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Editorial

Importance of Time-integrated Cumulative Parameters for Radiographic Progression Prediction of Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is one of the most common autoimmune diseases and is characterized by synovial hypertrophy and joint inflammation and damage [1,2]. RA affects up to 2% of adults worldwide and often causes substantial functional impairment and decreased health-related quality of life, relative to the general population [3,4]. The conventional synthetic disease-modifying antirheumatic drugs (DMARDs) (csDMARDs), including methotrexate and leflunomide, are still used as the first-line treatment for RA. However, the development of targeted treatments such as biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) have shown great promise at improving the disease outcomes [5,6].

Radiographs of hands and feet evaluate the bone resorption as erosions and cartilage degradation as joint space narrowing. These images are used to assess the structural progression of damage in clinical research trials in patients with RA, aiming to provide the disease-modifying capacity of a drug [7]. Recent studies have reported that ongoing disease activities, as reflected by elevated erythrocyte sedimentation rate (ESR) and C-reactive proteins (CRP) or composite indices including the 28-joint disease activity score (DAS28), are associated with severe radiologic joint destruction [8]. The disease composite indices are largely applied to therapeutic targets for treat-to-target (T2T) strategy targeting remission or low disease activity (LDA), resulting in better disease outcomes and quality of life [9]. However, clinical trials of bDMARDs in established RA patients after inadequate response to csDMARDs have reported a subsequent disconnect between disease activity and radiographic progression [10]. Furthermore, recent real-world data demonstrate that approximately 20% of RA patients with sustained remission or LDA still show radiographic progression [11,12]. Similarly, Brown et al. [13] found that 60%~80% of RA patients who fulfilled the American College of Rheumatology (ACR) and DAS28 remission criteria had synovitis or subclinical joint inflammation on magnetic resonance imaging or musculoskeletal ultrasonography. Subsequently, they observed that subclinical joint inflammation detected by imaging techniques explains the structural deterioration in RA patients in clinical remission [14]. Additionally, there may be challenges in assessing disease activity when patients are treated with interleukin-6 inhibitors and other drugs that directly affect levels of CRP [15]. The level of CRP is a component of composite indices measuring RA disease activity (DAS28-CRP, simplified disease activity index [SDAI], and ACR/European Alliance of Associations for Rheumatology [EULAR] remission). Therefore, assessment of disease activity based on the prompt reduction in the level of CRP may not reflect the actual improvement of disease activity in patients receiving interleukin-6 inhibitors [15,16]. In conclusion, although T2T results in an acceptable control of disease activity for a considerable proportion of RA patients, the current T2T paradigm under the real-world situation remains unfulfilled.

RA disease activity exhibits a fluctuating pattern and varies over time during the follow-up period [17]. Furthermore,

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satisfying remission or LDA according to T2T strategy may not completely reflect the presence of subclinical synovial inflammation [13]. Therefore, time-integrated cumulative methods could be more suitable than single evaluations of RA activity for summarizing the course of disease activity and promoting the assessment of cumulative outcome measures such as radiographic progression. Recently, Park et al. [18] demonstrated that cumulative values such as the cumulative ESR, cumulative tender joint count, cumulative swollen joint count (SJC), and cumulative DAS28-ESR are the major determinants of radiographic progression. Notably, they demonstrated that the cumulative SJC is the best predictive performance for radiographic progression. In this study, single measurement of RA activity, such as ESR, CRP, or DAS28 was not associated with radiographic progression. The only relevant baseline value, which predicts radiographic progression, was radiographic damage at the time of diagnosis. Fluctuations in disease activity are directly related to changes in radiologic progression. Hence, at a certain time point, radiographic damage could be also considered as the result of accumulation of disease activity [19].

Sustainability has not been considered in any of the composite indices evaluating RA disease activity or remission definition. However, the sustainability of the targeted disease activity would better capture the differential effects, and specifically, of novel targeted agents, including bDMARDs and tsDMARDs, on structural damage progression than that at a single time point [20]. Therefore, by including time value such as time-integrated cumulative methods in measuring the disease activity of RA would probably improve patient's outcome as measured by radiographic progression.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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