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Editorial

EDITORIAL

Long-term treatment in rheumatoid arthritis: do biological and targeted-synthetic DMARDs increase the risk of malignancy?

This editorial refers to 'Short- and longer-term cancer risks with b/tsDMARDs as used against rheumatoid arthritis in clinical practice', by Viking Huss *et al*. 2022;61:1810–18.

In this issue of *Rheumatology*, Huss et al. [1] analyse the long-term risk of cancer development in a large cohort of RA patients treated with biologic and targeted-synthetic DMARDs (b/tsDMARDs). In their well-conducted study, the authors provide valuable confirmation that long-term therapy with TNF alpha inhibitors (TNFi), anti-CD20- and anti-IL6 therapeutics does not lead to an increased incidence of malignancies. These data have important clinical relevance for the everyday care of patients affected by immune-mediated inflammatory diseases and provide additional security in the prescription and therapy adherence of b/tsDMARDs.

In recent decades, the interplay between the immune system and cancer cells has emerged as a prominent component in cancer development, promotion, and outcome [2]. As immune competence is pivotal for host responses to a malignancy, concerns have been raised that drug treatments interfering with immune pathways, such as b/tsDMARDs, could enhance the susceptibility to cancer development. These concerns have been reinforced by the observation that immune-mediated inflammatory disease patients have increased rates of cancer and suffer from poorer prognosis [3]. So far, studies on cancer associated with long-term therapy with b/tsDMARDs were characterized by relatively small sample sizes of RA patients (especially those for non-TNFi b/tsDMARDs) and inadequate follow-up times. Although predominantly reassuring, studies and meta-analyses on bDMARD-treated cohorts yielded contrasting results [4, 5] and did not allow definite conclusions to be drawn about the existence of drug class effects on cancer risk. For instance, some signals of concern had emerged for colon and ovarian cancer for TNFi [6] and for the overall risk of malignancies for IL inhibitors [5], rituximab [7] and abatacept [8], respectively. Recently, preliminary data from a completed trial revealed an association with increased risk of lung cancer and lymphoma [9]. Nonetheless, the majority of such reports are based on (i) non-real-life data, (ii) small sample sizes and (iii) follow-up periods shorter than 5 years. Thus, it has not yet been possible to reliably analyse the potential causal relationship of long-term treatment with b/ts-DMARDs with cancer development.

The observational registry-based nationwide study [1] is based on the longest published follow-up of cancer risk in patients with RA treated with b/tsDMARDs (69 308 RA patients, 658 589 person-years). Four study groups were analysed: a cohort with bDMARD-treated patients, one with tsDMARD-treated patients and two comparison cohorts, one with conventional DMARD-treated, b/tsDMARD–naïve patients and another from the general population. It was investigated (i) whether a higher general cancer risk existed in the treatment groups with b/tsDMARDs compared with the general population and the b/ts DMARD-naïve group, respectively, and (ii) whether the respective risks for cancer in general and specific cancer types differ for each of the immunomodulatory drugs compared with the general population and compared with a TNFi-treated group (drug-by-drug analysis). In line with previous reports, a slight increase in cancer risk was noted for all RA patients compared with the general population [4]. Nonetheless, the authors were able to show that RA patients treated with long-term TNFi, rituximab, and tocilizumab do not have an increased risk of developing cancer compared with those who receive conventional therapies. Specifically, no significant change in risk was observed at any time during treatment, as no yearly increase in incident cancer was registered in the TNFi, CD20 or IL6 cohorts. No conclusion could be drawn on JAKi, as data were too scarce, both in terms of observed cancer events and follow-up time. No significant results emerged when stratifying risk by age groups, although an increase in risk of malignancy proportional to age was noted in the b/tsDMARDs cohort. This finding is likely to be non-significant, considering the large sample size, and may reflect the well-known age-dependent increase cancer incidence. However, in the drug-by-drug analysis, some signals of concern emerged with respect to bDMARDs. For abatacept, 2–5 years of active treatment resulted in increased odds of developing malignancy [HR: 1.8 (95% CI 1.2, 2.6)] compared with the b/tsDMARD-naïve group, and incident cancer rates were significantly higher than in the TNFi cohort [HR: 1.2 (95% CI 1.0, 1.5)]. Also, when accounting separately for each of the 16 specific types of cancer included in the analysis, the risk of urinary tract malignancies increased for all b/tsDMARD treatments compared with the general population and with b/tsDMARD-naïve patients. However, the persistence of this observation among all the investigated drugs and the lack of previous reports may well indicate a confounding factor that is yet to be identified. For instance, smoking status, which is the major modifiable risk factor for urinary tract cancer, does not appear among the comorbidities considered for risk

normalization in this analysis. Nonetheless, although this was clearly not one of the aims of the study, no physiological hypothesis has been formulated to explain these contrasting findings. Therefore, replication in larger and more specific studies, as well as the formulation and testing of a pathophysiological hypothesis are required in order to draw conclusions. When analysing such large databases, some challenges might arise in unambiguously defining exposure variables and patient groups. As an example, the absence of a control group of untreated RA patients does not allow significant conclusions to be drawn about the malignancy risk that comes from therapy itself, only the malignancy risk that comes from the combination of RA diagnosis and treatment. Nonetheless, the statistical analyses were conducted with methodological rigour, and the population-based design of the study minimizes selection biases and improves the identification of relatively rare events such as some malignancies. From an epidemiological perspective, this study underscores the importance of establishing high-quality registries for studying the potential effects of long-term drug exposures on cancer development, especially for vulnerable patient groups, which is the case for immune-mediated inflammatory disease patients.

To summarize, although chronic inflammatory conditions are associated with an increased incidence of malignancy, the role of immunomodulatory therapy, and in particular TNFi, in determining this susceptibility seems to be minor. The magnitude of the observed signals, if any, is worthy of more in-depth study, but altogether it is unlikely to change clinical practice and the prescription of b/tsDMARDs in RA. In addition, these results also confirm the cautious position of the recent EULAR guidelines on cancer screening before or during b/tsDMARD therapy [10]. In summary, the results of the study by Huss and colleagues represent a milestone in the assessment of cancer risk with continuous treatment with b/tsDMARDs in RA patients, supporting previous treatment recommendations and providing further reassurance to physicians and patients for daily treatment practice.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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