INCREASED INFECTIOUS RISK IN RHEUMATOID ARTHRITIS

Patients with rheumatoid arthritis (RA) have long been recognized to suffer a greater burden of serious infection. The precise immune derangements of RA that predispose to infection are not clearly known. Patients with RA seem to have reduced capacity to generate new T lymphocytes, and their T-lymphocyte repertoire becomes severely contracted over time,\(^1\) a phenomenon perhaps akin to the immunosenescence observed in a normal aging host.\(^2\) However, it is likely that a variety of RA-associated host factors predispose patients toward infection, including the physical derangements (eg, destruction of articular surfaces, airway inflammation) that might also impair local immunity or provide a respite for circulating pathogens. In the prebiologic era, Doran and colleagues\(^3\) reported this heightened risk within an RA cohort study in Minnesota’s Mayo Clinic patient population (Table 1). Compared with matched non-RA controls, the investigators documented serious infections to occur nearly twice as frequently in patients with RA, at a rate of 9/100 patients per year.
This increased risk remained even after controlling for the effects of important comorbidities and other infectious risks, and similar to historical reports, these investigators documented pulmonary and skin/soft tissue infections to be the most common sites of RA-related infectious morbidity.

**PREDNISONE**

Although conflicting data (to be discussed later) foster debate regarding the infectious risks of biologic therapies, there is little debate regarding the ability of prednisone to cause infectious harm. Although a recent meta-analysis of glucocorticoid trials in rheumatic disease found no increased risk of serious infection associated with steroids, observational studies consistently report such an association. The prebiologic era observational study of Doran and colleagues documented a significant 1.5-fold to 2-fold increase in risk with corticosteroid therapy, with risk noted even at a low dose (eg, <15 mg/d) of prednisone. In 2006, Wolfe and colleagues produced similar findings with increased risks (hazard ratio 1.4, 95% confidence interval [CI] 1.1–1.6) noted even at doses of prednisone less than 5 mg/d. More recent registry data further attest to the association of prednisone with serious infection. In the United States, a national collaboration of observational databases (the Safety Assessment in Biologic Therapy [SABER]) compared the risk of serious bacterial infection in patients starting biologics with methotrexate-treated patients who start an additional nonbiologic disease-modifying antirheumatic drug (DMARD). These researchers also documented dose-dependent increases in risk, with relative risk (RR) up to 3-fold higher in patients using doses greater than 10 mg/d (Table 2). The Consortium of Rheumatology Researchers of North America (CORRONA) registry identified 1.5-fold higher risks with prednisone use for opportunistic infections, and other US studies support the idea that risk is increased even at low daily doses of 5 mg or less (1.3-fold–1.5-fold), escalating with increasing doses to 5-fold higher risk at doses of 20 mg or greater. Within Europe, the results have been no different. The British Society for Rheumatology Biologic Register (BSRBR), a UK cohort of patients with inflammatory arthritis, observed corticosteroids to double the risk of serious infection. In Germany’s biologic registry for patients with RA (RABBIT), the independent increase in relative serious infection risk observed with corticosteroids varied between 2-fold and nearly 5-fold at dosages less than 15 mg and 15 mg or greater daily, respectively.

### Table 1

The prebiologic era: frequency of infections among patients with RA and healthy controls from a Minnesota cohort

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>Incidence per 100 Patient-Years RA</th>
<th>Incidence per 100 Patient-Years Non-RA</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>4.0</td>
<td>2.4</td>
<td>1.7 (1.5–1.9)</td>
</tr>
<tr>
<td>Skin</td>
<td>3.0</td>
<td>0.9</td>
<td>3.3 (2.7–4.1)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.78</td>
<td>0.51</td>
<td>1.5 (1.1–2.1)</td>
</tr>
<tr>
<td>Septic joint</td>
<td>0.40</td>
<td>0.02</td>
<td>14.9 (6.1–73.7)</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>0.22</td>
<td>0.08</td>
<td>2.8 (1.4–6.2)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>0.17</td>
<td>0.01</td>
<td>10.6 (3.4–126.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposures</th>
<th>Events, Number</th>
<th>Person-Years, Number</th>
<th>Rate, per 100 Person-Years</th>
<th>Hazard Ratio (95% CI) for Propensity Score-Matched Cohorts</th>
<th>Adjusted Hazard Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA Nonbiologic regimens</td>
<td>326</td>
<td>4192</td>
<td>7.78</td>
<td>Ref.¹</td>
<td>Ref.¹</td>
</tr>
<tr>
<td>Tumor necrosis factor α antagonists</td>
<td>497</td>
<td>6089</td>
<td>8.16</td>
<td>1.05 (0.91–1.21)</td>
<td>1.05 (0.91–1.21)</td>
</tr>
<tr>
<td>Baseline glucocorticoid use, prednisone</td>
<td>None</td>
<td></td>
<td></td>
<td>Ref.¹</td>
<td></td>
</tr>
<tr>
<td>equivalents</td>
<td>&gt;0–&lt;5 mg/d</td>
<td></td>
<td>1.32 (1.10–1.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5–10 mg/d</td>
<td></td>
<td>1.78 (1.47–2.15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;10 mg/d</td>
<td></td>
<td>2.95 (2.41–3.61)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Beyond bacterial infections, corticosteroids increase the risk of tuberculosis (TB), nontuberculous mycobacterial disease (NTM), and other opportunistic infections.\textsuperscript{11–13} This risk has been particularly well documented with herpes zoster, in which the risk is increased 1.5 to 2 times in patients with RA who use corticosteroids.\textsuperscript{14–16} Pulmonary NTM disease, of which patients with RA are at higher risk, has been linked to systemic prednisone and even inhaled corticosteroid use.\textsuperscript{12–14} Disease caused by \textit{Pneumocystis jiroveci} occurs in the setting of high-dose prednisone use, although the threshold of dose and duration of prednisone use for causing \textit{Pneumocystis} has not been well described.\textsuperscript{17}

Collectively, these data suggest that systemic corticosteroid use is an important and potentially modifiable risk factor for serious infection. Further, the serious infection risks observed within these studies are similar and sometimes exceed those observed with biologic therapy. Despite these infectious risks and the advent of newer biologic therapies, corticosteroid use in RA remains common.\textsuperscript{18} Patients who use both biologic therapy and prednisone concurrently have an even higher risk of serious infection than patients who use only biologic therapy (\textit{Fig. 1}).\textsuperscript{10} Clearly, one of the potential benefits of DMARD therapy, either synthetic or biologic, is the opportunity to mitigate risks associated with corticosteroids by allowing for the reduction or elimination of prednisone.

\textbf{Biologic Therapies}

In little more than the last decade, biologic therapies targeting tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)), T and B lymphocytes, and various interleukins (IL) (including IL-6 and IL-1) have been developed and approved for use in RA and selected other rheumatic diseases. Additional drugs with novel targets are either approved or in trials for RA and other inflammatory conditions, including those that inhibit IL-12 to IL-23 and IL-17a.

\textit{Fig. 1.} Estimated incidences of serious infections in 100 patients per year by treatment and risk profile. Additional risk factors are 1 or 2 of the following: age greater than 60 years, chronic lung disease, chronic renal disease, or high number of treatment failures; 3 risk factors: 2 of these risk factors plus previous serious infections. TNFi, tumor necrosis factor inhibitor. (\textit{From} Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis 2011; 70:1914–20.)
Novel small molecules (technically not biologics) that target the janus activating kinases (JAK) and splenic tyrosine kinases are also in development, and at least one JAK inhibitor (tofacitinib) is under consideration by the US Food and Drug Administration (FDA) for approval.

**Infection risk**

Data from randomized controlled trials and long-term extension studies of biologic therapies have generally (but not always) suggested some increase in infectious risks associated with these compounds. For anti-TNF therapies, where abundant registry and administrative health care-based observational studies have been conducted, higher absolute infection rates among anti-TNF users have generally been observed, particularly in the 6 to 12 months after drug start. These rates observed in such real world settings have typically been higher than those observed during clinical trials and long-term extension studies. However, the assessment of infection risk with anti-TNF therapies in population-based studies is complex, and only in the last 1 to 2 years perhaps, a clearer picture has emerged. For the more recently approved biologics in RA with different mechanisms of action (ie, abatacept, tocilizumab, rituximab), rates of serious infection observed in clinical trials have largely been similar to those observed in anti-TNF trials. However, for these newer compounds, real world infection rates and risk estimates are largely missing, because such observational registry or database studies with these therapies have yet to be conducted.

**Anti-TNF therapy**

Five TNF blockers currently fill the marketplace: etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), and certolizumab (Cimzia). As a group, these drugs inhibit TNF-α, a proinflammatory cytokine expressed by activated macrophages, T lymphocytes, and other immune cells, known to play a crucial role in the host response against a variety of infections.\(^\text{14}\) TNF directly activates macrophages to phagocytose and kill mycobacteria and a variety of other pathogens, and the failure to control TB during TNF blockade seems intrinsically linked to an inability to control intracellular TB growth in macrophages residing within granulomas,\(^\text{19}\) rather than inhibiting the development granulomas per se.\(^\text{20}\) Murine studies suggest the importance of TNF in protection against other intracellular organisms such as *Listeria* and fungi, as well as against extracellular bacterial organisms like *Klebsiella pneumoniae* and *Streptococcus pneumoniae*.\(^\text{21–25}\)

**Risk of infection with anti-TNF therapy**

The overall risk of serious infections attributable to anti-TNF therapy is not precisely known, and our understanding of this issue depends largely on the study settings and methodology used to assess these risks. Further, much of the variability in an individual’s infection risk is not attributable to drug therapy, but rather to patient factors (eg, age, chronic lung disease, and other comorbidities) that are frequently not modifiable.\(^\text{8,10}\) Although conflicting evidence from a variety of study designs exists, it is our opinion that anti-TNF therapy independently increases the risk of serious infection, but that this risk is mitigated by a variety of measurable (and unmeasurable) factors after drug start. As suggested earlier, TNF blockers can, and should, serve as prednisone-sparing therapies, allowing for a reduction in prednisone-associated infection risk. Other physician-patient decisions such as TB screening, vaccination, counseling with regard to infection prevention, and other factors likely also serve to mitigate infectious risk associated with starting anti-TNF therapy. It is likely that patients starting anti-TNF therapies are treated differently with regard to these and other factors compared with patients starting nonbiologic DMARDs. This confounding by indication
can be difficult to measure and control for in “real world” observational studies that seek to measure differences in risk between anti-TNF and nonbiologic DMARD users. Our understanding of infection risk derives from individual randomized controlled trials and their meta-analyses, long-term open-label extension studies, and the observational (registry and database) studies, as discussed earlier. Meta-analyses of TNF-blocker trials generally observed RRs of serious infection to be slightly higher in those patients treated with anti-TNF therapy, but not always so, and frequently the observed effect has been mild and not statistically significant. Bongartz and colleagues\(^\text{26}\) analyzed monoclonal antibody trials (infliximab and adalimumab only) in RA and observed a 2-fold increase in serious infection risk. Leombruno and colleagues\(^\text{27}\) evaluated serious infection risk within RA trials of etanercept, infliximab, and adalimumab and found no statistically increased risk (RR 1.08 [0.81–1.43]) in those treated with anti-TNF therapy versus placebo overall, but did find a significant 2-fold increase in risk for those studies using higher-dose infliximab or adalimumab. More recently, Singh and colleagues\(^\text{28}\) preformed a Cochrane review of anti-TNF therapies across disease indications and found infliximab (odds ratio [OR] 1.45 [0.99–2.1]) and certolizumab (OR 3.5 [1.6–7.8]) to have the highest RR of serious infection compared with placebo, whereas no other TNF blockers were shown to have significant increased risk. There are great difficulties in understanding the infectious profiles relying on data from randomized controlled trials (eg, statistical power is low for individual trials, careful selection of patients), and even greater difficulties in comparing drugs across trials (eg, differences in inclusion criteria, populations, disease indications, others), such that it is unclear from such meta-analytical studies if drugs like infliximab or certolizumab carry any greater risk than other TNF blockers.

Lastly, it is worth noting that trials involving patients with ages and conditions associated with lower baseline infectious risk, such as psoriasis, have observed lower overall rates and relative risks of serious infection in patients using these therapies.\(^\text{29–31}\)

Several large observational studies and registries have also assessed the risk of infection with these compounds. Although these studies have heterogeneity in methods and cannot fully overcome issues of confounding (eg, confounding by indication), these studies have reported similar estimates of serious infection in patients using these therapies. The incidence of serious infection for patients with RA using TNF blockers generally hovers between 3 and 8/100 patient-years (Table 3), and both absolute and relative rates seem dependent on when they are measured after drug start.\(^\text{5,32,33}\) The BSRBR found a 4-fold increase in risk for serious infection in the first 90 days after anti-TNF start among patients with RA, and Curtis and colleagues\(^\text{8}\) reported a similar increased risk in the first 6 months after anti-TNF start.\(^\text{34}\) Both studies produced smaller RR estimates when longer periods of exposure were assessed. This finding is likely because of a survivor effect, but also potentially secondary to benefits of improved disease management, and changes in concomitant therapies, which occur after anti-TNF therapy start.\(^\text{10}\)

Grijalva and colleagues\(^\text{35}\) recently published results from the SABER collaboration, a population-based study that compared only new users in both groups: anti-TNF or nonbiologic DMARDs. Within RA, this comparison was restricted to those patients failing methotrexate who subsequently started either an anti-TNF drug (for the first time) or a new nonbiologic DMARD. Although the influence of baseline corticosteroid use, comorbidities, and disease severity was controlled for in modeling, changes taking place after drug start (eg, changes in prednisone, concomitant nonbiologic DMARD use, improved disease control) could not be assessed. Although investigators reported high rates of serious infection (8/100 patient-years for RA), no increased risk
was associated with anti-TNF therapy start (see Table 2) and contrary to the previous observational studies discussed earlier, no short-term increased risk was noted in the first 3 to 6 months after drug start. Within their RA cohort, these investigators found that infliximab starters were 20% to 25% more likely to suffer serious infection than those who started with either etanercept or adalimumab. However, patients starting infliximab were more likely to be on methotrexate after the index date than those starting etanercept or adalimumab, perhaps contributing to this increase in risk. Other population-based studies have failed to find a similar increase in RR for bacterial infections with infliximab compared with the other TNF blockers. The study reiterated the importance of patient factors to overall infection risk. For example, patients treated with anti-TNF with a history of chronic obstructive pulmonary disease (COPD) had rates of nearly 17 versus 7 per 100 patient-years for those without COPD.

Collectively, the observational studies conducted to date suggest that the overall or net infectious risk of biologic therapy is not straightforward to understand or calculate, and that one must account for time-varying risk factors during such study. Strangfeld and colleagues examined this issue using the RABBIT registry and were able to control for several factors that either increase or decrease the risk of infection after drug start. Their data suggest that anti-TNF therapy start improves disease control and decreases prednisone use, both lowering infectious risk, but that even when controlling for these changes, the start of anti-TNF therapy significantly increases the risk of serious infections 1.8-fold. This study arguably represents our most

<table>
<thead>
<tr>
<th>Country, Year</th>
<th>Crude Incidence per 100 Patient-Years Anti-TNF Treated</th>
<th>Crude Incidence per 100 Patient-Years Nonbiologic Comparator</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany, 2005</td>
<td>6.4, ETN 6.2, INF</td>
<td>2.3</td>
<td>2.2 (0.9–5.4) ETN 2.1 (0.8–5.5) INF</td>
</tr>
<tr>
<td>United Kingdom, 2007</td>
<td>5.5</td>
<td>3.9</td>
<td>1.3 (0.9–1.8) 4.6 (1.8–11.9)</td>
</tr>
<tr>
<td>United States, 2007</td>
<td>2.9d</td>
<td>1.4d</td>
<td>4.2 (2.0–8.8)d 1.9 (1.3–2.8)</td>
</tr>
<tr>
<td>Sweden, 2007</td>
<td>4.7</td>
<td>NR</td>
<td>1.4 (1.2–1.7)</td>
</tr>
<tr>
<td>United States, 2007</td>
<td>4.9</td>
<td>3.8</td>
<td>1.3 (0.8–2.1)</td>
</tr>
<tr>
<td>United States, 2011</td>
<td>8.2</td>
<td>7.8</td>
<td>1.05 (0.9–1.2)</td>
</tr>
<tr>
<td>Germany, 2011</td>
<td>4.8</td>
<td>2.3</td>
<td>1.8 (1.2–2.7)</td>
</tr>
<tr>
<td>Japan, 2011</td>
<td>6.4</td>
<td>2.6</td>
<td>2.4 (1.1–5.05)</td>
</tr>
</tbody>
</table>

Abbreviations: ETN, etanercept; INF, infliximab; NR, not reported.

- Relative rate using nonbiologic users as the referent.
- When restricted to the first 90 days of therapy, and adjusted for age, sex, disease duration, and severity, extra-articular RA, baseline steroid use, diabetes, chronic obstructive pulmonary disease, pulmonary disease, and smoking history.
- Adjusted relative rate when not restricted to the first 90 days of therapy.
- Analysis restricted to the first 6 months after initiation of anti-TNF therapy.
- Rate calculated at 1 year after starting treatment and adjusted for RA severity and comorbidities associated with infections.
- Adjustment for time-varying risk factors, treatment adaptations, and dropout.
- Rate up to 1 year after drug start.
complete understanding of the dynamic risk profile presented by these therapies. We know less regarding serious infectious risks of the 2 newer anti-TNF therapies certolizumab and golimumab, because large population-based studies of these compounds are lacking.

**Opportunistic infections with anti-TNF therapy**

Several intracellular and other opportunistic pathogens have been reported in the setting of anti-TNF therapy (Tables 4 and 5). These pathogens include severe and sometimes lethal infections with *Histoplasma*, *Coccidioides*, *Listeria*, *Salmonella*, *Aspergillus*, *Nocardia*, and nontuberculous mycobacteria. Of these infections, TB is most clearly associated with TNF blockade, and a clear distinction in risk can be made between the fusion receptor construct etanercept, and that of the monoclonal antibodies infliximab and adalimumab. Although TB risk has been documented to be clearly increased with all 3 drugs, it is 3-fold to 4-fold more common in adalimumab-treated and infliximab-treated patients relative to etanercept. Several animal and in vitro studies support the biological plausibility of these observations. Potential explanations range from differential granuloma penetration to differential downregulation of antigen-stimulated interferon-γ to differential affects on antimicrobial-producing CD8 effector cells. Cases of TB have been reported from clinical trial experience of certolizumab and golimumab, but few population data exist by which to compare their RR with the other TNF blockers.

The incidence of TB and RR of anti-TNF therapy directly reflects the a priori risk of the exposed population. Early population-based studies from regions of low TB prevalence generally reported rates of TB 5 to 20 times higher than background populations, including early studies from the United States (incidence of 52/100,000) and Sweden (incidence of 118/100,000) largely before the widespread introduction of mandatory screening for TB before biologic initiation. Spanish investigators reported estimated rates of 1900/100,000, approximately 10-fold to 20-fold higher among RA anti-TNF users compared with biologic-naive patients with RA. These rates have since decreased dramatically with institution of widespread screening for latent TB infection before anti-TNF use. More recently, formal observational studies conducted within France, the United Kingdom, and the United States have documented rates of between 56 and 117/100,000 (see Table 5). Work in the United States suggests that disease caused by nontuberculous mycobacteria occurs approximately

<table>
<thead>
<tr>
<th>Country, Year</th>
<th>Outcome Studied</th>
<th>Crude Incidence per 100,000 Patient-Years Anti-TNF Treated</th>
<th>Crude Incidence per 100,000 Patient-Years Nonbiologic Comparator</th>
<th>Adjusted RRb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom,33 2006</td>
<td>OI</td>
<td>192b,c</td>
<td>0b</td>
<td>NR</td>
</tr>
<tr>
<td>France,92 2006</td>
<td>OId</td>
<td>152a</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>United States,93 2010</td>
<td>OI</td>
<td>3000b</td>
<td>1600b</td>
<td>1.7 (0.95–2.9)</td>
</tr>
</tbody>
</table>

 Abbreviations: NR, not reported; UNDEF, undefined.

 a Rate adjusted for age and sex.
 b Cohorts restricted to patients with RA.
 c Rate not published, but was estimated using data provided within the article.
 d OI outcomes did not include TB.
Infections and Biologic Therapy in RA

twice more frequently than TB in the anti-TNF setting, perhaps not surprising given the low background TB prevalence in the country.\(^40,47\) In the context of biologic therapy, pulmonary NTM disease is associated with RA, because these environmental organisms (most commonly \textit{Mycobacterium avium} complex) have a predilection for patients with underlying lung disease.\(^40\) Like TB, extrapulmonary manifestations of NTM disease seem to be more common among patients using anti-TNF therapies.\(^48\)

For other intracellular and opportunistic infections, there remain fewer data by which to estimate risk. Several studies have looked at opportunistic infections, although risk estimates vary widely between studies because study methods and case definitions for opportunistic infections frequently differ (see Table 4). The CORRONA database documented rates of opportunistic infections 20 times higher than the French study, but CORRONA consider all cases of herpes zoster within their outcome where the French study considered only multidermatomal zoster cases.

Table 5
The biologic era: rates and RRs of specific opportunistic infections in patients with RA using anti-TNF therapy from European and North American observational cohort studies

<table>
<thead>
<tr>
<th>Country, Year</th>
<th>Outcome Studied</th>
<th>Crude Incidence per 100,000 Patient-Years Anti-TNF Treated</th>
<th>Crude Incidence per 100,000 Patient-Years Nonbiologic Comparator</th>
<th>Adjusted RR(^b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom, 2010</td>
<td>TB</td>
<td>95(^b)</td>
<td>0(^b)</td>
<td>UNDEF</td>
</tr>
<tr>
<td>France, 2011</td>
<td>TB</td>
<td>117(^a)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>United States, 2011</td>
<td>TB</td>
<td>56(^b)</td>
<td>9(^b)</td>
<td>NR</td>
</tr>
<tr>
<td>United States, 2011</td>
<td>NTM</td>
<td>105(^b)</td>
<td>19(^b)</td>
<td>NR</td>
</tr>
<tr>
<td>France, 2006</td>
<td>Legionella pneumonia</td>
<td>37.5(^c)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>United States, 2009</td>
<td>Zoster</td>
<td>1060</td>
<td>1118</td>
<td>NR</td>
</tr>
<tr>
<td>Germany, 2011</td>
<td>Zoster</td>
<td>980(^b)</td>
<td>560(^b)</td>
<td>1.63</td>
</tr>
<tr>
<td>United Kingdom, 2011</td>
<td>Zoster</td>
<td>1600</td>
<td>800</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; NTM, nontuberculous; TB, tuberculosis; UNDEF, undefined.

\(^a\) Rate adjusted for age and sex.

\(^b\) Cohorts restricted to patients with RA.

\(^c\) Average of estimated rate.

Infections and Biologic Therapy in RA

Abbreviations: NR, not reported; NTM, nontuberculous; TB, tuberculosis; UNDEF, undefined.

\(^a\) Rate adjusted for age and sex.

\(^b\) Cohorts restricted to patients with RA.

\(^c\) Average of estimated rate.
in rates, risk estimates, and study methodologies, the overall picture is that anti-TNF therapy does increase the risk of many infections considered opportunistic, in particular those that involve granulomatous host response. Like for TB, the risk of many other opportunistic infections such as the endemic mycoses (histoplasmosis, coccidioidomycosis, blastomycosis) vary according to geography and baseline risk.

THE OTHER BIOLOGICS: ABATACEPT, RITUXIMAB, TOCILIZUMAB, AND ANAKINRA

Primarily reserved for those patients who have failed or have contraindications for anti-TNF therapy, these newer biologics are important additions to the RA therapeutic armamentarium. rituximab (Rituxin), approved for RA in 2006, is an anti-CD20 B-lymphocyte depletion agent; abatacept (Orencia), a CTLA-4 ligand, blocks CD80/86 interactions on CD4 T lymphocytes and mitigates their activation; and tocilizumab (Actemra) blocks the IL-6 receptor. Given these mechanisms of action, a variety of related infections are possible, and similar infection profiles have emerged with these agents to those with anti-TNF agents, although with some notable exceptions and a caveat that postmarketing experience and observational data are young with these compounds.

Risk of Serious Infections, Including Opportunistic Infections

Clinical trials with rituximab among patients with RA did not suggest a significantly increased risk of serious infection. Long-term extension studies and meta-analyses data suggest that small subgroups of treated patients develop persistent hypogammaglobulinemia and are at increased risk of serious infection. One observational study examined hospitalized infection rates among patients switching biologics, and found that those switching to rituximab had a similar risk to those switching to etanercept, adalimumab, and abatacept (and significantly lower risk than those who switched to infliximab). There are case reports of both TB and NTM disease in patients on rituximab, although these patients have also been on methotrexate and prednisone. Rituximab use in patients with chronic hepatitis B virus (HBV) is contraindicated, and treated patients (primarily reported from the lymphoma setting) have suffered HBV reactivation and death. In addition, rare cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients with RA using rituximab and more rarely anti-TNF therapies. In general, PML is rare outside the setting of human immunodeficiency virus (incidence in RA estimated at 1/1,000,000) and the risk is unknown in those using rituximab or other biologic therapies. At least 14 cases of PML occurring in rituximab-treated patients with inflammatory diseases have been reported to the FDA, although 10 were using other immunosuppressive therapies in addition to rituximab and only 1 patient lacked any other identifiable potential risk factors for PML.

For abatacept, some clinical trials suggested a small increased risk of serious infection, particularly respiratory infections and exacerbations in those with COPD. The risk of serious infections was significantly increased when abatacept was combined with anti-TNF therapy. Subsequent meta-analyses of randomized controlled trial data suggested a nonsignificant trend toward an increase in serious infection compared with placebo, and similar analyses that included open-label extension data documented rates of hospitalized infection of 2.7/100 patient-years for patients using abatacept. For TB and other opportunistic infections, cases have been reported, although the RR of these types of infections is not yet known. The rate of observed TB in the double-blind portion of abatacept RA trials was 60/100,000 patient-years. In animal studies, abatacept does not seem to negatively affect the
immune system of mice that are exposed to TB. In humans, Schiff and colleagues recently conducted a randomized trial to compare the efficacy and safety of abatacept with infliximab. At 12 months of follow-up, patients using abatacept suffered significantly fewer serious infections than infliximab-treated patients (1.9% vs 8.5%), with a rate similar to that seen in the placebo group at 6 months’ follow-up (2.7%). No cases of opportunistic infections were seen in the abatacept-treated group, although 5 such cases were seen in the infliximab group, including 2 cases of TB and 1 case of *Pneumocystis jiroveci* pneumonia.

For tocilizumab, the rates and types of serious infection from randomized controlled and long-term extension trials were generally similar to those from other biologic trials. Serious infection rates were 4.9 per 100 patient-years in patients using 8 mg/kg dosing, whereas rates (3.5/100 patient-years) were observed in those receiving placebo or low-dose tocilizumab. Postmarketing population-based observational data are limited, although a group in Japan recently published from their tocilizumab postmarketing surveillance program, which included 3881 treated patients. Serious infection rates of 9/100 patient-years were observed, and rates of herpes zoster were 6.1/1000 patient-years. In addition, 4 cases of TB were recorded (incidence rate 220/100,000), a rate approximately 10-fold higher than the background Japanese population, but a rate similar to that observed in the postmarketing experience for anti-TNF therapies in Japan.

**ANAKINRA**

This recombinant IL-1 receptor antagonist is used infrequently within RA. It has been shown to significantly increase the risk of serious infection, particularly when combined with prednisone or anti-TNF therapy. Clear warnings exist that concurrent anti-TNF therapy with anakinra should be avoided.

**TOFACITINIB**

Few data have been published regarding the infectious risks of tofacitinib, a novel small molecule that inhibits JAK 1/3 and is technically not a biologic, data from a large international clinical development program in RA were recently presented to the FDA and a decision regarding licensure is pending. In vitro, this drug has been shown to diminish CD4 T-lymphocyte production of INF-γ and IL-17. Infections such as TB, herpes zoster, or others that are dependent on host INF-γ responses could be expected given this mechanism of action, and some cases of opportunistic infections have been reported in abstract form. Only several small phase II studies from the RA program have been published in the peer-reviewed literature. In these small trials, patients receiving 5-mg and 10-mg twice daily doses had serious infection rates, similar to that in placebo groups, although neutropenia did occur more frequently with tofacitinib.

**Prevention of Infection in Patients Using Biologics (Screening and Vaccination)**

It is likely that the serious bacterial infections most common in this setting, such as community-acquired pneumonia and skin/soft tissue infections, are caused by the same types of organisms seen in the general public. Most skin/soft tissue infections are likely caused by *Staphylococcus aureus* and *Streptococcus* sp., although few organism-level incidence data have been published in this setting. It is unclear whether such infections can be prevented, and it is unclear whether colonization with *Staphylococcus aureus* is a risk for subsequent infection in patients who go on to biologic therapy. Many patients with RA are also hospitalized each
year with community-acquired pneumonia, and these infections too are likely caused by the same organisms that cause pneumonia in general populations: *Streptococcus pneumoniae*, *Haemophilus influenza*, *Staphylococcus aureus*, gram-negative bacilli, and influenza are some of the most common causes. For *Streptococcus pneumoniae*, patients are recommended to receive 23-valent pneumococcal vaccine before initiating anti-TNF and other long-term immunosuppressive therapies (primarily for protection against invasive pneumococcal disease). Immunogenicity to this vaccine is poor and diminished by methotrexate as well as some other biologic drugs (eg, rituximab), but is relatively unaffected by anti-TNF therapy. Recently, the FDA has approved the new 13-valent conjugate pneumococcal vaccine (PCV13) for use in adults. This vaccine theoretically provides longer and improved protection against pneumococcal disease. The American College of Immunization Practices recently voted to recommend PCV13 in patients with certain immunocompromising conditions, although their formal and official recommendation with regard to its use (particularly in those formerly vaccinated with pneumovax) is still pending publication.

**Opportunistic and viral infections**

An influenza vaccination should be given yearly and is efficacious when given during biologic therapy (although less efficacious during rituximab treatment). It is unclear whether higher-dose influenza vaccines provide improved protection in such patients. Either usual-dose or higher-dose products are recommended until further data are available. However, the use of live intranasal influenza vaccine is contraindicated in patients using anti-TNF and other biologic therapies.

In many areas of the world, chronic hepatitis B and C are prevalent; the epidemiology of HBV closely mirrors that of TB, with similar regions of endemnicity throughout the globe. Although the anti-TNF compounds seem relatively safe in patients with hepatitis C virus, HBV progression can occur in patients using anti-TNF therapy, and patients should be screened for HBV before using such therapies. Optimal screening algorithms should include evaluation of hepatitis B serum antigen, core antibody, and surface antibody, and it should include pretreatment HBV DNA evaluation in anyone with evidence of previous infection (ie, hepatitis B core antibody). HBV progression and poor outcomes have been reported in patients using rituximab, although primarily from the lymphoproliferative disease setting. Data for the other non-TNF blocking biologics are scarce given their more recent introduction. Only 1 case of HBV progression has been reported in a patient using abatacept, and several patients with HBV have successfully used tocilizumab in the context of antiviral prophylaxis. Although rituximab should be contraindicated in patients with active HBV, the other biologics have been successfully used in the context of concomitant antiviral therapy and close laboratory/clinical monitoring.

The reactivation of varicella virus (ie, herpes zoster) remains a potentially preventable disease for patients with RA using biologic therapy. Regardless of whether biologic therapy increases the risk of herpes zoster, it is clear that patients with RA as they age are at increasing risk of this often debilitating disease. Zostavax is licensed for patients older than 50 years for the prevention of shingles and has been shown to reduce overall zoster risk by 67% in those vaccinated. This live vaccine is contraindicated during biologic therapy, although a recent observational study suggested that patients inadvertently vaccinated while receiving anti-TNF therapy were not harmed. Given the high morbidity and prevalence of this disease in RA and the inability to vaccinate patients with RA using biologic therapies, efforts should be made to evaluate the safety and efficacy of this vaccine in this context.
Of the other opportunistic infections, it is primarily TB that is truly preventable in the setting of biologic therapy. Recommendations for TB screening have been issued by various public health authorities and professional societies.28,86,87 Interferon-γ release assays (IGRAs), QuantiFERON-TB Gold In-Tube (Cellestis, Valencia, CA), or the T-SPOT.TB assay (Oxford Immunotec, Abingdon, UK), which measure lymphocyte interferon-γ response to antigens highly specific to TB, are becoming increasingly used in this setting. Given the improved specificity of these tests in patients with a history of bacille Calmette-Guérin (BCG), they are preferentially recommended in regions where BCG is used. However, data suggest that screening with IGRAs or tuberculin skin test alone does not sufficiently identify all patients at risk, as false negative results can occur particularly in immunosuppressed individuals.88 A dual testing strategy of both tuberculin skin test and IGRA (or in the case of a BCG-vaccinated individual, a dual IGRA strategy) is likely warranted, particularly in patients with risk factors for TB. Patients diagnosed with latent TB should start prophylactic antibiotic therapy before beginning their biologic.

For nontuberculous mycobacteria and fungal disease, there are few preventive tools for the clinician to use. Patients with RA are at increased risk for pulmonary NTM, and presumably some of these patients are identified during TB screening.40,89 Screening for NTM disease before anti-TNF treatment is largely theoretical, but could be considered in any patients with abnormalities on their baseline radiograph or in those with unexplained chronic cough. Such workup could include chest computed tomography and culture of respiratory specimens.90 Whether it is safe to pursue anti-TNF or other biologic therapy in patients with active NTM disease, treated or untreated, is unknown. For the endemic mycosis such as Histoplasma capsulatum and Coccidioides immitis and posadasii, the usefulness of serologic or other screening has not been established and is difficult to conceptualize in this setting. For other intracellular pathogens such as Listeria or Salmonella that are foodborne, avoidance of certain foods (uncooked meats, unpasteurized milk products), thorough cooking of meat, and washing of produce can help to prevent disease.

**SUMMARY**

Patients with RA are at higher risk for serious infections and death from infection than the general public. Prednisone and biologic agents increase this risk, although risk can be mitigated when such agents act as prednisone-sparing therapies. Some of the important causes of infectious morbidity in this setting are preventable with screening (ie, TB) or vaccination (ie, herpes zoster). As newer biologic, targeted therapies are developed, new infectious challenges will arise, with established and emerging pathogens. Population-based observational studies should be conducted to further elucidate the risk of the newer biologics in the marketplace, and will be of continued importance as additional agents with novel mechanisms become part of the rheumatologist’s armamentarium.

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