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Editorial

The Patient Experience of Drug Side Effects in Rheumatoid Arthritis: Intriguing Data From an Exploratory Online Survey

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Understanding adverse events (AEs) of disease-modifying antirheumatic drugs (DMARDs) for treatment of rheumatoid arthritis (RA) is critical to both patients and clinicians. AEs—"side effects" from the patient perspective—contribute significantly to patients' disease experience by interfering with activities of daily living and quality of life (QOL).[1] They are also an important source of treatment nonadherence, with deleterious effects on disease outcomes.[2,3] Gaining insight into patients' experiences with medication side effects could help inform the development of new shared decision-making approaches to enhance treatment adherence and long-term disease and health outcomes.

In this issue of *The Journal of Rheumatology*, Hazlewood and colleagues report the findings of their exploratory study of patient-reported AEs of RA medications using an online survey.[4] Eligible participants were required to have a self-reported diagnosis of RA, to be taking at least 1 RA medication, and to be under the care of a rheumatologist. Participants were not provided any remuneration. The investigators utilized the Patient-Reported Outcomes of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), which was developed and validated for oncology clinical trials. The purpose here was to describe the frequency of symptomatic AEs among items included in the PRO-CTCAE, to identify important items that were not included, and to determine the associations of these AEs with RA drug use. This could be a starting point toward the development of a rheumatology-specific patient-reported outcome measure for medication AEs.

Because recruitment for the survey through an academic rheumatology clinic in Calgary was encumbered by the COVID-19 (coronavirus disease 2019) pandemic, the authors performed a web-based survey implemented by Qualtrics. They chose to include all questions in the PRO-CTCAE survey guide—a total of 80 symptomatic AEs—because the few irrelevant questions enabled a check on the validity of the findings. They advertised the survey on social media sites and through Canadian patient advocacy organizations. This has proven to be a valuable recruitment strategy for other online surveys of patients with RA.[5] A major strength of their approach is the involvement of 2 patient research partners from study conception through completion and additional input from Arthritis Research Canada's Patient Advisory Board.

The findings of the study are novel and merit consideration. However, at first blush, the high frequency of AEs raises concern for the face validity of the results. Only 6% of participants reported no side effects of their RA medications; conversely, 94% of patients reported current side effects. Incredibly, 38% of the patients reported more than 20 current side effects.[4] Some clinicians may justifiably question if these observations align with their experience in evaluating side effects of medications in daily practice. Considering the cross-sectional design of the study, the results beg the question of temporality (ie, when did the reported side effects occur in relation to medication initiation, as well as the timing of the survey). On this point, the authors report that 45 (56%) of the 80 possible AEs were experienced by 15% or more of participants within the 7 days preceding the survey.[4]

Additionally, the authors investigated the degree to which the side effects bother patients. Impressively, 39% of patients reported being bothered by AEs "quite a bit" to "very much" within the past 7 days. This is a high percentage of patients reporting substantially bothersome drug side effects. Among patients not bothered at all by side effects, the median number of symptomatic AEs was 8, indicating patients experience a high number of AEs even when not experiencing interference by them.[4]

Importantly, the patterns of AEs reported in this study corroborated known toxicity profiles for several medications. The authors analyzed the numbers of AEs associated with each

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drug with a frequency of at least 15% among the 45 symptomatic AEs identified. Unsurprisingly, the frequency of AEs was highest for prednisone[6] (n = 26), followed by nonsteroidal antiinflammatory drugs (n = 22), sulfasalazine (n = 8), methotrexate (MTX; n = 4), Janus kinase inhibitors (n = 4), biologic DMARDs (n = 2), and hydroxychloroquine (n = 2). MTX side effects included nausea, hair loss, and memory difficulties, and hydroxychloroquine reportedly caused sun sensitivity; biologics reportedly caused easy bruising, implying injection site reactions, although this was uncertain. Analysis of free text identified 119 additional AEs reported by 89 patients using "ever" attribution. Of these, 32 overlapped with the PRO-CTCAE, suggesting that the oncology-purposed instrument would need modification for rheumatology purposes.

The authors should be commended for conducting this exploratory study with the aim of collecting data about frequency and bother of medication AEs directly from patients. As noted by the authors, the findings of this cross-sectional, web-based survey research study cannot be taken to imply causation between medications and the reported AEs in all cases. There was overlap of several of the AEs with typical RA symptoms (eg, fatigue, aching joints), which is a phenomenon also observed in clinical trials. However, there are some potentially important limitations to consider.

Web-based surveys always have the potential for selection bias, as noted by the authors.[7] Only 575 of 913 participants completed the survey once they started it; the ethics board required patients to be allowed to withdraw from the study. It is impossible to know how many people saw the survey invitation but did not click the link. The included patient sample was 95% female; this differs from the expected percentage of around 70% based on disease epidemiology, suggesting underrepresentation of men in this study. Other web-based surveys of people with RA have had a similar bias to inclusion of women.[5,8-12] The mean age of 44 years with mean disease duration of 8 years suggests a relatively young patient sample, which makes sense because young people tend to be more computer literate and to participate in social media. There is the potential for patients who are high reporters of side effects to self-select themselves for participation in this study. The lack of data about disease activity, severity, and comorbidities is an important limitation of this study that precludes full understanding of the generalizability of the results. For example, the effects of depression or anxiety on the reported frequency or bother of medication AEs could be important but are not available in this study.

What do we learn from this study? Patients report many symptomatic AEs (side effects) that they attribute to their RA medications. Collectively, these AEs substantially interfere with their daily lives and activities. The findings corroborate the study by Curtis et al, which illuminated an underrecognized burden of medication AEs in a younger, predominantly female population of patients.[13] Also, the findings suggest that some side effects, such as "brain fog" and "mood swings," may be important to patients but are often not captured in routine clinical practice.[13] However, it is known from clinical trials that nonspecific, nonserious symptoms are commonly reported by patients allocated randomly to placebo. Further, there is potential overreporting of side effects when patients are presented comprehensive checklists for consideration.

The redeeming value of this study is underscored by the increasing importance of involving patients directly in research that affects them.[14,15] Major international rheumatology organizations are increasingly requiring meaningful patient involvement in clinical research, from study conception to final publication.[16] Selected examples of this movement in both the public and private sectors include the Outcome Measures in Rheumatology (OMERACT), Patient-Centered Outcomes Research Institute (PCORI), the Agency for Healthcare Research and Quality (AHRQ), the Canadian Institutes of Health Research (CIHR), and Evidera. Investigation of patient-centered importance of medication AEs is critical to understanding patient perspectives on the balance of drug benefits vs harms, when it is necessary to stop or change medications, and adherence.

Are we as rheumatologists and healthcare professionals listening well enough to our patients? From a place of empathy, we wish to avoid reacting inappropriately by discounting information provided by patients about their medication-related concerns. This brings to mind the situation where a clinician finds that a patient's disease has progressed with structural joint damage while review of historical clinical notes reveals consistent documentation that the patient is "doing well." In an analogous manner, "patient tolerating medications well" may similarly underappreciate the degree to which patients experience and suffer from medication side effects. Previous studies have shown substantial discordance in the assessment and attribution of drug AEs between patients and their clinicians.[13,17] For example, Sun et al found that the rheumatologist-estimated median frequencies of AEs for MTX and leflunomide were 15%, whereas patient-reported frequencies for these medications were 39.6% and 33.7%, respectively.[18] Physicians rate seriousness by objective laboratory or imaging abnormalities, while patients judge seriousness by interference of their QOL or function. This discrepancy may arise partly from therapeutic inertia; that is, the desire of patients and/or their clinicians to avoid switching medications out of fear or concern that the next drug will cause more problems than the current one.

This study highlights important knowledge gaps regarding the patient experience of medication AEs from both the clinical and research perspectives (Table). In view of the limitations, the first question surrounds the true population frequency and bother of AEs of RA medications. Future studies should consider a new-user design using a similar survey approach to define the temporality and causation between medication exposure and patient-reported AEs. Determination of the frequencies and bother of AEs that are acceptable from a patient standpoint is critical to inform shared decision making with patients. A large, international study reported variability of patients' acceptance of AEs of medications, which was higher for weight gain, fertility effects, skin reactions, and hair thinning, and lowest, understandably, for cardiovascular effects and malignancies.[19] It is also crucial to understand how healthcare factors relate to patient-reported AEs, including access to care for medica-

Table 1. Research agenda.

Medication Adverse Effects
· What is the population frequency of patient-reported AEs for each RA medication?
· What is the distribution of bother associated with AEs for each RA medication?
· What are patient-acceptable levels of AE frequency and bother for clinical trials and shared decision making in practice?
· How should information on medication side effects be collected in clinical practice?
Online Patient-Centered Research Surveys
· How do we identify and enroll a representative sample of patients with definite RA using online, web-based platforms?
· Should investigators complement online surveys with clinic-based recruitment strategies to target male or older populations?
· What is the best approach to elicit medication AEs, such as electronic symptom diaries?
· What are the implications for patient education and shared decision making?

AE: adverse event; RA: rheumatoid arthritis.

tion problems, education received about medications, provider attitudes, patient trust in providers, and social and economic support.[20] A previous study has shown that the degree to which treatment with medications is adapted to individual patients and the degree to which patients and physicians agree on the plan for treatment are important determinants of medication adherence.[21] Ultimately, it may be fruitful to delve deeper into patients' feelings and perceptions about their medications, both positive and negative, as these may shape their experience of side effects.[22] Therefore, understanding the effect that patients and physicians have on patient experience of treatment AEs is likely to be important.

Online, web-based, or app-based survey research studies will continue to play an important role in these efforts, but we need to consider how to enroll samples that are fully representative of populations of people living with RA globally. The PRO-CTCAE needs to be modified based on the results of this study[4] to be relevant to rheumatology medications and patient populations. How to collect information about AEs in the most valid and meaningful way needs further work for both practice and clinical trials. As suggested by the authors,[4] mobile health applications may be a useful way to track drug side effects with further development. Information about AE frequency and bother needs further validation in terms of relationships to disease characteristics and potential confounders, as well as their effect on adherence and health-related QOL.

The results of this study highlight the importance of empathic communication in clinical practice. The importance of being mindful of our role in health care and healing is crucial to being prepared to consider the meaning of symptoms that may represent true AEs of medications. Ultimately, active listening and reflection with patients about their experiences with medications and side effects are likely to contribute to a meaningful relationship and strong therapeutic alliance, and ultimately, to achieving the best treatment outcomes possible.

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