Cervical cancer risk with the use of tumour necrosis factor inhibitors in rheumatoid arthritis: to worry or not to worry?

Jasvinder A Singh^{1,2,3}

Wadstrom *et al* studied whether tumour necrosis factor (TNF) inhibitors (TNFi) increase the risk of cervical neoplasia in patients with rheumatoid arthritis (RA)?¹ Study authors performed a nationwide study using Swedish databases. The main findings from the study were that biologic-naïve women with RA had more screenings (HR=1.08; 95% CI 1.06 to 1.10), were at greater risk of cervical intraepithelial neoplasia (CIN) 1 (HR=1.53; 95% CI 1.23 to 1.89) and CIN 2–3 (HR=1.39; 95% CI 1.16 to 1.66), but not of invasive cervical cancer (HR=1.09; 95% CI 0.71 to 1.65), compared with the general Swedish female population without RA. Patients who initiated TNFi therapy had similar screening patterns (HR=1.01; 95% CI 0.98 to 1.05), were not at increased risk of CIN 1 (HR=1.23; 95% CI 0.87 to 1.74), but were at increased risk of CIN 2–3 (HR=1.36; 95% CI 1.01 to 1.82), and invasive cervical cancer (HR=2.10; 95% CI 1.04 to 4.23) compared with biologic-naïve women with RA. The estimates for the association of TNFi use (incident or ongoing) with invasive cervical cancer were attenuated when the study period was restricted to 2006–2012 and the biologic-naïve comparator restricted to those individuals who had received dispensing of two or more different conventional disease-modifying antirheumatic drugs (DMARDs), HR=1.36 (95% CI 0.59 to 3.13) and was absent when restricted to the new users of TNFi 2006 or later (only one case during 18 110 person-years).

Study strengths were the use of Swedish national databases making it a population-based study, linkage between various

databases allowing authors to examine various stages of cervical cancer, the use of an approach similar to a validated approach for RA diagnosis in this database,² and the performance of analysis by time periods.

Study limitations must be carefully considered while interpreting findings. Key study limitations to consider include confounding bias, channelling bias, detection/lead-time bias and the small number of cervical cancer cases detected. Several important confounders could not be adjusted even in this well-conducted population-based study. These include previous exposure to DMARDs other than TNFi, rates and duration of tobacco use and the rates of human papilloma virus infection/sexually transmitted disease that can potentially contribute to the risk susceptibility to cervical cancer. Channelling bias is a possibility and people who have more severe disease or longer disease duration, more likely to receive TNFi, may also have higher chronic inflammation burden and higher likelihood of conventional DMARD/cytotoxic drug exposure (longer duration; higher number of DMARDs) and either may increase the risk of cervical cancer; RA disease severity or functional class (disease activity measures) or the duration of RA, were not adjusted in the analysis. Lead-time bias is another limitation due to the study design. Despite a large sample size, the number of invasive cervical cancers was 7 for biologic-naïve and 10 for TNFi in those with a normal baseline smear, limiting the power to make firm conclusions for the risk of invasive cervical cancer with TNFi. Nevertheless, this is one of the largest studies examining TNFi biologics as a potential risk factor for cervical cancer risk in patients with RA. These findings must be interpreted in the context of the existing knowledge in this area.

RA is associated with an increased risk of lymphoma, and the risk of solid cancer may be increased slightly in patients with RA compared with the general population. In a population-based study using

the Swedish national data, compared with the general population matched for age, sex, marital status and residence, the overall HRs (95% CI) of cancers were increased in the first 10 years following the diagnosis of RA for lymphoma, 1.75 (95% CI 1.04 to 2.96) and other cancers 1.23 (95% CI 1.08 to 1.40).³ Among other cancers, only prostate and lung cancers occurred at significantly higher rates in RA with HRs of 1.66 (95% CI 1.27 to 2.18) and 2.24 (95% CI 1.49 to 3.36), respectively;³ breast, colorectal and skin cancers were not significantly different than non-RA general population. Evidence suggests that risk of lymphoma in patients with RA increased dramatically with higher disease activity and worsening American College of Rheumatology (ACR) functional class.⁴ In another study, Askling *et al* reported that compared with age, sex and calendar year-matched Swedish general population, the risk of solid cancers increased slightly in patients with RA, with an HR of 1.05 (95% CI 1.01 to 1.08), and this was due to increased overall solid cancer risk in men, 1.19 (95% CI 1.13 to 1.26), since hazard among women was not increased at 0.97 (95% CI 0.93 to 1.02).⁵

What is known about TNFi and cervical cancer risk? To my knowledge, studies examining the risk of cervical cancer or its recurrence are limited and the current study is one of the largest, well-conducted studies in this area. Two studies with much smaller sample sizes (<250 patients each) examined patients who had RA with carcinoma-in-situ or premalignant cervical lesion and reported no cervical cancers in TNFi-treated patients;^{6,7} however, the number of patients was too small to exclude a possible link. In a study of 238 patients with RA and carcinoma-in-situ of cervix in the British Society for Rheumatology Biologics Register (BSRBR), two genital cancers occurred in conventional DMARD and none in the TNFi-treated patients, leading to an incidence rate of 13/1000 per year in DMARD versus 0/1000 per year in TNFi groups.⁸

There are data related to cancer risk with TNFi that provide additional insight. These studies indicated that the risk of cancer or cancer recurrence was not increased with TNFi. Dixon *et al* reported an age-adjusted and sex-adjusted incidence rate ratio of 0.58 (95% CI 0.23 to 1.43) for recurrent incident cancers for the TNFi-treated cohort compared with the conventional DMARD-treated cohort in patients who had RA with prior cancer, with respective incidence rates of 25.3

¹Medicine Service, Birmingham VA Medical Center, Birmingham, Alabama, USA; ²Department of Medicine at School of Medicine, Division of Epidemiology at School of Public Health, University of Alabama at Birmingham (UAB), Birmingham, Alabama, USA; ³Department of Orthopedic Surgery, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Correspondence to Dr Jasvinder A Singh, University of Alabama, Faculty Office Tower 805B, 510 20th Street S, Birmingham AL 35294, USA; Jasvinder.md@gmail.com

events versus 38.3 events per 1000 person-years, respectively, using the BSRBR.⁹ On the other hand, among patients with prior melanomas, 3 (18%) of 17 in the TNFi cohort developed an incident malignancy, compared with 0 of 10 in the DMARD cohort.⁹

In contrast, a study from the German register showed an equally non-significant increase for recurrent cancer with TNFi compared with conventional DMARDs.¹⁰ Crude recurrence rates of recurrent cancer per 1000 patient-years were 45.5 (95% CI 20.8 to 86.3) for patients exposed to TNFi, 32.3 (95% CI 0.8 to 179.7) for anakinra and 31.4 (95% CI 10.2 to 73.4) for conventional DMARDs only, leading to an incidence rate ratio of 1.4 (95% CI 0.5 to 5.5) for TNFi versus conventional DMARDs, which was not significant (p value=0.63). The differences between study findings from the British and the German registers might be explained by the large differences in time since prior cancer at treatment start with TNFi (5 years in Germany vs 11.5 years in the UK), the longer waiting time with TNFi than with conventional DMARDs in the UK study (8.5 years in conventional DMARDs), some differences in demographics (67% German vs 81% UK patients treated with TNFi were female) and the follow-up duration (2.1 for German vs 3.1 for UK study), and possible differences in cancer surveillance due to study setting (Germany vs UK), as well as. The number of prior conventional DMARDs used (3.7 in the German vs 4 in the UK study) and the median RA disease duration (10 years in the German vs 11 years in the UK study) in these TNFi cohorts were similar.

In a case-control study of Swedish database by Raaschou *et al*, the adjusted HR of the recurrence of breast cancer with TNFi was 1.1 (95% CI 0.4 to 2.8); respective crude incidence rates (per 1000 person-years) were 15 in TNFi versus 16 in matched biologic-naïve patients.¹¹

Askling *et al* reported that a total of 240 incident first primary cancers occurred among 6366 patients with RA who had started TNFi therapy (25 693 person-years; etanercept, infliximab or adalimumab) versus 4244 cancers among 61 160 TNFi-naïve patients (330 498 person-years), leading to crude incidence rates of 9.3/1000 person-years in TNFi-treated versus 12.8/1000 person-years in TNFi-naïve patients.¹² Compared with TNFi-naïve patients, the relative risk (RR) of incident primary cancer with TNFi was 1.00 (95% CI 0.87 to 1.17). Patients who had RA treated with TNFi

had a cancer risk that was similar to that of patients starting methotrexate (MTX) therapy and that of patients starting conventional DMARD combination therapy.¹² This RR did not change with increasing cumulative time receiving active TNFi therapy, for example, was 0.96 (95% CI 0.50 to 1.86) for those with ≥ 6 years of TNFi therapy. Each of the three TNFi (etanercept, infliximab or adalimumab) displayed somewhat different cancer risks during the first year of follow-up, but not thereafter.

Askling *et al* observed 26 malignant lymphomas during 26 981 person-years of follow-up in 6604 TNFi-treated patients with RA, which corresponded to an RR of 1.35 (95% CI 0.82 to 2.11) versus TNFi-naïve patients with RA (336 lymphomas during 365 026 person-years) and 2.72 (95% CI 1.82 to 4.08) versus the Swedish general population comparator (1568 lymphomas during 3 355 849 person-years).¹³ Risk did not vary significantly by time since start of first treatment or with the accumulated duration of treatment, nor with the type of anti-TNF agent. This study indicated that TNFi do not further increase the risk of lymphoma beyond what is associated with the presence of RA.¹³

In a US study using the National Arthritis Databank sample, Wolfe and Michaud studied incident cancer among 13 001 patients (49 000 patient-years of observation) during 1998–2005.¹⁴ There were 623 incident cases of non-melanoma skin cancer and 537 cases of other cancers. The ORs (95% CI) with biologics compared with the US National Cancer Institute Surveillance, Epidemiology, and End Results data were as follows: all cancers, 1.0 (95% CI 1.0 to 1.1); breast cancer, 0.8 (95% CI 0.6 to 0.9); colon cancer, 0.5 (95% CI 0.4 to 0.6); lung cancer, 1.2 (95% CI 1.0 to 1.4); lymphoma, 1.7 (95% CI 1.3 to 2.2); non-melanoma skin cancer, 1.5 (95% CI 1.2 to 1.8) and melanoma, 2.3 (95% CI 0.9 to 5.4). The OR (overall risk) of any cancer was 1.0 (95% CI 0.8 to 1.2).¹⁴

In a recent study of incident solid cancers using the BSRBR, Mercer *et al* reported 427 solid cancers in 52 549 patient-years of follow-up in the TNFi-treated and 136 cancers in 11 672 patient-years in the conventional DMARD-treated patients with RA.¹⁵ Respective crude incidence rates of solid cancer were 8.1/1000 person-years (95% CI 7.4 to 8.9) versus 11.7 (95% CI 9.8 to 13.8); in analyses adjusted for baseline characteristics, TNFi were not associated with any increase in the risk of solid

cancers compared with conventional DMARDs, the HR was 0.83 (95% CI 0.64 to 1.07).¹⁵

Thus, the majority of the evidence to-date supports no increase in the overall risk of solid cancers with TNFi, above and beyond, the slight increase in risk associated with RA. Thus, the current study is among the first to show an increased risk of cervical cancer with TNFi, compared with biologic-naïve patients in the main analyses.¹ However, the finding could not be confirmed in sensitivity analyses that were limited to the most recent time period (2006–2012) and the use of two or more conventional DMARDs (HR=1.36; 95% CI 0.59 to 3.13) and was absent when restricted to new users of TNFi 2006 or later (one case during 18 110 person-years).

What guidance do RA treatment recommendations provide us about this? European League Against Rheumatism (EULAR) recommendations for the treatment of RA do not address the issue of cancer risk when choosing between biologics or between conventional DMARDs and biologics.¹⁶ According to the 2015 ACR treatment guideline for RA, the recommendation is to treat a patient who had RA with a previously treated solid organ cancer the same as a patient without this condition; no preference for any specific DMARD or TNFi or non-TNF biologic was stated.¹⁷ However, neither guideline addresses the issue of cancer risk in patients without any known cancers, which is the area this study provides best evidence for.

What impact should this evidence have on RA treatment guidelines? How should this knowledge change clinical practice? Should it change clinical practice? Patients with RA who are starting biologics are often concerned about the potential side effects/risks with new drugs such as biologics, including infections and cancer. Although declining in prevalence and mortality due to effective screening programmes over time, cervical cancer is among the most common cancers in women, who are disproportionately affected by RA. While this study does not provide the definitive answer to this important question, it adds new knowledge to this area. The findings from this study should facilitate discussions related to these risks between patients and their physicians at the time of treatment decision-making. This will likely lead to a more patient-centred approach, since it addresses an important patient issue that might impact their long-term adherence to treatments such as TNFi.

To find a definitive answer to this question of whether TNFi truly does or does not increase the risk of cervical cancer, we need confirmation of these findings in other independent samples. I concluded this based on the finding from the current study that shows this association in the main analysis, but not in the sensitivity analyses. In addition, longer-term studies in even larger samples may be needed for a definitive answer regarding the risk of cervical cancer with TNFi. Just as important would be studies that examine the risk of other solid cancers, in population-based samples. A reasonable approach could be a joint data analysis of the biological registers, as has been done for lymphomas and malignant melanomas.

In my view, one must view this slight possible increase in risk of cervical cancer in context of the benefits of TNFi, which are associated with significant improvement in the quality of life, function and symptoms in patients with RA.¹⁸ Comparison to biologic-naïve is appropriate from an epidemiological study perspective. However, patients who are candidates for TNFi, usually after failing DMARDs, have non-TNF, oral small molecule (tofacitinib) or combination conventional DMARD therapy as alternate treatment options. A change in RA treatment strategy to use TNFi or non-TNF or tofacitinib or combination conventional DMARD therapy for this patient population (DMARD-failure) can only occur, if more data becomes available that can well establish the RR of cervical cancer, other cancers and other significant side effects and relative benefits of these comparators versus TNFi.

In conclusion, this population-based study showed that the risk of cervical cancer might be slightly increased with TNFi in patients with RA. Caution may be needed when patients with RA are presented with a treatment option that includes TNFi. However, despite a robust design, study findings do not warrant in the change in current practice of using TNFi versus other treatment options in RA.

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