimensions than the healthy control group ($p < 0.0001$). In addition, the parent proxy-report correlated highly with child self-report for physical and academic functioning while lower correlations were observed for emotional and social functioning. The Brazilian Portuguese version of PedsQL™ was found to be non time consuming, easily administered and correlated not only with the previously translated Brazilian Portuguese versions of the CHAQ and Childhood Health Questionnaire (CHQ) ($p <$

0.005 in all correlations),[29,30] but was also consistent with previous PedsQL™ translations.

With the availability of new outcome data, childhood rheumatic diseases can no longer be considered a benign disease. Early, aggressive pharmacologic intervention is a critical component of optimal disease management in order to prevent further disease progression, restore organ function, and promote normal growth and development. By adopting a multifaceted approach to the management of childhood rheumatic diseases that encompasses early, aggressive pharmacologic treatment strategies, appropriate physical and occupational therapy, and psychosocial support, long-term functional impairment is likely to be reduced or prevented, and QOL will be improved in children with these diseases.

Although joint counts and laboratory values are important parameters of disease improvement, tools such as the CHAQ and the PedsQL™ as introduced in its Portuguese version in the article mentioned above, will become the ultimate indicators of measuring true treatment success.

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