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Perspective on the risks of infection and malignancy with rheumatoid arthritis therapy

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Tumor necrosis factor-α antagonists (anti-TNF agents) have been associated with increased risks of malignancies and serious infections in rheumatoid arthritis. However, available data on these risks remain sparse, and at times conflicting. Thus, at present, there are no precise and robust estimates of the risks of serious infections and malignancies with anti-TNF agents in rheumatoid arthritis. Discrepancies in data may be owing, in part, to methodological issues related to observational studies, including differences in study populations, comparison groups, definitions of outcomes and duration of follow-up, as well as possible channeling bias and precision error. Obtaining better estimates of uncommon risks with anti-TNF agents in rheumatoid arthritis will be challenging. Observational studies using large administrative databases, patient registries and postmarketing surveillance systems have the potential to add important information on the safety of these new therapies.

New DMARDs, and in particular biologic agents, have revolutionized the treatment of rheumatoid arthritis (RA) in the last decade, and led to significant improvements in patient outcomes. This notwithstanding, these new therapies have also been associated with increased risks of malignancies and serious infections, although considerable uncertainty still remains as to the presence and magnitude of these risks. In part, this uncertainty may result from methodological difficulties in identifying relatively small risks. In an attempt to better understand the issues at stake, we review some of the available evidence concerning the risks of malignancies and serious infections associated with new treatments for RA, and some of the methodological shortcomings of this data.

What do we know regarding the risk of malignancies associated with treatments for RA?

A thorough review by Chakravarty *et al.* found that RA was not associated with a significantly increased overall risk of malignancies compared with the general population [1]. A recent meta-analysis of 21 observational studies by Smitten *et al.* found a small but significant increase in overall risk (standardized incidence ratio [SIR]: 1.05; 95% confidence interval [CI]: 1.01–1.09) [2]. However, more importantly, this meta-analysis demonstrated that such overall findings obscure the more informative fact that RA may be associated with a greater increase in some site-specific malignancies, in particular, lymphoproliferative and lung cancers, and a decrease in other cancers, in particular those of the digestive tract. In the abovementioned meta-analysis, there was a twofold increase in the risk of lymphoma (SIR: 2.08; 95% CI: 1.80–2.39) and an increase in the risk of lung cancer (SIR: 1.63; 95% CI: 1.43–1.987), but a decrease in the risk of colorectal cancer (SIR: 0.77; 95% CI: 0.65–0.90) [2].

However, the relationship between RA and malignancies is complex. There are multiple theoretical pathways by which RA and malignancies may be associated [3]. Two such pathways are the disease *per se*, and the drugs used to treat the disease. As far as the disease is concerned, autoimmune dysfunction and chronic inflammation have been proposed as mechanisms whereby the risk of certain malignancies, especially lymphoproliferative cancers, may be increased in RA. In particular, higher disease severity in RA has been associated with a greater risk of lymphoma [4]. On the other hand, drugs used to treat RA modulate the immune system and may, in part, also be responsible for the increased risk of malignancy [5]. However, lacking a randomized trial, it may be difficult to tease apart the effects of the disease and the drugs to the extent that stronger immunosuppression is used in more severe disease, so that any observational study would be subject to intractable confounding by disease severity. Finally, to add to the complexity, the question of how the possible risks of malignancy resulting from the

Keywords
epidemiology ■ malignancy ■ rheumatoid arthritis ■ serious infections ■ study design ■ tumor necrosis factor-α antagonists

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disease or the drugs relate, whether additively, synergistically or perhaps negatively with, for example, the reduction of the chronic inflammation by the drugs mitigating the risk associated with the disease itself, remains unresolved. At present, most studies showing increased risk of malignancies in RA patients do not separate treated from untreated patients, and it is thus impossible to know, with confidence, to what extent the increased risk of malignancies in RA is owing to the disease or the drugs.

As far as biologic agents are concerned, none of the individual randomized trials of anti-tumor necrosis factor-α (anti-TNF) therapies in RA showed a significantly increased risk of lymphoma or cancer. However, a meta-analysis of nine trials (N = 5014) of 12 or more weeks duration (range 12–54 weeks) with infliximab or adalimumab in patients with RA showed a threefold increase in the overall risk of cancer relative to placebo (pooled odds ratio: 3.3; 95% CI: 1.2–9.1) [6]. However, the absolute rates were fairly low, with 29 malignancies reported in 3192 patients on treatment (0.9%), compared with three in 1428 (0.2%) of those on placebo. A follow-up report placed the relative risk at 2.02 (95% CI: 0.95–4.29) when additional trial data were added [7]. On the other hand, a meta-analysis of etanercept trial data in patients with rheumatic diseases (18 RA, two psoriatic arthritis and two ankylosing spondylitis trials with 6798 person-years of exposure) showed no increased risk with this drug [8], although the exact number of malignancies in the treated and control patients was not reported. Finally, the results of a US FDA-requested analysis was published in response to the meta-analysis of infliximab and adalimumab data and reported no increase in the risk of malignancy in patients with RA with infliximab and adalimumab when compared with general population rates available from the Surveillance, Epidemiology and End Results (SEER) database and with etanercept when compared with placebo [9].

Observational studies of RA patients treated with anti-TNF drugs have failed to show a significant increase in the risk of cancer overall or lymphoma in particular compared with patients not receiving those drugs [10–14]. In a large US study [11], biologic therapy was only associated with an increased risk for skin cancer, but not solid tumors or lymphoproliferative malignancies, when compared with the SEER database. The risk for individual anti-TNF agents was not different, although this analysis was limited by small numbers.

Thus, at present, the data from meta-analyses and observational studies are conflicting, at least insofar as adalimumab and infliximab are concerned. It is possible that some of the discrepancies are due to methodological problems. Among other things, it could be argued that a negative channeling bias in the observational data, whereby patients felt to be at high risk were not offered anti-TNF drugs, may have obscured an increased risk in these studies. In addition, most malignancies have long latency periods and the short duration of exposures in the above-mentioned studies may therefore have made the identification of a latent risk more difficult. Moreover, these databases may not have sufficient information on other DMARDs used prior to the anti-TNF agents under study, making the channeling problem more acute.

What do we know regarding the risk of serious infections associated with the treatment for RA?

In general, RA is known to be associated with approximately a twofold increase in the risk of serious infections compared with the general population [15,16]. However, again the relative contribution to this increase in risk from the disease *per se* or the drugs is difficult to tease apart. Indeed, in observational studies, patients with more severe disease are more likely to receive stronger immunosuppression, thereby further confounding the effect of the disease and the drug.

The data on whether anti-TNF drugs further increase the risk of serious infections are, however, inconsistent. Again, although most individual trials did not show a significant increase in the risk of serious infections with anti-TNF drugs, they had low power to detect such an increase [17]. A meta-analyses of trials with infliximab or adalimumab in patients with RA showed a twofold increase in the risk of serious infections [6]. The absolute rates were 3.6% in the treated patients (126 serious infections in 3493 patients) compared with 1.7% in the patients who received placebo (26 in 1512). However, here again, a meta-analysis of trial data with etanercept reported no increase in the risk of serious infections with this drug [8]. Observational studies have had conflicting data, showing results ranging from no increase [18] to a doubled or more increase [19]. Differences in study populations, comparison groups, definitions of outcomes and duration of follow-up, may, at least in part, explain the discrepancies. Some have suggested that discrepancies in results could be reconciled by considering

treatment duration, with higher risks of serious infections being present during the first few months of anti-TNF treatment followed by decreasing (and even reduced) risks after the first year of treamtment [20,21]. However, whether the early increased risk is real or reflects bias (with physicians having a lower threshold for treating infections earlier in the treatment) remains unclear. Furthermore, channeling bias, whereby patients with more severe disease may be more susceptible to infection, but also preferentially treated with anti-TNF drugs, could also wrongly suggest an association between anti-TNF therapy and serious infections [22].

As for specific infections, there is evidence showing that the risk of TB, although low, is substantially increased in RA patients treated with anti-TNF drugs [23]. Estimates of risk have ranged from seven cases per 100,000 patient-years of exposure with etanercept [101], to 53 cases per 100,000 patient-years of exposure with infliximab [24].

Future perspective

A review of the abundant literature on the possible risks of malignancies and serious infections associated with RA and new treatments for this disease results in a disquieting observation: robust and precise estimate of these risks remain elusive. In addition, data suggesting possible differences in risk profiles between the different anti-TNF drugs (and in theory supported by differences in structures and mechanisms of action), are rare. In addition, many other questions remain. For example, the proper use of biologics in patients with past cancers, current malignancies on treatment or with premalignant lesions, and the risks of nonserious but common infections (such as upper respiratory tract infections and urinary tract infections) and postoperative infections with these drugs remain entirely unknown.

From a methodological standpoint, obtaining better estimates of risk of malignancies and serious infections with anti-TNF drugs in RA will be challenging. Large, long-term randomized trials would be necessary to tease out the effects of the disease from those of the drugs, but are very expensive and are unlikely to be carried out with head-to-head comparisons of different drugs. Moreover, trials often include the 'best' patients, and may suffer from problems of generalizability for the 'usual' patients who commonly have comorbidities and co-therapies. Pharmacoepidemiologic studies using large administrative databases offer several advantages, including larger sample sizes to identify uncommon and, at times, latent risks, and better generalizability. On the other hand, administrative data are often collected for other purposes and may be incomplete with respect to the study at hand (e.g., severity of disease, other medications, comorbidities, important confounders such as smoking and so on). Thus, they are susceptible to inherent biases that cannot be easily overcome. Postmarketing surveillance systems have the advantage that they may identify signals for unexpected adverse events. However, they rely on voluntary reporting and are likely to be incomplete and possibly biased. Registries of patients with RA have been developed specifically around the issues of safety of new biologic agents. While these registries include very accurate clinical information on the disease, their size remains somewhat limited to assess rare adverse events. For example, the Swedish national registry for biologic agents reported two relative risks of lymphoma with anti-TNF drugs, namely 5.0 (95% CI: 0.9–27.0) [10] and 1.1 (95% CI: 0.6–2.1) [13], using different versions of the registry and comparison cohorts, with low statistical precision being a possible explanation for the discrepancy. Nevertheless, with time, registries have the potential to produce important information on several safety outcomes.

The problem may become even more complex if we consider other comorbidities of RA and the impact that anti-TNF drugs may have on those. For example, it is now well accepted that the risk of cardiovascular disease is increased in RA [3]. On the other hand, some [25], although not all [26], studies have found that anti-TNF therapy in RA could be cardioprotective. Thus, the net effect of all risks and benefits of anti-TNF drugs in RA remains to be resolved. Moreover, none of these issues are unique to anti-TNF drugs. New, potent biologic agents with mechanisms of action different from those of anti-TNF drugs, for example CD20 or IL-6 antagoinsts, are currently or will soon be available for the treatment of RA. Given the differences in mechanisms, these drugs will likely have different risk/benefit profiles compared with anti-TNF drugs. These profiles will have to be defined and inevitably compared with those of anti-TNF drugs in order to make optimal treatment decisions for our patients.

In a time of diminished public tolerance of risk and uncertainty, what are we to do? First, physicians must keep well-informed and must keep some perspective on the balance between the great benefits and the small known and possibly as yet unknown risks associated with the

new drugs available to treat RA. Second, securing patient participation in the therapeutic process becomes especially important when there is doubt regarding the best course of action. Finally, perfection should not stand in the way of progress – there may never be one perfect study, but several rigorously designed and analyzed studies conducted in various populations may provide incremental knowledge that, in time, will shed light on the complex questions at stake.

Financial & competing interests disclosure

S Suissa has received grants from Sanofi-Aventis and Wyeth, and is a consultant for Bristol-Myers-Squibb. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Tumor necrosis factor-α drugs (anti-TNF agents) have led to significant improvements in outcomes of patients with rheumatoid arthritis (RA).
- However, these new therapies have also been associated with increased risks of malignancies and serious infections in RA.
- Meta-analyses of randomized trials have shown that infliximab and adalimumab were associated with up to a threefold increase in the overall risk of malignancy relative to placebo, but no increase relative to the general population.
- Meta-analyses of etanercept trial data showed no increased risk of malignancy with this drug relative to placebo.
- Observational studies of RA patients treated with anti-TNF drugs failed to show a significant increase in the risk of malignancy overall or lymphoma in particular, compared with patients not on those drugs.
- A meta-analysis of trials with infliximab and adalimumab in RA showed a twofold increase in the risk of serious infections compared with placebo, whereas one with etanercept reported no increase.
- Observational studies have had conflicting data on the risk of serious infections with anti-TNF agents, with results ranging from no increase to a doubled or more increase.
- As for specific infections, the risk of TB, although low, is substantially increased in RA patients treated with anti-TNF drugs.
- Discrepancies in data may be owing, in part, to methodological issues, including differences in study populations, comparison groups, definitions of outcomes and duration of follow-up, as well as possible channeling bias and precision error.
- Obtaining better estimates of uncommon risks with anti-TNF drugs in RA will be challenging, although pharmacoepidemiologic studies using large administrative databases, patient registries and postmarketing surveillance systems have the potential to produce important information on safety outcomes with these new drugs.

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