Does the risk of lymphoma in patients with RA treated with TNF inhibitors differ according to the histological subtype and the type of TNF inhibitor?

We read with interest the paper by Mercer et al focusing on the risk of lymphoma in patients included in the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) and treated with tumour necrosis factor inhibitors (TNFi). Based on data from a prospective cohort including >120 000 patient-years of exposure to TNFi or conventional synthetic disease-modifying drugs (csDMARDs), the authors pointed out that treatment with TNFi in patients with RA was not associated with an increased risk of lymphoma compared with csDMARD treatment. RA is associated with an increased risk of lymphoma, disease activity being the main risk factor of lymphoma occurrence. Thus, patients with RA treated with TNFi, which have more severely active disease, are supposed to have an increased baseline risk of lymphoma. In this context, the impact of TNFi themselves is unclear. They might decrease the risk of lymphoma over time by controlling activity of the disease. But they also might alter antitumour immunosurveillance and increase the risk of lymphoma as observed in post-transplant lymphoproliferative disease. Thus, large epidemiological studies focusing on the long-term safety of TNFi use as the one presented by Mercer et al are crucial. This important study, in line with results from large cohorts and registers, supports an overall absence of increased risk of lymphoma associated with TNFi compared with csDMARDs, which is very reassuring. However, since there are differences between this 2016 study and a previous one published in 2013 based on the same BSRBR registry, we have some concerns about the origin of these discrepancies. Moreover, taking advantage of the very large number of patient-years in this study, we would be very interested in having additional analyses concerning the specific risk of diffuse large B cell lymphomas (DLBCLs) and the potential difference of risk of DLBCL according to the type of TNFi; DLBCL being the lymphoma type that is clearly linked to disease activity.

The question of a different impact of the two types of TNFi (monoclonal antibodies compared with the soluble receptor) on the risk of lymphoma is justified by several observations. First, it is recognised that efficacy profile varies depending on the type of TNFi. Etanercept is not effective in inflammatory bowel disease and is probably less effective than monoclonal in uveitis and psoriasis. Second, infectious safety profile differs since the risk of opportunistic infections and of reactivation of tuberculosis has been shown to be higher with monoclonal anti-TNF. These differences support specificities in the mechanism of action (same inhibition of soluble TNF but less inhibition of membrane TNF with the soluble receptor) that might differentially impact the risk of lymphoma. As discussed by Mercer et al, the French registry RATIO has raised the question of a possible differential effect on lymphoma between the monoclonal antibodies and etanercept. In this prospective pharmacovigilance study, it has been shown that the standardised incidence ratio of lymphoma compared with the general population was 3.7 (95% CI 2.6 to 5.3) with monoclonal antibodies (that could be expected in a population of severe RA) but does not exceed the risk of the general population in patients treated with etanercept: 0.9 (95% CI 0.4 to 1.8). In the RATIO study, 31/38 patients with lymphoma had been exposed to only one TNFi, which makes the interpretation of the results robust.
REFERENCES


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