EDITORIAL

Precision medicine in rheumatoid arthritis: are we there yet?

Karen Salomon-Escoto[1]

Rheumatologists have long acknowledged the importance of quantitative assessment of disease activity in rheumatoid arthritis (RA). The advent of biologic therapies further underscores the need for systematic surveillance of patients' response to treatment, ultimately leading to "treat-to-target" (T2T) recommendations proposed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). In this context "target" refers not to a specific inflammatory cytokine, but rather to a disease state. Experts agree that remission is the ultimate treatment target, and defining remission is an ongoing endeavor.

In 1981, Pinals et. al. [1] proposed remission criteria based on morning stiffness, fatigue, self-reported joint pain, tender joint count, joint or tendon sheath swelling, and erythrocyte sedimentation rate. Remission was defined as the absence of five or more of these parameters. At the time, achieving this endpoint was ambitious, but biologics have revolutionized the treatment of RA and remission is now achievable and expected by patients. Measuring a heterogeneous disease, however, is complex, therefore multiple scoring systems exist [2, 3], perhaps too many and studies show that incorporating T2T guidelines in clinical practice is not entirely feasible [4, 5]. Most scoring systems include swollen joint counts, which studies have shown correlate with radiographic progression [6]. These composite scores include the Disease Activity Score in 28 joints (DAS28), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity (SDAI). Patient-reported outcomes such as the Health Assessment Questionnaire (HAQ) [7] and Routine Assessment of Patient Index Data 3 (RAPID 3) [8] capture other aspects of disease including fatigue and physical function, and are favored by busy clinicians in the USA [5] as these can be quickly scored after the patient answers a brief survey. EULAR however,

does not endorse scoring methods that exclude joint counts [9]. A multi-biomarker disease activity (MBDA) score is available to rheumatologists too. This consists of 12 serum biomarkers and has been shown to predict response to triple-therapy in patients with early RA with moderate or high disease activity (per DAS28) after 3 months of methotrexate monotherapy [10]. However, unmet needs remain in the field, with regard to accurate prediction of the most effective treatment in individual RA patients.

Since 2007 [11] ACR and EULAR have committed to defining remission and providing internationally-accepted disease activity assessment guidelines for use in clinical trials and routine practice. These recommendations were last updated in 2011 [12], and two strict remission definitions remain: a Boolean approach and SDAI ≤ 3.3. These are most applicable to clinical trials, as they require lab data (C-reactive protein) which is often not present at the time of the visit in routine clinical practice. There is abundant evidence demonstrating the superiority of a T2T approach in RA, compared with care without quantifying disease activity systematically [13–15]. Numerous barriers however interfere with widespread adoption of these guidelines in routine care [16].

In this issue, Johnson et. al. describe a common scenario in daily rheumatology practice: biologic switching. They emphasize the need for a predictable choice of biologic, thereby expediting treatment optimization and ultimately disease remission. The authors propose switching TNF primary non-responders to a biologic with alternate mechanism of action (MOA), as opposed to trying a second TNF inhibitor (TNFi). This contradicts the findings of the GO-AFTER study, in which golimumab was effective in patients who had failed one or more TNF inhibitors. Thus, current T2T guidelines recommend trying a second TNFi after failing one, but not after failing the second agent [9]. The authors cite a 2017 retrospective study of commercial and Medicare Advantage claims data focusing on biologic use. The study found 935 (61.7%) TNFi cyclers and 581 (38.3%) MOA switchers. Mean 1-year healthcare costs were significantly higher in TNFi cyclers. These findings highlight a major barrier rheumatologists face every day, the discordance between

✉ Karen Salomon-Escoto
  Karen.salomon-escoto@umassmemorial.org

[1] Division of Rheumatology, Department of Medicine, UMass Memorial Medical Center and University of Massachusetts Medical School, 119 Belmont St, Worcester, MA 01605, USA

rheumatology society RA treatment guidelines and real-life third-party payor algorithms, formularies, and drug tiers. Rheumatologists are drowning in a sea of "prior-authorizations" while patients wait for a "preferred" drug to be approved. It is an ongoing dance between medical judgement and a cumbersome reimbursement system which makes RA management more challenging than it needs to be.

Johnson proposes a precision medicine approach in RA, such as that used by oncologists in the treatment of cancer. There is definitely a need for a reliable test that predicts response to a particular treatment. This would completely change the current treatment guidelines, which consist of gradual drug escalation until an acceptable target is reached. Precise treatment selection would fast-track patients to ideally remission. Such biomarker is being developed and will warrant thorough study before it can be adopted into the current T2T guidelines.

Predicting response to treatment in RA has been a long-standing quest. Ongoing combined ACR/EULAR efforts have led to the development of sound evidence-based treatment guidelines, yet defining remission, in particular sustained-remission requires continuous review. The discovery of new treatment targets inevitably creates a need for novel bio-markers as well. Can a single blood test, however, fully define disease activity in all patients with RA? Are we ready to give up joint counts and imaging? The future is uncertain but exciting. Innovation has changed the way we treat RA today compared to 1981 when remission was first defined. Undoubtedly, innovation will also change the way we measure disease activity and better yet, how we select the most effective treatment for individual patients.

Compliance with ethical standards

Disclosures None.

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