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Editorial

Ample Room for Improvement

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In keeping with other immune-mediated inflammatory rheumatic diseases, treatment choices for axial spondyloarthritis (axSpA) have expanded beyond nonsteroidal antiinflammatory drugs (NSAIDs) and physical therapy in the last 20 years. We now have 10 advanced therapies from 3 distinct modes of action (ie, tumor necrosis factor inhibitors [TNFi], interleukin 17 inhibitors [IL-17i], and Janus kinase inhibitors [JAKi]), and novel modalities are being investigated. It would not be incongruous if one believed that these new choices of novel therapies combined with well-publicized treatment strategies such as treating to target (T2T), or at least early aggressive therapy, would lead to remission or low disease activity (LDA) in most patients with axSpA who have access to them. The reality may be much more sobering, as shown by Choquette et al in their UNISON-Axial SpA study on Canadian patients with axSpA enrolled in 3 regional registries, published in this issue of *The Journal of Rheumatology*.[1]

The study by Choquette et al aimed to evaluate residual disease activity and the burden of disease in Canadian patients with axSpA in a multiregistry, observational, retrospective analysis of 980 patients enrolled in the Rhumadata (Québec), Spondyloarthritis Research Consortium of Canada (SPARCC; Ontario and other regions), and Follow-up Research Cohort of Ankylosing Spondylitis (FORCAST; Alberta) registries between January 2010 and December 2020.[1] Patients were included if they had at least 12 months of follow-up data available after initiating their latest therapy. The primary endpoint was the proportion of patients who failed to achieve sustained LDA, which was defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score < 3 at both 6 and 12 months after the most recent treatment change. Interestingly, they included not only patients with axSpA starting TNFi or IL-17i but also those initiating NSAIDs. Since the data were collected between January 2010 and December 2020, no patients enrolled in these registries had access to JAKi. They found that the failure to achieve LDA ranged from 49.5% (Québec) to 65.8% (Ontario) at 6 months, and the rates of sustained LDA were worse at 62% (Québec) to 81% (Ontario) at 12 months. Persistent inflammation (C-reactive protein [CRP] > 5 mg/dL) was observed in 17.5% to 36% of patients at 12 months, whereas pain (visual analog scale > 30 mm on BASDAI question 2) persisted in nearly half of patients at 12 months, with rates as high as 63.8% in Ontario. NSAIDs and TNFi were the most commonly used therapeutic agents (in 4.7-32.6% and 55.2-83.4% of patients, respectively) in this study.

The study highlights the stark reality of substantial residual disease activity and burden of disease among Canadian patients with axSpA, and represents many unmet clinical and research needs in axSpA management. Although the authors appropriately underscored the limitations of current treatment options, there are many important concepts that we need to consider in light of these findings, such as the inadequacies of outcome measures used in axSpA, the underlying causes of persistent disease activity, and the need to educate rheumatology providers about optimum therapeutic strategies.

Although the concept of T2T may not be ready for prime time in axSpA and is not endorsed by the American College of Rheumatology (ACR)–Spondylitis Association of America (SAA)–Spondyloarthritis Research and Treatment Network (SPARTAN) treatment guidelines[2] nor the latest Canadian treatment recommendations,[3] early aggressive treatment in axSpA should undeniably be universally accepted and implemented to reduce long-term disability and improve quality of life. There are many possible clinical strategies to try to achieve better control of disease activity with a relatively limited arsenal of biologics. Some examples of optimizing axSpA treatment that are often employed in rheumatology practices are adding a conventional synthetic (cs-) disease modifying antirheumatic drug (DMARD) such as sulfasalazine or methotrexate for peripheral or extramusculoskeletal manifestations of axSpA, or injecting

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See Residual axSpA in Canada, *page xxx*

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glucocorticoids for peripheral inflammatory arthritis or upper extremity entheses. In the case of biologics, either increasing the dose or frequency of infliximab infusions, increasing the frequency of adalimumab injections, or doubling the dose of secukinumab can be attempted. Simply changing the frequency of certolizumab pegol from 400 mg every 4 weeks to 200 mg every 2 weeks may help reduce disease activity in those few patients who are not responding to the original dose. Granted, some of these dose-increase strategies may not be possible in many parts of the world and certain provinces of Canada, but no information is available as to whether any efforts of aggressive management were employed in the treatment of patients enrolled in these 3 registries. Considering the time period of data collection, Canadian rheumatologists realistically had access to 5 TNFi and 2 IL-17i as advanced therapies beyond NSAIDs, but it is unclear why between 1.8% (in Alberta) and 26.6% (in Ontario) of patients remained on NSAIDs alone at 12 months when they had not achieved LDA at 6 months, especially when the disease duration (see below) since diagnosis was between 6 and 18 years. A concerted effort to educate rheumatology providers on the early use of biologics or targeted synthetic DMARDs (tsDMARDs) in patients with uncontrolled disease activity is warranted.

The outcome measures used in the registries to assess LDA and inactive disease are appropriate and are the most practical measures for daily clinical practice (ie, BASDAI < 3 as a marker of LDA and Axial Spondyloarthritis Disease Activity Score–Inactive Disease [ASDAS-ID] as a marker of inactive disease). However, these outcome measures, including the ASDAS, rely heavily on subjective questionnaires and lack objectivity beyond CRP measurement in ASDAS calculation. Although both BASDAI and ASDAS can reflect disease burden, they may not accurately assess disease activity or the state of inflammation since CRP is lacking in sensitivity. Not surprisingly, magnetic resonance imaging (MRI) of the sacroiliac joints and spine were not reported in any registry as it is not possible to obtain MRI scans in routine clinical practice at 6-month intervals owing to financial reasons. This highlights the need for a biomarker for inflammation beyond CRP and MRI for use in clinical practice and clinical trials. The SPARTAN organization is embarking on this research path through the Biomarkers in Axial Spondyloarthritis Investigative Study (BASIS); if a biomarker is indeed found, this would necessitate a change in the current markers used to measure disease activity and would provide a target for aggressive therapy.

One of the main factors that contributes to residual disease activity using currently available subjective outcome measures is the noninflammatory (eg, nociplastic) pain that patients with axSpA continue to experience despite effectively treating the inflammatory pathway with advanced therapies. Nociplastic pain is defined as pain that arises from altered nociception even when there is no evidence of tissue damage, inflammation, or nerve irritation causing the pain. The current study shows that although 62% to 81% of patients failed to achieve LDA at 12 months, 17.5% to 36% had objective inflammation at 12 months based on CRP levels.[1] This disconnect makes it important to acknowledge the importance of subjective symptoms—mostly pain, fatigue, and stiffness—that comprise disease activity in axSpA. This also highlights the importance of phenotyping pain as well as understanding and potentially targeting noninflammatory and nociplastic pain pathways in axSpA. The authors excluded patients with a diagnosis of fibromyalgia from the study.[1] Multiple studies have shown that a substantial percentage of patients with axSpA (up to 46%) have a central sensitization component[4-6] (one of the main mechanisms behind fibromyalgia), and excluding these patients from the study could have skewed the results further.

The UNISON-Axial SpA study reported that mean time since diagnosis ranged from 6.2 to 18 years, but it does not report the time since the first symptom, which would undoubtedly add to the real disease duration, considering the delay in diagnosing axSpA is an average of 6.7 years.[7] In peripheral immune-mediated inflammatory arthritis conditions such as rheumatoid arthritis, it was shown that the highest incidence and risk of developing chronic pain is within the first 2 years after diagnosis.[8] Considering the diagnostic delay, plus the prolonged time since diagnosis reported in patients enrolled in this study, the risk of chronic pain development is significantly increased. This is also reflected by the failure to achieve LDA based on the current definitions. This highlights the importance of early diagnosis to try to prevent disease progression and chronic pain development.

The patient sample that was included in this study was mostly HLA-B27 positive (60-75.9%) and male (55.7-73.1%). A significant percentage met the modified New York classification criteria for ankylosing spondylitis. Recent epidemiologic studies showed that nonradiographic disease can affect male and female individuals in a 1:1 ratio and that the disease burden is heightened in women.[9] Increasing nonradiographic axSpA and female representation can potentially further increase the percentage of patients failing to achieve LDA. No information is available on factors that were associated with achieving remission or lack thereof. Further analyzing the data based on sex, age, disease duration, and comorbidities like depression can shed light on possible reversible factors that could be targeted to increase the odds of achieving LDA or remission in patients with axSpA.

The findings by Choquette et al are critical for understanding the real-world challenges faced by patients and clinicians in managing axSpA. We agree with the authors about the need for new effective therapies, but we also want to highlight efforts required toward the unmet needs of health providers' education regarding early aggressive treatment strategies, understanding the role of noninflammatory pain, and refining outcome measures based on new biomarkers of inflammation to achieve the best possible outcome in patients with axSpA.

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