Summing Up: Quality of Life in Chronic Immune-Mediated Inflammatory Diseases

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ABSTRACT. A series of reports is summarized in which measurement of quality of life (QOL) in various immune-mediated inflammatory diseases (IMID), the parameters that contribute to QOL, and the interrelationship between inflammatory diseases in specific organ systems and psychosocial domains are explored. Current treatment trials in IMID include QOL measures, particularly clinical trials of biologic therapy. There is increasing evidence that several available therapies benefit QOL. Among the factors that contribute to QOL, fatigue, depression, and stress are common and deserve attention from clinicians managing these patients. (J Rheumatol 2011;38 Suppl 88:62–5; doi:10.3899/ jrheum.110908)

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Chronic immune-mediated inflammatory diseases (IMID) are increasingly prevalent in both children and adults. In the proceedings of a meeting published in this supplement to *The Journal* a number of international experts reviewed key aspects contributing to the quality of life (QOL) in individuals with these diseases. QOL encompasses well-being from the perspective of all physical, emotional, and social domains. This series of reports explores measurement of QOL in various IMID, parameters that contribute to QOL, and interrelationships among inflammatory diseases in specific organ systems and psychosocial domains. Numerous studies have demonstrated that patients with IMID have a significantly worse QOL compared to the general population.

Although neither generic nor disease-specific health-related QOL (HRQOL) instruments are perfect, their combination makes it possible to determine the minimum clinically important difference that predicts a relevant improvement upon which clinical and policy-related decisions can be made.

QOL TOOLS FOR ADULTS WITH IMID

Wells, *et al*[1] describe the necessary components in developing HRQOL tools, including defining the relevant domains, developing the tool, testing it, modifying it, and finally validating it. Russell, *et al*[2] report on disease-specific and generic QOL measurement tools used in arthritides, psoriasis, and inflammatory bowel disease (IBD). The Health Assessment Questionnaire (HAQ) and modified HAQ are 2 of the most commonly used functional measures in rheumatology. Generic measures, such as the Medical Outcomes Study Short-Form 36 and the EuroQoL-5 dimensions, are commonly used but may lack the ability to register changes. Fatigue has been found to correlate with IMID activity, but where studied in adult arthritis, fatigue was not considered to be an inflammatory variable nor to have a unique association with either osteoarthritis or rheumatoid arthritis (RA) or treatment. Psoriasis surveys have reported very high rates of subject frustration, shame, and embarrassment as well as depression. In IBD, the Inflammatory Bowel Disease Quality of Life Index has long been used as a QOL measure in clinical trials and correlates highly with disease activity[3]. Impairment of QOL by this disease-specific measure and by generic measures has been widely reported for those with active disease, but QOL in those with inactive disease approaches that of the general non-affected population[4]. In another report in these proceedings Rosenbaum, *et al*[5] review that markedly poorer visual functioning in uveitis is associated with poorer overall health status compared to healthy subjects, which contributes to severely impaired QOL. Compounding the impaired QOL in these diseases is that many IMID overlap, such that inflammatory arthritis, uveitis, inflammatory skin diseases, and IBD may be seen in combination in any individual patient.

QOL TOOLS FOR PEDIATRIC PATIENTS WITH IMID

Duffy, *et al*[6] review disease-specific tools available in pediatric rheumatic diseases and IBD. Several juvenile idiopath-

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ic arthritis (JIA)-specific measures of functional status and HRQOL have been developed[7]. These include the Childhood Health Assessment Questionnaire, the Pediatric Quality of Life Inventory (PedsQL) 3.0 Rheumatology Module, and the Juvenile Arthritis Quality of Life Questionnaire. Although the IMPACT questionnaire (and its most recent iteration IMPACT III) is the most widely used and validated tool for pediatric IBD available, it is still in evolution in studies utilizing large numbers of individuals[8]. There are generic instruments as well, such as the PedsQL Multidimensional Fatigue Scale, PedsQL 4.0 Generic Core Scales, and the Children's Depression Inventory. The PedsQL Multidimensional Fatigue Scale was developed to measure child and parent perceptions of fatigue and has been validated in a variety of pediatric chronic diseases including JIA and IBD.

In JIA it was determined that disability and pain were the important determinants of physical and psychological well-being, irrespective of geographic area[9]. Children with IBD often suffer from depression, anxiety, social isolation, altered self-image, family conflict, medication adherence problems, and school absenteeism. A child with IBD might also have difficulties maintaining social activities. Up to 60% of children with Crohn's disease experienced prolonged absences from school, 67% were unable to participate in sports on a regular basis, 60% felt unable to leave the house, and 50% were unable to play with their friends[10].

FATIGUE, DEPRESSION, AND STRESS

Three factors that may greatly contribute to QOL — fatigue, depression, and stress — were reviewed in these proceedings[11,12,13,14]. IMID-related fatigue negatively affects patient physical and cognitive well-being. This form of fatigue, often described as "overwhelming weariness" and "exhaustion," is also one of the most prevalent concerns in patients with IMID[15,16,17,18]. Clinically relevant fatigue is reported in about 50% of patients with RA and ankylosing spondylitis. Rates may be even closer to 75% in psoriatic arthritis. In IBD 70% of patients with active disease complain of fatigue, but as many as 30% with inactive disease have fatigue, which may be at most only slightly higher than the general population[18]. In both RA and IBD, the association between fatigue and inflammation appears to be relatively weak, suggesting that psychosocial factors play a more important role in IMID-related fatigue than inflammatory factors. Clinicians treating patients with IMID usually put significant effort towards managing pain and disability. However, fatigue in this patient population should not be ignored. Addressing fatigue in the clinic should begin with clinician awareness of this formidable problem and would also depend on a strong physician-patient relationship.

Patients with major depression, with or without other medical illness, have been found to have activated inflammatory pathways[19,20,21,22,23]. The association between depression and inflammation is bidirectional, with a depressed state triggering release of proinflammatory cytokines and an inflamed state releasing cytokines that may trigger depression. Hence treatment of depression may possibly improve inflammation, as has been shown in animal models[24]; and treatment of the inflammation may also improve depression. Depression is common in the general population, with lifetime prevalence rates of 29% and 21% for anxiety and mood disorders, respectively[25]. Community studies also indicate that a great deal of the functional impairment and disability associated with health conditions are related to the presence of anxiety or depression. Reciprocal influential processes between an IMID and depression likely exist.

Major depressive disorder is 2–3 times more common in RA than in the general population, affecting 13%–15% of RA patients[26]. Depression correlates with disease activity. In one study of RA, depressed patients had higher disease activity scores using 28-joint counts (DAS28) at all timepoints[27]. A high prevalence of psychiatric disorders in patients with psoriasis has been reported in numerous studies and in many different populations[28,29,30]. A recent study found that patients with psoriasis are at increased risk of depression, anxiety, and suicidal ideation compared to controls[31]. Further, those with severe psoriasis were significantly more prone to depression and suicidal thoughts than patients with mild disease. Higher levels of depression and anxiety versus community controls have also been reported in IBD[32,33]. Several studies also suggested that anxiety and depressive symptoms are more likely to be elevated during periods of increased disease activity[34,35,36,37]. The prospective studies, although limited, consistently indicate that depression plays a role in disease exacerbation, and as such should be taken into consideration when initiating treatment[34,35].

Recent data suggest that psychiatric comorbidities may exacerbate chronic health conditions through a number of mechanisms, including decreased adherence to prescribed treatments[38], suppressed immune system functioning, and increased autonomic nervous system or hypothalamic-pituitary-adrenal axis activity[39]. Effective management of anxiety or depressive disorders can decrease patients' suffering and lead to improved functioning and QOL.

While there are data that both support and refute the contention that stress can affect the course of these diseases, the balance of evidence supports a role for stress, and in particular having high perception of stress as being associated with adverse disease course. Much of the evidence for this comes from IBD. The strongest evidence came from a recent prospective study that, using a population-based IBD sample and directly comparing potential risk factors for disease flare, found that the rates of major life-related stressful events, high perceived stress, and negative mood were significantly different between those who experienced flare

and those who were in remission[40]. The flare group was more likely to have a major stressful event in the 3-month period before the relapse ($p = 0.01$) and the flare group reported a higher total stress impact of major events (7.2 vs 4.95; $p < 0.01$) compared to those without flare. Stress has also been shown to exacerbate psoriasis[41,42]. The exact mechanisms of how stress might influence IMID are unclear. In regard to IBD, it is known that activation of the autonomic nervous system in response to stress causes further stimulation of the sympathetic and parasympathetic nervous systems, which communicate with the enteric nervous system in the gut; this in turn controls and regulates motility, exocrine and endocrine functions, and microcirculation of the gastrointestinal tract. This may in turn affect immune function in the gut and, further, even the gut microbiome.

It stands to reason, then, that therapies aimed at reducing stress or enhancing stress management may in turn lead to better IMID control. While this is plausible in principle, in practice the evidence is lacking. Studies that better define the relationship between stress and disease activity and that determine how stress management techniques influence disease course are needed. Further, the effects of stress on the immune responses considered to be specific to individual IMID may shed light on the adverse effect stress may have, and may provide another therapeutic target in preventing disease relapse.

In summary, the reviews published in these proceedings dissect the components of QOL in IMID and the interrelationship between a variety of psychological, physical, and disease-specific factors that contribute to QOL. Current treatment trials in IMID include QOL measures, and this has been a particularly important aspect of clinical trials of biologic therapy. There is increasing evidence that several of our available therapies benefit QOL. Fatigue, depression, and stress are common factors contributing to QOL that deserve special attention from clinicians managing these patients. Further research on better defining the role of these factors in the disease course is warranted.

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