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Overview of safety of non-biologic and biologic DMARDs

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Abstract

Safety data come from a number of sources. Randomized clinical trials tend to be relatively short, exclude patients with significant comorbidity, have limited numbers of subjects and are primarily powered for efficacy. The most useful post-marketing data come from large national registries, such as Britain's BSRBR, Sweden's ARTIS, Germany's RABBIT, France's DANBIO, Spain's BIODASER and North America's CORRONA. Among the most commonly used non-biologic DMARDs, MTX is associated with risks of hepatotoxicity and cytopenia, as well as pneumonitis, particularly during the first year of treatment. Regarding TNF inhibitors, there is an increased risk of infection (including serious infections) by bacterial pathogens, atypical fungi and opportunistic pathogens. When possible, pneumococcal and influenza vaccines should be given before initiation of treatment with any biologic DMARD. Screening for latent tuberculosis is recommended for all TNF inhibitors, and has been shown to reduce the risk of reactivation. Evidence from registries suggests that there is no increased risk of solid tumours with TNF inhibitor treatment; however, non-melanoma skin cancers are more common. Specific risks with other biologic DMARDs include gastrointestinal perforation with tocilizumab, progressive multifocal leucoencephalopathy with rituximab and pulmonary infections with abatacept. Overall, the safety of biologic and non-biologic DMARDs appears to be reasonable, particularly compared with the risks associated with the disease itself.

Key words: rheumatoid arthritis, biologic DMARDs, methotrexate, safety, infection, vaccination, latent tuberculosis screening, herpes zoster, non-melanoma skin cancer.

Introduction

Rheumatologists have long recognized that safety issues are a critical aspect of treatment decisions in RA. No medication is free of potential toxicity, and as earlier and more aggressive therapy of RA has become the standard of care, awareness of these toxicities has become increasingly important. For many DMARDs, and more specifically for biologics and MTX, one of the primary concerns is the risk of infection, although individual agents have unique side effect profiles that may impact the selection and screening of patients.

Clinicians rely on safety data from a number of different sources, including randomized, controlled clinical trials, open-label extensions, post-marketing registries and anecdotal reports of adverse events published in the literature and reported to regulatory agencies. Each source has its own strengths and weaknesses. Randomized, controlled clinical trials include relatively small numbers of subjects and follow them for a relatively short period of treatment; these trials are generally powered to assess efficacy, but not safety, end points. Moreover, these studies typically exclude patients with active comorbidities, who may be at higher risk for toxicity, and may thus present a more favourable impression of risk than may be seen in clinical practice. For some adverse events, such as infection, RA itself confers a greater risk [1], a risk that applies equally to the treatment and control arms and may confound interpretation of small differences between the two groups. Open-label extension studies can provide information from longer periods of treatment, but these studies are also limited by patient selection and by the lack of a comparison group.

Post-marketing reports, including published case reports and series, can be a useful source of information on specific safety signals but rarely provide helpful

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guidance on the true risk of a certain toxicity, as the denominator of patients treated is usually imprecise at best. Regulatory agency registries, such as the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) usually rely on voluntary reporting and may receive reports on only a fraction of actual events. The most useful post-marketing data come from large national registries, such as Britain's British Society for Rheumatology Biologics Register (BSRBR), Sweden's Antirheumatic Therapies in Sweden (ARTIS), Germany's Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT), Denmark's DANBIO (a nationwide registry of biologic therapies in Denmark), Spain's BIODASER (a registry of patients suffering from rheumatic diseases exposed to TNF antagonists) and North America's Consortium of Rheumatology Researchers of North America, Inc. (CORRONA) registry. These registries are able to follow a large cohort of real-world patients, often for long periods of time, and can provide estimates of risk for both individual agents and drug classes.

Non-biologic DMARDs

MTX is frequently used as the backbone of RA therapy, combined both with other non-biologic DMARDs and with biologics. Although most patients tolerate MTX well, monitoring is essential. ACR guidelines call for monitoring liver enzymes and blood counts at least every 3 months [2]. The British Society for Rheumatology and the British Health Professionals in Rheumatology (BSR/BHPR) guidelines for DMARD therapy recommend monitoring blood count, urea and electrolytes as well as liver function tests every 2 weeks until dose and monitoring is stable for 6 weeks, then monthly [3]. Monitoring frequency can be reduced afterwards based on clinical judgement, with due consideration for risk factors including age, comorbidity and renal impairment. Common practice is to restrict alcohol intake in patients receiving MTX, although recent data question the contribution of alcohol to the risk of hepatotoxicity [4]. Pneumonitis remains a concern with MTX therapy, particularly in the first year; elderly patients and those with diabetes may be at particular risk for this complication [5]. An ongoing prospective study suggests that the risk for this particular toxicity is lower than once presumed [6].

While infections are certainly seen in association with MTX use, the true risk associated with this drug is not entirely clear. An early prospective study suggested that RA patients treated with MTX had a higher risk of infection or treatment with antibiotics than those not receiving the drug, with a relative risk of 1.52 (95% CI 1.04, 2.13) [7]. Data from the US CORRONA found a similarly increased risk of infection in a prospectively followed cohort of 7971 RA patients when comparing MTX use with the use of other DMARDs (incidence rate ratio 1.30, 95% CI 1.12, 1.50) [8]. Data from a prospective cohort of 609 RA patients followed by the Mayo Clinic for a mean of 12.7 years, however, found that RA patients were at greater risk for infection than non-RA patients matched for age and comorbidities, and that DMARD use, including MTX, did not contribute to this risk [1, 9].

Other widely used non-biologic DMARDs, besides MTX, include LEF, SSZ and HCQ. LEF shares many of the same potential toxicities as those of MTX, including cytopenias and hepatotoxicity; as with MTX, regular laboratory monitoring of blood counts and liver enzymes is indicated [2]. In a systematic review of published data on MTX and LEF therapy, both were associated with similar rates of liver enzyme abnormalities, gastrointestinal complaints (nausea, diarrhoea) and infection [10]. Rates of liver enzyme abnormalities were also similar in the CORRONA cohort [11]. MTX and LEF have been combined safely in the clinical trial setting [12], although practitioners in Europe are cautioned against using this combination in practice.

The most worrisome toxicity of HCQ is retinal damage, a risk that is greatest with longer duration of therapy. The Royal College of Ophthalmologists recommends a maximum daily dose of no more than 6.5 mg/kg of lean body weight (typically 200–400 mg/day). Their guidelines suggest annual review by an optometrist, with consultation with an ophthalmologist for patients receiving more than 5 years of therapy [3]. The American Academy of Ophthalmology recently published updated guidelines for HCQ monitoring, which, because most US patients are treated with 400 mg/day, no longer focus on weight-based dosing [13]. The new guidelines call for a baseline examination, then an initial follow-up examination at 5 years and annually thereafter. These guidelines no longer recommend Amsler grid testing but focus on several newer objective measurements that assess visual fields and visual function.

SSZ has a low risk of serious toxicity, although nausea is a common side effect. Leucopenia may be seen when treatment is initiated however, so close monitoring is warranted during the first months of therapy. Neither SSZ nor HCQ has been associated with an increased risk of infection.

Biologic DMARDs

The availability of biologic DMARDs has revolutionized the management of RA, but their use has been accompanied by concern over toxicity related to their unique mechanisms of action. TNF inhibitors block an overexpressed signalling protein in RA; in doing so, however, they also inhibit an important signalling protein in the normal immune response. The primary result of this process is an increased risk of infection by both bacterial pathogens and more atypical fungal and opportunistic pathogens. When possible, pneumococcal and influenza vaccines should be administered prior to therapy with TNF inhibitors or any biologic DMARD [2]. Annual influenza vaccination and periodic revaccination with pneumococcal vaccine should be performed as well, even in patients receiving the β-cell-depleting agent rituximab, where there is evidence of at least a partial protective immune response [14].

Five TNF inhibitors have now become available for clinical use, beginning with etanercept and infliximab, then adalimumab and, most recently, certolizumab and golimumab. Overall infection rates do not differ between arms in trials with these agents, in large part because of the high background rate of infection in RA [1]. Most trials have shown a numerically, but not statistically, greater incidence of serious infections (hospitalization or use of i.v. antibiotics) in the treatment arm than in the control or placebo arm.

Meta-analyses may be useful in overcoming the size limitations of individual studies, but these analyses themselves may need to be viewed with caution. An early meta-analysis of clinical trials of infliximab and adalimumab in the treatment of RA found a higher risk of serious infection with these agents and suggested that the risk increased with dose [15]. A more recent meta-analysis that assessed the risks with these agents when used for all conditions found an increased risk of serious infection with certolizumab (OR 3.51; 95% CI 1.59, 7.79) but no increase with the other agents in the class, including adalimumab and infliximab [16]. This discrepancy highlights the impact that study selection may have on the results of a meta-analysis. In the end, the most appropriate conclusion that one can draw from clinical trials of TNF inhibitors is that they demonstrate a small, but likely real, increase in serious infection rates.

Registry data does appear to confirm that there is a higher risk of serious infection with the use of TNF inhibitors. In two registries, the ARTIS registry and the BSRBR, the risk was clearly higher in the first year of therapy [17, 18]. One proposed explanation for this is that patients destined to develop infections are going to do so early and then discontinue therapy [18]. Alternatively, it may be that the risk of infection due to RA itself is related to disease activity [19] and that this additive risk diminishes as patients respond to therapy. In any case, it should be noted that the risk of serious infection with TNF inhibitors likely pales in comparison with the increased risk associated with the CS use that these agents may be able to reduce [19, 20]. The impact of age and comorbidities, such as diabetes, on infection risk with TNF inhibitors is controversial, although evidence suggests that elderly patients can be treated safely with careful monitoring [21]. Patients with chronic infections and a history of recurrent infections should avoid these and other biologic therapies when possible.

Fungal and granulomatous infections, although quite rare, clearly occur at a rate that is higher than the background rate in the population, although, again, the contribution of CS use to these infections cannot be discounted. The first recognition of the risk of tuberculosis (TB) came in a report from the FDA AERS database, to which cases of presumed TB reactivation had been reported in the first years after the drug's approval [22]. TB infection has been reported with all TNF inhibitors and is presumed to be a class effect, although some reports have suggested that the risk may be lower with etanercept [23, 24]. Screening for latent TB prior to therapy is recommended for all agents in the class and has been shown to reduce the risk of reactivation [25].

TB screening in the USA has historically relied on the tuberculin skin test (TST), but the more recently developed IFN-γ release assay may be a useful alternative, particularly when the Bacillus Calmette–Guérin (BCG) vaccine has been used and may produce a false-positive TST. A positive screen (including a TST of >5 mm, as used for immunocompromised hosts) should trigger a full course of therapy for latent TB, which should be initiated before TNF inhibitor therapy is begun. The British Thoracic Society recommends a chest radiograph in addition to a TST and also recommends 2 months of anti-tuberculous therapy before initiating a TNF inhibitor in patients with evidence of latent TB [26]. The value of repeat screening in patients who are on therapy is unknown, although some have recommended repeat screening for patients in endemic areas [27]. In the USA, at least, atypical mycobacterial infections have become more common than TB in patients treated with TNF inhibitors [28]. Unfortunately, there are no screening procedures for these infections.

Other unusual infections seen in patients treated with TNF inhibitors include histoplasmosis, coccidioidomycosis, pneumocystis pneumonia, and *Listeria* and *Legionella* infections; the latter two infections were recently added to the black box warnings for these agents on the US package inserts. Some of these infections, such as histoplasmosis (Ohio River Valley) and coccidioidomycosis (American Southwest), tend to be regional, but clinicians should be aware of them in patients travelling to endemic areas.

Certain viral infections have been seen with increased frequency following treatment with TNF inhibitors. Herpes zoster, in particular, has been associated with these therapies [29, 30]. While vaccination against herpes zoster is often recommended prior to therapy in the USA, this vaccine is not recommended in the UK, on the grounds of limited efficacy. As a live vaccine, it would be contra-indicated once any biologic DMARD therapy has been started. Hepatitis B reactivation has also been reported following treatment with TNF inhibitors [31].

After infection, the greatest worry with the use of TNF inhibitors has been the risk of malignancy, out of concern that the impact of these agents on immune response might inhibit tumour surveillance. Early evidence from clinical trials suggested that these agents were associated with an increased risk of lymphoma, although interpretation of these data is complicated by the increased risk of lymphoma associated with RA itself [32]. Subsequent post-marketing data, in fact, have suggested that the risk of lymphoma in patients receiving these agents is more properly associated with RA than with the treatment [33, 34]. A particularly severe hepatocellular T-cell lymphoma has been reported in children and young adults treated with adalimumab or infliximab, usually for Crohn's colitis [35], and all agents in the class carry a labelled warning against the possibility of an increase in the risk of childhood malignancies.

Evidence from post-marketing registries also suggests that there is no increased risk of solid tumours with TNF inhibitor therapy [33, 36, 37]. Non-melanoma skin cancers, on the other hand, are more common with this treatment; in a recent Veterans Affairs study, non-melanoma skin cancers were increased in patients receiving TNF inhibitors, with a hazard ratio of 1.42 (95% CI 1.24, 1.63) [38]. Registry data also indicate that the risk of melanoma may be increased with TNF inhibitor therapy, although the CIs on this estimate are wide [37].

Two unique safety concerns with TNF inhibitors are the risk of congestive heart failure (CHF) and demyelinating disease. A pilot study of infliximab for the treatment of CHF identified an increased risk of death in patients treated with the highest dose [39]; this class of agents is generally considered contra-indicated in patients with class III or IV CHF. Likewise, the risk of worsening demyelinating disease suggests that these agents should be contra-indicated in patients with a history of multiple sclerosis or optic neuritis [40]. Severe infusion reactions can occur with infliximab, although the package insert reports that these occur in $<$1% of patients; this risk can be reduced by co-therapy with MTX or LEF. Injection site reactions or burning are common with the self-injectables but are seldom a reason to discontinue therapy; injection site discomfort occurs less often with certolizumab than with the other agents [41]. Finally, cytopenias and hepatic enzyme elevations have been reported with TNF inhibitors, but the incidence is quite rare.

Treatment with anakinra, the recombinant human IL-1 receptor antagonist has been shown in a meta-analysis to cause a modest increase in the risk of serious infections [42]. Opportunistic infections were not reported in anakinra clinical trials nor was the risk of malignancy increased, although there are few post-marketing data to confirm these findings [42].

Tocilizumab, the antibody to the IL-6 receptor, is the most recent cytokine-directed therapy to gain approval in the USA. In a meta-analysis of clinical trials, tocilizumab was not associated with a higher risk of serious infections than was placebo, but a Japanese publication has suggested that the drug may be associated with an increased risk of serious respiratory infection [16, 43]. Clinical trials with tocilizumab did not report a higher number of opportunistic infections, although TB screening prior to therapy is recommended based on protocols in place during the trials. There are, as yet, no published post-marketing data available to inform the risk of infection or malignancy with tocilizumab. One unique concern identified with the use of tocilizumab is the risk of gastrointestinal perforation. During clinical trials, 26 individuals developed perforations, 3 of whom died [44]. Most perforations occurred in patients with a history of diverticulitis, and tocilizumab should be avoided in these individuals. Minor elevations in transaminases occur commonly in patients treated with tocilizumab, and these laboratory values should be monitored closely, especially in patients receiving concurrent MTX, although it is unclear which drug needs to be modified in the event of an abnormal test. Finally, lipid elevations can be seen with tocilizumab treatment, and lipid profiles should be measured after treatment is initiated. Because of the increased risk of cardiovascular disease associated with RA, it would be appropriate to initiate statin therapy when lipid levels become elevated.

Abatacept, the T-cell costimulatory modulator, carries a labelled warning about the risk of pulmonary infections in patients with comorbid chronic obstructive pulmonary disease, based on a randomized, controlled clinical trial showing an increased risk of infection in this population [45]. Meta-analyses of multiple clinical trials, however, have not found an increased risk of serious infection in patients treated with abatacept [16, 42]. Combining abatacept with other biologic therapies is contra-indicated because of much greater risk of serious infection [45]; indeed, combinations of any biologics should be avoided in the absence of additional data to guide this approach. Abatacept, unlike TNF inhibitors, has not been associated with an increased risk of opportunistic infection. Indeed, abatacept did not exacerbate infection in a mouse model of chronic TB [46]. Data from clinical trials have not suggested that abatacept is associated with an increased risk of malignancy [47].

The B-cell-depleting agent rituximab has not been associated with a statistically greater incidence of serious infections in clinical trials, and there is no evidence to date that the risk of infection increases with long-term treatment despite concerns about decreasing Ig levels sometimes seen with multiple courses of therapy [42, 48]. Opportunistic infections have not generally been reported with increased frequency during rituximab therapy with the exception of progressive multifocal leucoencephalopathy, a progressive CNS infection caused by the ubiquitous John Cunningham virus [49]. This event is quite rare, with only a few cases reported to date in RA patients treated with rituximab. Unfortunately, screening is impractical because of widespread population exposure to the virus, and there have been no factors identified that predict greater risk for infection.

As with tocilizumab, there are no post-marketing data to provide guidance on the risk of infection or malignancy with either abatacept or rituximab. Data from one registry has suggested that low pre-treatment levels of serum IgG may be associated with a higher risk of infection during rituximab treatment, but this has not been confirmed in other cohorts, and the value of following Ig levels, either before or during therapy, remains unclear [50]. Clinicians should be careful not to assume that rituximab has a lower risk of malignancy simply because it is used in the treatment of lymphoma and other haematological malignancies.

Finally, it should be noted that safety issues with both non-biologic and biologic DMARDs should always be considered in light of their benefits. Evidence for both MTX and TNF inhibitors suggests that cardiovascular morbidity may be reduced with the use of these agents [51–53]. Data from the BSRBR does not suggest that TNF inhibitors are associated with increased mortality when compared with non-biologic DMARDs [54]. Indeed, given the

influence of cardiovascular complications on mortality in RA, it seems likely that these agents may well reduce mortality in this disease, and there is data to support this [55]. While a full discussion of the impact of DMARDs on cardiovascular disease and mortality in RA is beyond the scope of this article, such outcomes are an important part of the context for the use of DMARDs in this disease, and this is an area that will need to be watched closely.

Conclusions

Overall, the safety of biologic and non-biologic DMARDs is quite reasonable, particularly in light of the efficacy of these agents. Careful monitoring by physicians familiar with the agents used is warranted, along with screening where indicated. Whereas some risk factors for toxicity are clear (chronic or recurrent infections), others are more controversial (chronic obstructive pulmonary disease as a risk for pulmonary infection with abatacept), so that clinical judgement may be necessary, along with consideration of the risks of no treatment. Clinical trials provide helpful data on individual risk signals, but registry data have provided, and continue to provide, the most helpful data on the true risk of therapy in clinical practice.

Rheumatology key messages

- Registries following large cohorts of real-world RA patients provide estimates of risk for several agents.
- An important concern with TNF inhibitor therapy in RA is the risk of opportunistic infections.
- In light of the efficacy of DMARDs, their overall safety profile in RA is quite reasonable.

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