Editorial

Fibromyalgia as a Contextual Factor Influencing Disease Activity Measurements in Spondyloarthritis and Psoriatic Arthritis

Psoriatic arthritis (PsA) and spondyloarthritis (SpA) are chronic inflammatory conditions that cause progressive joint damage and disability. Apart from causing swelling and pain in multiple joints and entheseal sites, they are associated with fatigue, emotional effects, and poor health-related quality of life (HRQOL). Fibromyalgia (FM) is a chronic condition probably related to variations in central pain processing[1] and is characterized by widespread bodily pain associated with somatic symptoms including fatigue and sleep disturbance. These manifestations of FM may overlap with those of PsA and SpA. It is also well known that FM may coexist with various rheumatic diseases. For example, the prevalence of FM among patients with rheumatoid arthritis (RA), systemic lupus erythematosus, and Sjögren syndrome was higher than that expected in the general population[2].

In this issue of *The Journal*, Wach, *et al*[3] and in a recent issue, Brikman, *et al*[4], described the coexistence of FM in 17.8% of PsA and 17.5% of SpA patients, respectively. Women had a higher prevalence of concomitant FM in both conditions. Patients who had concomitant FM-PsA or FM-SpA in these studies had worse disease activity scores. Wach, *et al* also demonstrated that outcome measures [Ankylosing Spondylitis Disease Activity Score–C-reactive protein (ASDAS-CRP)] that incorporated objective measurement of systemic inflammation (CRP) were less influenced by concomitant FM. Symptoms of FM-like bodily pain and fatigue can mimic disease activity, while objective biomarkers of inflammation are less likely to be falsely positive and may thus reflect disease activity more accurately.

These findings were consistent with another study in axial PsA and ankylosing spondylitis, which reported that the version of ASDAS that incorporated both CRP and erythrocyte sedimentation rate (ESR) was superior in distinguishing the overall health status to the purely patient-reported Bath Ankylosing Spondylitis Disease Activity Index[5]. These reports highlight the need for awareness of the effects of concomitant FM in patients with PsA or SpA, and show that caution is needed in interpreting disease activity assessments (especially when based purely on patient reports) in such patients.

Assessment of disease activity is critical for optimizing treatment outcomes for patients with inflammatory arthritis, including PsA and SpA. The use of patient-reported outcomes has become core to rheumatology, as has their incorporation into the assessment of disease activity and as responder criteria. From the experience with patients with RA, there have been reports of concomitant FM (FM-RA) overestimating objective RA severity measured by composite 28-joint Disease Activity Scores (DAS28)[6,7]. The higher DAS28 scores in FM-RA were driven by patient global assessment and tender joint count, but not by swollen joint count and ESR. Interestingly, patients with FM-RA had lower radiographic damage than patients without FM-RA[6], suggesting that FM can lead to increased levels of patient-assessed components of disease activity scores without influencing longterm joint damage. Because pain, patient global assessment, fatigue, and tender joint counts are commonly used for the assessment of disease activity in PsA and SpA, disease activity may also be overestimated among patients with FM-PsA and FM-SpA.

Following the advocacy of the Outcome Measures in Rheumatology (OMERACT) to standardize a core domain set for a given rheumatic disease before considering instruments to select to measure outcomes[8], the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has separated both skin and joint disease activity as a different core concept (domain) as compared to other domains such as fatigue and HRQOL in the updated core outcome set for PsA[9]. This represents a needed and

See Effect of FM on SpA, *page 2056; and* Effect of FM on PsA, *page 1749, September 2016 issue*

important move toward more objective measurement of disease activity as distinct from other domains, which serve different purposes in clinical trials and daily practice. Although the perfect instruments that represent joint or skin activity have yet to be validated or endorsed, there is potential that one of the composite indices, such as the Composite Psoriatic Disease Activity Index, or the Disease Activity Index for Psoriatic Arthritis, which combines active joint count and CRP, could fulfill the OMERACT filter of "truth" for the measurement of disease activity.

For SpA, where assessment of disease activity using physical signs is not possible, and where routine imaging for assessment is not feasible, assessing disease activity using patient-reported outcomes remains a common practice. This may lead to inappropriately high disease activity scores in patients with FM-SpA. Incorporating objective measures such as CRP in the ASDAS could partially improve the performance of the instrument. However, only 40% to 60% of patients with axial SpA may have an elevated CRP. Emerging biomarkers such as high-sensitivity C-reactive protein may represent disease activity more accurately in patients with SpA[10]. A panel of biomarkers may also hold promise: for example, in RA, a panel of 12 biomarker proteins in serum was shown to be more sensitive than CRP alone in reflecting disease activity in RA patients with and without FM[11]. Other measures such as the synovitis scores and power Doppler signals on ultrasound were not affected by FM in patients with RA, which may help distinguish inflammatory arthritis disease activity from FM[12]. Ultrasound was capable of distinguishing SpA versus mechanical-related enthesitis[13]; however, its role in distinguishing enthesitis in SpA from FM is unclear.

There has been increasing recognition of the need to consider the effect of contextual factors (CF) in outcome measurement. There are currently 2 main definitions of CF. The International Classification of Functioning, Disability and Health of the World Health Organization defines CF as variables belonging to the background of the patient (personal factors) or environment (environmental factors) that can influence the functioning and disability of the individual[14]. More emphasis has been given to environmental factors. OMERACT defines a CF as a "variable that is not an outcome of the study, but needs to be recognized (and measured) to understand the study results"[15]. Under OMERACT, the concept of CF is strictly defined and is different from the "context" as used to define "setting" of a clinical trial[15]. Comorbidities, differences in healthcare systems, and psychological status are all potential CF. The concept of CF is relatively new in the field of rheumatology and OMERACT, and which CF should be considered as "core" or "important" for the domain set of different disease entities has yet to be defined, let alone measured[8]. This may lead to confusion as to which factors should be labeled core domains versus CF. An example of possible confusion is emotional well-being, which could be a direct or indirect effect of PsA. Patients have consistently rated emotional well-being as an important core domain in PsA. Confusion can arise because the end of the spectrum of emotional well-being, depression, could also be a CF in the assessment of PsA disease activity. For instance, depression may increase the perception and reporting of pain level, patient global assessment, and even the number of tender joints, which are typical components of disease activity.

Given the contrasting patho-etiologies between FM and inflammatory arthritis, FM can be a CF in measurement of disease activity in chronic inflammatory arthritis. However, the pathology of FM is increasingly described as a disorder of central sensitization. Over the last decade, there has been a shift away from defining FM as a trigger point disorder and towards a definition as a syndrome of widespread pain and its associated psychological and somatic effects. Multiple-site chronic pain is now thought of as a continuum of experience, rather than a discrete disorder[16]. Central sensitization has also been described as a continuum of experience in various chronic arthritis conditions, including osteoarthritis (OA)[17] and RA[18]. Patients with these chronic forms of arthritis had a lower pressure pain threshold (a surrogate of central sensitization) as compared to healthy controls, and the pain threshold may improve after effective treatment, such as arthroplasty in OA[19]. The extent to which FM affects disease activity and to which chronic pain from joint inflammation induces central sensitization remains enigmatic.

In short, the coexistence of FM with PsA and SpA is recognized and can confound the objective assessments of disease activity of PsA and SpA. Thankfully, there are newer biomarkers (biochemical or imaging) that may better reflect the "truth" aspect of disease activity to guide in both clinical practice and trial settings. While the new OMERACT framework is helping to improve understanding of the importance of CF, the question of whether CF such as FM interact with disease activity and longterm outcomes remains unanswered. Evidence with patients with RA has shown that FM not only influences the assessment of disease activity, but also continues to worsen disability outcomes in inflammatory arthritis over a 5-year followup period[20]. On the other hand, chronic pain from PsA and SpA can induce central sensitization and in turn lead to FM. Further research on the neurophysiologic mechanisms of chronic pain in different types of inflammatory arthritis will elucidate the possible pathological link between these conditions.

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