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Editorial

Rheumatoid Arthritis and Malignancy: What Should We Do With DMARDs?

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Patients with rheumatoid arthritis (RA) tend to have more co-morbidities than the general population, but remain at risk of insufficient rheumatological care despite high disease burden and poor outcomes [1]. As life expectancy increases, rheumatologists have more opportunities to see patients with co-morbidities. Although malignancy is a frequent cause of morbidity and mortality, information on the management of RA in patients with malignancy is scarce. In this respect, the study that Joo et al. [2] published in the previous issue of *Journal of Rheumatic Diseases* provides valuable information on current practice among such patients, suggesting the unmet clinical needs of this population.

According to a recent meta-analysis that investigated the pooled data from previous cohort studies, the overall risk of developing malignancy is slightly increased in RA patients. Regarding site-specific risk, the risk of lymphoma and lung cancer was particularly increased [3,4], and it is postulated that a shared etiology such as smoking [5,6] or chronic persistent immune activation may play a role in the development of neoplasms [7,8].

Apart from the inherent risk of malignancy in RA patients, there have been concerns regarding the influence of disease-modifying antirheumatic drugs (DMARDs) on the risk of developing malignancy. There is conflicting evidence about the relationship between TNF-α inhibitors (TNFis) and malignancy risk; some meta-analyses and patient registry studies have shown that the risk of malignancy is not increased in patients receiving TNFis, whereas other studies have reported increased risk of nonmelanoma skin cancer [9]. Non-TNFi biologics were not linked with increased risk of malignancy in some claims-based studies and registry data [10,11]. As for new target synthetic DMARDs, Janus kinase inhibitors showed no effect on the overall incidence of malignancy from the general population or those taking biologic DMARDs, although the age- and sex-matched standard incidence ratio of lymphoma was higher than that of the general population [12]. Despite a few reports of increased malignancy risk related to cyclosporin and azathioprine, conventional synthetic DMARDs are generally considered not to increase malignancy risk [13].

There also are some theoretic concerns that concurrent DMARDs might suppress the immune system, thus increasing the risk of malignancy recurrence. However, recent meta-analyses of observational studies showed that the recurrence rate of malignancy in patients who are on DMARDs was not different from that in patients without DMARDs [14].

Drawing firm conclusions about the effects of DMARDs on malignancy risk is challenging. The data provided by randomized controlled studies (RCTs) regarding the risk of malignancy with DMARDs are quite limited; a history of prior malignancy is usually an exclusion criterion of those studies, and considering the long latency of malignancy, RCTs generally do not involve sufficient follow-up duration to detect events. Therefore, a large-scale registry study would be a better choice for addressing the problems [4,15].

Due to the paucity of large-scale studies and insufficient data, there have been few reliable evidence-based guidelines for the treatment of RA in patients with malignancy, and they are largely dependent on expert opinions or physician experience. However, a recent systematic review indicated that most guidelines

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still agree on some points despite the lack of evidence; DMARDs should be discontinued and resumed under supervision of specialists in the case of de novo malignancy, and initiation of DMARD in patients with active malignancy or premalignant conditions is not recommended [16]. Most recommendations advised caution when prescribing DMARDs for patients who had been treated for malignancy within the past five years and warned against use of TNFis for patients with lymphoma or hematologic malignancies [16].

In the study by Joo et al. [2], a substantial number of patients continued DMARDs (switching regimen in 35%, maintenance in 32.5%) immediately after a diagnosis of malignancy. Moreover, a large proportion (69.2%) of patients who discontinued DMARDs eventually resumed drugs within a few months after diagnosis [2]. This illustrates that a significant number of patients still need DMARDs while being treated for malignancy due to persistence or aggravation of RA. Despite the small number of cases and insufficient data on arthritic activity, this was the first study to explore patterns and outcomes of DMARD prescription in RA patients with malignancy.

In conclusion, to better understand the impact of RA treatment on malignancy and to establish safer and more effective treatment strategies for patients with RA and malignancy, a large-scale registry study should be planned and conducted. In the meantime, given the paucity of treatment guidelines based on robust data, a more individualized approach should be used to meet the needs of patients with RA and malignancy.

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CONFLICT OF INTEREST

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

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