REPORT

Serious infections with antirheumatic therapy: are biologicals worse?

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This paper reviews the current evidence for the role of antirheumatic therapy in the development of serious infections in patients with rheumatoid arthritis (RA). Prednisone is clearly associated with increased infectious risk, but no definitive data link methotrexate to infection. Emerging data suggest that biological agents also pose increase infectious risk, particularly when used in combination with corticosteroids or methotrexate. Further research is needed in this important aspect of RA treatment. In the meantime, the author recommends that physicians should remain vigilant for serious infections in their patients with RA and use appropriate vaccines and screening procedures to mitigate their risk.

Rheumatoid arthritis (RA) is an inflammatory state characterised by immune cell dysfunction and dysregulation that potentially predisposes patients to infection. Case series and anecdotal reports from the past several decades support this idea and suggest that patients with RA have more bone/joint, lung, and soft tissue infections.^{1–3} In addition, mortality due to infectious diseases is higher among RA patients compared with the general population.^{4–5} It is unclear, however, what portion of this increased infectious morbidity and mortality is due to RA itself, and what portion represents sequelae of immunosuppressive therapy directed at RA.

Relatively few controlled studies have described the magnitude of increased infection among RA patients, and they are primarily from the pre-biological therapy era. In 1994, Wolfe *et al* found death rates due to pneumonia to be five times higher in RA than in the general population.⁵ In 2002, Doran *et al* retrospectively observed a Mayo clinic cohort of RA patients with virtually no exposure to biological therapy. They selected 609 RA patients and appropriately matched non-RA controls, and found rates of documented infection (defined as positive culture or radiographic evidence) and serious infection (requiring hospitalisation) to be nearly twofold higher in RA patients, even after adjusting for smoking, diabetes, chronic lung disease, and other risk factors.⁶ Consistent with historical reports, they found that most of the increase in infections was attributable to pneumonia (relative risk (RR) 1.7, 95% confidence interval (CI) 1.5 to 1.9) and skin infections (RR 3.3, 95% CI 2.7 to 4.1). Although bone and joint infections occurred less often, they occurred 10–15 times more frequently in patients with RA. RA severity and extra-articular disease, and increasing age were independently associated with infection. Perhaps most importantly, however, they found that corticosteroid therapy was independently associated with serious infections.⁷

THERAPEUTIC AGENTS AND THE RISK OF INFECTION IN PATIENTS WITH RA

Corticosteroids

The infectious risks of corticosteroids are well known, but generally not well quantified in RA and other populations.

For example, the risk of corticosteroids and tuberculosis is considered mantra, but is largely a historic notion based on anecdotal reports from the mid to late twentieth century.⁸ The tuberculosis targeted screening and treatment statement issued by the US Centers for Disease Control and Prevention in 2000 states that prednisone treatment at doses of 15 mg/day for more than one month represents a risk for tuberculosis.⁹ However, a review of the literature from the time of that statement would yield virtually no observational or prospective data to support such an assertion. The idea was supported by two studies that showed suppression of tuberculin skin test reactivity at such prednisone doses,⁹ while in contrast, a variety of small retrospective and prospective studies up to that date failed to demonstrate any increased tuberculosis risk with corticosteroids.⁸ Recently, however, a large, controlled epidemiological study from the UK's population database definitively demonstrated an increase in tuberculosis risk among corticosteroid users, even at doses lower than 15 mg/day. The study reviewed all cases of tuberculosis in the UK occurring during 1990–2001, and matched cases with controls for age, sex, geographic residence, and time clinically followed. After adjustment for tuberculous risk factors and antirheumatic therapy, patients with tuberculosis were nearly five times more likely to have been using corticosteroids at the time of their diagnosis.¹⁰ This study provides the best data to date suggesting that tuberculosis and corticosteroids go “hand in hand”, and that even “low dose” corticosteroids pose a tuberculosis risk to the general population.

In RA populations, few controlled studies have examined the relation of low dose corticosteroids and serious infection (generally defined as infection requiring hospitalisation and/or parenteral antibiotics). In 2006, Wolfe *et al* reviewed the national databank for rheumatic diseases in the USA. They followed over 16 000 patients for 3.5 years and observed the risk of hospitalised pneumonia in RA patients to be 1.7 times higher in those receiving corticosteroid therapy. The investigators also found a dose response with risk even at doses ≤ 5 mg/day (hazard ratio (HR) 1.4, 95% CI 1.1 to 1.6), and even higher risk at 10–15 mg/day (HR 2.3 95%CI 1.6 to 3.2).¹¹ In addition, prednisone use in this cohort was common (38%). Interestingly, despite these infectious risks and the advent of newer therapies, corticosteroid use in RA remains quite prevalent. Recent estimates range from 47% in the USA before the widespread usage of biological therapy,⁷ to 49% in a recent survey of RA patients in the UK.¹²

Methotrexate

Like prednisone, physicians frequently use methotrexate in RA patients. A recent survey found that 54% of patients were taking this drug either alone or in combination with other antirheumatic therapies.¹¹ Methotrexate interferes with purine/pyrimidine synthesis. It has been shown to decrease antigen stimulated T cell proliferation, neutrophil chemotaxis, and superoxide generation, as well as to decrease

the release of tumour necrosis factor α (TNF α) and interferon γ from T cells in patients with RA. Not surprisingly perhaps, there are numerous case reports of infection in RA patients taking methotrexate,^{13–15} and several small case series that suggest the possibility of increased infectious risk. Antonelli *et al* retrospectively described 187 patients with no control group, and thought they measured an increase in herpes zoster as compared with the general population.¹⁶ Van der Veen *et al* followed 228 RA patients and controls for one year and found slight increases in patient self-reported skin infections and antibiotics usage.¹⁷

However, unlike prednisone, no large observational or prospective studies have definitively linked methotrexate to an increased risk of infection in RA patients. In fact, the two recent large observational studies that have examined this question failed to find any independent risk for serious infection associated with methotrexate.^{7–11}

Biological agents

In addition to methotrexate and prednisone, newly developed drugs targeting specific components of the RA inflammatory cascade are now in frequent use. Drugs inhibiting TNF α (infliximab, adalimumab, and etanercept) and IL-1 (anakinra) have been in widespread use for several years, and the CD4 cell costimulation modulator (abatacept) and CD20+ B-cell antibody (rituximab) were only recently approved for RA.

Anti-TNF α agents

To date, reports of tuberculosis and serious infections have primarily occurred with the widely used anti-TNF α compounds.¹⁸ TNF α is expressed by activated macrophages, and T and B lymphocytes. It is integral to granuloma formation and maintenance, and activates macrophages to ingest and kill mycobacteria and other pathogens.¹⁹ Mice deficient in TNF α /p55 signalling pathway are more susceptible to *Mycobacterium tuberculosis*, *Histoplasma capsulatum*, *Listeria monocytogenes*, *Klebsiella*, *Streptococcus pneumoniae*, and numerous other pathogens.^{20–24} Recent human case reports¹⁸ of these and other infections in patients receiving anti-TNF α therapy raise the question: do biological therapies cause more serious infections?

This question is complicated and difficult to answer for a variety of reasons:

- Clinical trials are not typically powered to detect adverse events, so that more infrequent adverse events are not discovered until drugs are in widespread use.
- Use of biological drugs is often associated with RA severity, confounding our ability to separate infectious risk due to RA severity from that potentially due to biological therapy.
- There is a high rate of comorbidities in many of these RA patients that confer infectious risk.
- Perhaps most importantly, biological drugs are frequently employed concomitantly with prednisone, methotrexate, or other disease modifying antirheumatic drugs (DMARDs).¹²

Clinical trial data

Randomised controlled trial (RCT) data suggest early answers to our question. In the ASPIRE (Active controlled Study of Patients receiving Infliximab for treatment of Rheumatoid arthritis of Early onset) trial, 1049 patients randomised into three groups were followed for 54 weeks. Background corticosteroid use was 38% in all groups. Those receiving infliximab in addition to methotrexate were over twice as likely ($p < 0.05$) to experience serious infections than those receiving methotrexate alone. Much of this difference was attributable to pneumonia.²⁵ The PREMIER trial ($n = 799$) with adalimumab similarly found an increased

risk of serious infection in those treated with the combination of adalimumab and methotrexate as compared with either drug alone ($p < 0.05$ combination compared with adalimumab alone, $p =$ not significant for comparison with methotrexate alone).²⁶ Similar to the ASPIRE trial, background corticosteroid usage was fairly high (36% in all study groups). Taken together, these studies suggest an increase in infectious risk when these biologicals are employed in combination with methotrexate. Unfortunately, neither study reported whether corticosteroid use modified the infectious risk of biological or methotrexate therapy.

Published RCT experience with etanercept, on the other hand, does not support a similar increased infectious risk. Klareskog *et al* followed 686 patients with high background corticosteroid use of 57–64% for 52 weeks. There was no difference in the incidence of serious infections between those receiving methotrexate and etanercept in combination versus either drug alone (4% for all groups).²⁷ Similarly, Bathon *et al* followed 632 patients for 12 months with background steroid usage of 39–42%. There was no difference in the rates of serious infections in those receiving methotrexate versus those receiving etanercept (<3% both groups).²⁸

Observational data

In an effort to improve surveillance and understanding of infectious and other adverse events associated with biological therapies, a number of patient registries have been established. These observational databases offer a chance to improve upon the inherent shortcomings of RCT data in surveillance for adverse events. Recently, Listing *et al* published preliminary findings from the German Biologic Registry.³¹ Patients were enrolled between May 2001 and September 2003, and then followed until September 2004. They found physician documented infections were more common in RA patients receiving either infliximab (RR 3.0, 95% CI 1.8 to 5.1) or etanercept (RR 2.3, 95% CI 1.4 to 3.9). This increased risk was independent of RA severity or duration, rheumatoid factor seropositivity, concomitant steroid use, diabetes, lung disease, or a patient's likelihood of being treated with biologicals ("propensity score").

Anti-IL1 therapy

Unlike the anti-TNF α trial data, RCT data with anakinra has examined the effect of background corticosteroid usage on infectious sequelae during biological therapy. Fleischmann *et al* recently reported the results of 1346 patients enrolled in a six month RCT followed by 2.5 years open-label extension study.²⁹ The investigators found that patients taking anakinra had higher rates of serious infections, particularly when used in combination with corticosteroids. Patients taking both anakinra and steroids had over a threefold increase in serious infections as compared with controls, who were not taking anakinra (5.4 v 1.65 per 100 patient years, respectively). Patients taking anakinra without steroids still had elevated risk but markedly less so when compared with controls during the first six months of the study (2.9 v 1.65 serious infections per 100 patient years, respectively). Genovese *et al* evaluated the safety and efficacy of anakinra when combined with anti-TNF α therapy.³⁰ The investigators followed 244 patients for six months, of whom 49% were receiving background corticosteroid therapy and 100% were taking methotrexate. Serious infections were significantly increased in patients given anakinra in combination with etanercept when compared to etanercept alone (5.5% v 0%, respectively, $p < 0.05$). Because all patients were taking methotrexate, and because the effect of steroids on infectious outcomes was not reported, it is unclear whether the combination of anakinra and etanercept alone was responsible for the observed

increased infectious risk, or whether synergy between the various immune suppressants contributed.

CONCLUSIONS AND RECOMMENDATIONS

Patients with RA are at increased risk for infection, particularly of lung, bone/joint, and skin. This risk is due to RA, and independent of any disease modifying therapy. This risk is further elevated with the use of prednisone, even when adjusting for RA severity and comorbid disease. To date, there is no clear evidence that methotrexate raises infectious risk when used alone. Importantly biological drugs appear to pose additional risk, particularly when dosed in combination with other RA therapies. Infliximab and adalimumab increase the risk of serious infections when dosed in combination with methotrexate. Anakinra poses increased risk, especially when dosed in combination with corticosteroids. Limited observational registry data suggest there is increased risk of serious infection with both etanercept and infliximab, and that these risks might be similar. Clearly, more research is needed to further assess the risks of concomitant therapy with biologics and DMARDs/steroids.

In the meantime, prevention of infections is paramount:

- Clinicians should maintain vigilance for both routine and opportunistic pathogens in all patients with RA, particularly those treated with corticosteroids and/or biologicals.
- Efforts to prevent serious infection should include routine use of pneumococcal polysaccharide vaccine every three to five years. Physicians should note that decreased protective antibody responses occur in RA patients taking methotrexate, but not biological drugs, and patients should be vaccinated when off methotrexate if possible.³²
- Influenza vaccine should be administered yearly, and although antibody response is diminished in RA patients, it is not affected by prednisone, methotrexate, infliximab, or etanercept.³³
- Prevention of tuberculosis with screening and treatment has been successful in diminishing tuberculosis associated with infliximab³⁴ and adalimumab,³⁵ and such efforts should continue prior to any anti-TNF α therapy in accordance with local guidance.³⁶⁻³⁷

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