The Need for Biological Outcomes for Biological Drugs in Psoriatic Arthritis

Perhaps no disease has been bedeviled more than psoriatic arthritis (PsA), with its proliferation of different clinical outcome measures. The development of these various measures to a large degree reflects both an inability to fully grasp disease pathogenic mechanisms and the difficulty in measuring them, especially in the context of the disease’s clinical heterogeneity. The absence of biological outcome measures, including an immunological or inflammation-related serum marker, makes the tomographic ability of magnetic resonance imaging (MRI) to directly measure inflammation arguably the most useful surrogate for PsA biological disease assessment. This is important because outcome measures to assess PsA are mushrooming (Figure 1).

In this issue of The Journal, Bird and colleagues apply MRI to therapy response assessments and show that high-field MRI is more sensitive than low-field MRI for detection of MRI synovitis, tenosynovitis, and osteitis reactions1. Although small, the study should kindle interest in research efforts to accurately evaluate the role of conventional synthetic disease-modifying antirheumatic drugs (DMARD), targeted synthetic DMARD, and biological agent optimization in PsA.

Although clinically heterogeneous, PsA is characterized by inflammation at the entheses2, with secondary synovitis and osteitis consequent to enthesitis3,4. The extensive inflammatory reaction in disease is likely due to the nature of the synovio-entheseal complex, where structures adjacent to the entheses — which form part of the enthesis organ — are affected5. Several studies have shown a high burden of enthesopathy in psoriasis, with a small study also suggesting these entheseal changes predate clinical arthritis6,7.

From experimental model systems including tumor necrosis factor (TNF) and interleukin 23 overexpression systems, it is clear that polyarticular “rheumatoid-like” disease commences at the enthesis, but with the passage of time, severe synovial-based joint destruction akin to rheumatoid arthritis (RA) is evident8,9. Recognition that the initial “blast zone” at the enthesis as its epicenter leads to diffuse soft tissue inflammation including subcutaneous inflammation, tenosynovitis, synovitis, and diffuse osteitis should help investigators define strategies to better measure the disease process.

This is all the more relevant because joint involvement in PsA can mimic other common forms of arthritis, making it difficult to differentiate PsA from degenerative arthritis3; compared to RA, joint disease in PsA is associated with a lesser degree of pain and stiffness. The need to accurately measure all these entheseal-related articular joint–associated inflammatory manifestations is key to accurately defining true biological responses to therapy and for determining which therapies are most effective.

Given the lack of a good serum biomarker for PsA and the diffuse nature of entheseal-associated disease, it appears that imaging will play a key role in determining the true biology of the underlying disease. This is especially the case because the ever-increasing number of disease measures have clearly failed to fully define the inflammatory features of PsA (Figure 1).

In that regard, given its ability to measure all disease manifestations, including osteitis, MRI is very useful for assessment, in contrast to ultrasound. Bird, et al show how MRI can be used to evaluate early response to anti-TNF therapy in a small cohort of patients with PsA1. Comparatively inexpensive, low-field MRI was compared to the more expensive high-field MRI — because the former would be a handy surrogate for disease assessment in a real-world setting and not just confined to clinical trials. Bird, et al show good intraobserver reliability for both high- and low-field MRI. However, low-field MRI failed to demonstrate osteitis, reflecting the inferior fat suppression of the technique and poorer spatial resolution.

Their data are interesting in that they demonstrated MRI responsiveness in PsA, page 75
Figure 1. The use of clinical outcome measures in (A) psoriatic arthritis (PsA) compared to (B) rheumatoid arthritis (RA) over the decades. There is an exponential increase in PsA outcome measures compared to RA because of the multidimensional nature of the disease, which makes it more difficult to assess adequately. The relatively more complex nature of PsA provides a challenge in developing a good tool that can measure joints, skin, nails, and entheses, resulting in the creation of multiple tools in the search for the ideal all-in-one outcome measure. Because biological drugs specifically target the immune system, MRI, with its ability to measure inflammation in different tissues, is the technique best able to measure most of the changes in PsA. The lists of outcome measures may not be exhaustive. MRI: magnetic resonance imaging; PASI: Psoriasis Area and Severity Index; MEI: Mander Enthesitis Index; SF-36: Medical Outcomes Study Short Form-36; HAQ: Health Assessment Questionnaire; BSA: body surface area; DLQI: Dermatology Life Quality Index; PsARC: Psoriatic Arthritis Response Criteria; DAPSA: Disease Activity in PsA; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Function Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ACR: American College of Rheumatology; PsAMRIS: PsA MRI Scoring; FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue; PEST: Psoriasis Epidemiology Screening Tool; MASES: Maastricht Ankylosing Spondylitis Enthesis Score; SPARCC: Spondyloarthritis Research Consortium of Canada; EI: Enthesitis Index; LEI: Leeds Enthesitis Index; LDI: Leeds Dactylitis Index; NAPSI: Nail Psoriasis Severity Index; mNAPSI: Modified Nail Psoriasis Severity Index; NPF-PS: National Psoriasis Foundation Psoriasis Score; PGA: Physician Global Assessment; PsAQOL: PsA Quality of Life; PASDAS: PsA Disease Activity Score; CPDAI: Composite Psoriatic Arthritis Disease Activity Index; RAIAI: PsA Joint Activity Index; RAI: Ritchie Articular Index; EULAR: European League Against Rheumatism; DAS28/44: Disease Activity Score 28/44 joints; RADAI: RA Disease Activity Index; RAMRIS: RA MRI Scoring; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; RAPID-3: Routine Assessment of Patient Index Data 3.
in dactylitis, and is directly linked to microenthesitis\textsuperscript{12,13,14}. When compared with RA, tenosynovitis is seen more frequently in PsA, and where flexor tenosynovitis is more common than the extensor counterpart\textsuperscript{15,16,17}. Nevertheless, studies in RA have also found tenosynovitis to be a feature that also responds rapidly to anti-TNF therapy\textsuperscript{18}, so much so that consideration to include tenosynovitis into the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System scores for RA is on the recent OMERACT (Outcome Measures for Rheumatology initiative) research agenda\textsuperscript{19}.

However, even though both PsA and RA share common general good inflammatory response to anti-TNF, the process is driven by different molecular mediators\textsuperscript{20,21}. The differential vascularity in the inflammatory process in the 2 arthritides may also explain the differential responses. There is also anatomic variation to the response to therapy between RA and spondyloarthritis, including PsA, as seen in the different regions of the knee joint\textsuperscript{22}. Macroscopic data have shown distinct vascular pattern in PsA compared to RA, where the vasculature was described as tortuous and bushy in PsA\textsuperscript{23}. Certainly there have been reports on the histology of enthesitis in dactylitis demonstrating hypervascular tenosynovium\textsuperscript{24}. Studies have noted that dactylitis in PsA appears to respond better to some anti-TNF agents compared to others, but this may be because the outcome measures used could not measure the primary pathology of PsA — i.e., enthesitis — in a feasible and accurate manner, resulting in difficulty quantifying true biological therapy response\textsuperscript{25}.

In general, the inflammatory process in PsA can be diffuse and affects multiple structures, including the extracapsular tissues, which can be more difficult to quantify, in comparison to more discrete and focal lesions such as synovitis. PsA clinical trials occasionally tend to adopt RA measures to measure outcome because more specific disease tools in PsA are lacking. This can lead to inaccurate reflections of therapy outcomes, in particular when changes such as enthesitis and extracapsular inflammation more reflective of PsA pathology are not being identified appropriately. Bird, \textit{et al} used a modified Psoriatic Arthritis Magnetic Resonance Imaging Scoring System (PsAMRIS) scoring method\textsuperscript{26}, and confined the analysis to changes within anatomical boundaries such as the tendons (tenosynovitis), joint capsule or synovium (synovitis), and bone (bone edema), and did not look at periarticular inflammation — a characteristic change in PsA.

Dynamic contrast-enhanced MRI (DCE-MRI), which allows quantification of synovial inflammation, is often used in RA to identify the quantity and intensity of synovitis and for therapy monitoring\textsuperscript{27}. Although DCE-MRI has also been used to monitor disease in PsA\textsuperscript{11}, the technique is not completely ideal for PsA, because it relies on a semiquantitative method involving a manual creation of regions of interest (ROI). Articular synovitis can be delineated relatively easily, but enthesis is often diffuse and outside the joint capsule, and it can be difficult to visualize an outline for an ROI. As a result, most if not all studies tend to “ignore” the soft tissue inflammation in PsA, and at best, the measurement of synovitis, tenosynovitis, bone edema, and erosions on MRI represents a “surrogate” marker for disease in PsA.

In PsA, there appear to be numerous outcome measures developed over time, suggesting that the heterogeneous nature of the disease makes creation of a single comprehensive outcome measure (that is also feasible to use) difficult (Figure 1)\textsuperscript{28}. Unlike RA, a common presentation of PsA is not confined to the joint, but also the skin, nails, and entheses. In a recent systematic literature review, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis Enthesitis Working Group found that, for the assessment of enthesitis in various clinical trials in PsA, there were different enthesitis indices used in different studies\textsuperscript{29}.

In the absence of a globally agreed-upon tool, Bird, \textit{et al} have used the best available imaging tool for measuring disease activity in PsA — one that mirrors “true” disease activity as closely as possible — for now. High-field MRI appears to be better if osteitis is to be evaluated (which should always be assessed because it may be a forerunner of joint erosion). Although the modified PsAMRIS scores used were adequate to show a change with therapy, it will be useful to see more trials adopting the full PsAMRIS scoring, which includes periarticular changes that are more representative of PsA.

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