Beyond Tumor Necrosis Factor Inhibition: The Expanding Pipeline of Biologic Therapies for Inflammatory Diseases and Their Associated Infectious Sequelae

S. A. Novosad and K. L. Winthrop

Patients with rheumatoid arthritis and other immune-mediated inflammatory diseases are at higher risk for infectious morbidity and mortality, partially due to the therapies used to treat these conditions. Both prednisone and targeted biologic therapies such as tumor necrosis factor antagonists have been implicated to various degrees, although in some cases firm data are lacking with regard to certain types of infections. To date, there is a paucity of information regarding the infectious risks associated with the newer biologic agents. As new biologic agents become available for use, their potential infectious risks will challenge infectious disease clinicians who must work to prevent, diagnose, and treat infections in this setting. This article reviews our current understanding of infectious risk in the setting of targeted therapies and provides an update of the immune system targets and potential infectious sequelae of both current and emerging biologic therapies.

Keywords: biologic therapies; opportunistic infections; anti-TNF agents; infection; autoimmune disease.

Biologic therapies against immune-mediated inflammatory diseases (IMIDs) are increasingly commonplace. With the development of infliximab and etanercept targeting tumor necrosis factor alpha (TNF-α) in 1998, a number of subsequent agents targeting proinflammatory mediators have been developed (Table 1) [1]. The understanding of their infectious risks is limited, as population-based observational studies exist for only 3 anti-TNF agents. For newer TNF blockers and compounds with different immune targets, only clinical trial data exist to provide an early glimpse at safety. The biologic therapeutic pipeline is currently vast, and our understanding of their infectious sequelae is ever changing.

INFECTION RISK

Rheumatoid arthritis (RA) patients suffer 1.5- to 2-fold higher rates of hospitalization due to infections independent of therapy [2]. Patients with systemic lupus erythematosus have disproportionately high infectious morbidity and mortality [3]. Whereas other IMID groups might also suffer higher infectious morbidity due to underlying disease, this is less clear for some disease states such as psoriasis [4]. Beyond the immunodysregulation intrinsic to each IMID, certain therapies also increase infectious risk. Before discussing biologic therapies, clinicians should be reminded that “old” drugs such as prednisone can also impart risk. Population-based studies have repeatedly identified higher infection rates with glucocorticoids. A meta-analysis of 42 observational studies described a dose-dependent increase in serious infection risk of 1.5- to 4-fold for doses of <5 mg to >20 mg/day, respectively [5]. Beyond the outcome of “serious” infection (ie, that requiring hospitalization), corticosteroids are associated with an increased risk of tuberculosis, nontuberculous mycobacterial disease.

**ANTI-TNF AGENTS**

There are currently 5 licensed TNF blockers: 4 monoclonal antibodies and 1 soluble receptor fusion protein. These medications inhibit TNF-α, a proinflammatory cytokine expressed by activated macrophages and other immune cells. TNF-α is involved in a variety of pathways in the immune system, ranging from macrophage activation to recruitment of neutrophils to granuloma activation [12].

**INFECTION RISK**

Meta-analyses of randomized controlled trials (RCTs) and long-term extension studies have generally found a slightly increased risk of serious infection with anti-TNF therapy with pooled odds ratios (ORs) ranging from 1.21 to 2.0 [13–16] and rates of serious infections ranging from 1.9 to 3.6 per 100 patient-years [14, 17]. A Cochrane review of anti-TNF therapy clinical trials across disease indications found certolizumab (OR, 4.75 [95% CI, 1.52–18.5]) to have the largest risk of serious infection compared with placebo and no others were shown to have significantly increased risk of infection [18]. However, it should be noted that clinical trials are generally powered to study efficacy and involve highly selected patient populations, such that population-based studies provide more appropriate “real-world” estimates of safety.

**OBSERVATIONAL STUDIES/REGISTRY DATA**

Only the 3 oldest anti-TNF therapies (etanercept, infliximab, and adalimumab) have undergone rigorous population-based observational study to date. Studies from large national registries and other population-based data sources have reported absolute incidence rates of serious infection of 3–8 per 100 patient-years [19, 20], with rates typically 1.5- to 2.0-fold higher with anti-TNF therapies compared to nonbiologic therapies, particularly 3–6 months after drug start [19] (Table 2). Some analyses have found no increase in risk, however, and it is clear that much of an individual’s risk of infection is driven by patient factors including comorbidities and steroid use [19, 24]. A mitigating factor with regard to infectious risk is the potential for anti-TNF therapy to improve disease control and allow for steroid dose reduction or elimination, limiting any increase in risk intrinsic to anti-TNF therapy [24, 28]. Whereas a number of observational studies have found no differential risk

<table>
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<td><strong>TNF-α inhibitors</strong></td>
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<tr>
<td>Infliximab (Remicade)</td>
<td>Monoclonal antibody against TNF-α</td>
<td>1998</td>
<td>Rheumatoid arthritis, Crohn’s disease, ulcerative colitis, psoriasis, ankylosing spondylitis</td>
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<tr>
<td>Etanercept (Enbrel)</td>
<td>Receptor fusion protein</td>
<td>1998</td>
<td>Rheumatoid arthritis, psoriasis, ankylosing spondylitis, juvenile idiopathic arthritis</td>
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<td>Adalimumab (Humira)</td>
<td>Monoclonal antibody against TNF-α</td>
<td>2008</td>
<td>Rheumatoid arthritis, Crohn’s disease, ulcerative colitis, psoriasis, ankylosing spondylitis, juvenile idiopathic arthritis</td>
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<tr>
<td>Certolizumab (Cimzia)</td>
<td>Monoclonal antibody against TNF-α</td>
<td>2008</td>
<td>Rheumatoid arthritis, Crohn’s disease, psoriasis, ankylosing spondylitis</td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>Monoclonal antibody against TNF-α</td>
<td>2009</td>
<td>Rheumatoid arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis</td>
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<tr>
<td><strong>Other agents</strong></td>
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<tr>
<td>Rituximab (Rituxan)</td>
<td>Monoclonal antibody against CD20 which is found on the surface of B cells</td>
<td>1997</td>
<td>Lymphoma, rheumatoid arthritis, chronic lymphocytic leukemia, granulomatosis with polyangiitis and microscopic polyangiitis</td>
</tr>
<tr>
<td>Anakinra (Kineret)</td>
<td>IL-1 receptor antagonist</td>
<td>2001</td>
<td>Rheumatoid arthritis</td>
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<td>Abatacept (Orencia)</td>
<td>CTLA-4 ligand, selective T-cell costimulation modulator</td>
<td>2005</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Ustekinumab (Stelara)</td>
<td>Monoclonal antibody against IL-12 and IL-23</td>
<td>2009</td>
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<td>Tocilizumab (Actemra)</td>
<td>Monoclonal antibody IL-6 receptor</td>
<td>2010</td>
<td>Rheumatoid arthritis, juvenile idiopathic arthritis</td>
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<tr>
<td>Belimumab (Benlysta)</td>
<td>Monoclonal antibody against B-cell activating factor</td>
<td>2011</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Tofacitinib (Xeljanz)</td>
<td>Janus kinase inhibitor</td>
<td>2012</td>
<td>Rheumatoid arthritis</td>
</tr>
</tbody>
</table>

*Abbreviations: CLTA-4, Cytotoxic T-Lymphocyte Antigen 4; FDA, US Food and Drug Administration; IL, interleukin; TNF, tumor necrosis factor.*
for serious infection between infliximab, adalimumab, and etanercept [21, 29], a recent analysis involving Medicare, Medicaid, and health plan data in the United States found infliximab users to suffer 25% more infections than users of nonbiologic regimens, etanercept, or adalimumab [20]. However, infliximab users were more likely to concomitantly use methotrexate than those treated with other anti-TNF therapies, which may have explained the higher infection rates observed. Other studies found the adjusted hazard ratio (HR) during the first 3 months following treatment initiation to be higher for infliximab in patients aged <65 years but not those older than 65 [25].

Most of these studies evaluated the risk of hospitalized infection but did not report organism-level data. However, an increased rate of invasive skin and soft tissue infections have been reported [30], as well as invasive staphylococcal infections [31]. The rates of septic arthritis in those on anti-TNF therapy were twice that of those on nonbiologic disease-modifying anti-rheumatic drugs (DMARDs) [29]. The most common organism implicated was Staphylococcus aureus (57%) in the anti-TNF group, but species less frequently associated with septic arthritis such as Listeria, Salmonella, and Pseudomonas were also reported.

**RISK OF OPPORTUNISTIC INFECTION**

Infections with a number of intracellular pathogens have been reported among those using anti-TNF therapies; granulomatous infections have been most clearly linked. The risks of some infections are driven by geography and a priori risk within certain populations (ie, tuberculosis) [32, 33]. Rates also differ

| Table 2. Selected Observational Studies of Anti–Tumor Necrosis Factor Agents and the Risk of Serious* Infection |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Country, Source of Data         | Year Published  | Patient Population (Anti-TNF Treated) Adjusted Rate Ratio Comments |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Observational cohort studies    |                 |                 |                 |                 |
| Germany, RABBIT registry [21]   | 2005            | 858 RA patients 2.2 (95% CI, 0.9–5.4) | Etanercept compared to DMARD |
|                                 |                 |                 | 2.1 (95% CI, 0.8–5.5) | Infliximab compared to DMARD |
| Sweden, ARTIS and other national registries [22] | 2007 | 4167 RA patients 1.43 (95% CI, 1.18–1.73) | First year of treatment |
|                                 |                 |                 | 1.15 (95% CI, 0.8–1.51) | Second year of treatment |
|                                 |                 |                 | 0.82 (95% CI, 0.62–1.08) | After second year of treatment |
| United States, large US healthcare organization [19] | 2007 | 2393 RA patients 4.2 (95% CI, 2.0–8.8) | First 6 mo after anti-TNF start |
|                                 |                 |                 | 1.9 (95% CI, 1.3–2.8) | Overall rate for anti-TNF compared to methotrexate |
| United Kingdom, BSRBS registry [23] | 2007 | 8659 RA patients 4.6 (95% CI, 1.8–11.9) | First 90 d after starting therapy compared to DMARD |
|                                 |                 |                 | 1.22 (95% CI, 0.88–1.69) | During treatment compared to DMARD |
| North America, SABER registry [20] | 2011 | 10 242 RA patients 1.25 (95% CI, 1.07–1.48) | Infliximab compared with nonbiologic regimens |
|                                 |                 |                 | 1.26 (95% CI, 1.07–1.47) | Infliximab compared with etanercept |
|                                 |                 |                 | 1.23 (95% CI, 1.02–1.48) | Infliximab compared with adalimumab |
| Germany, RABBIT registry [24]   | 2011            | 3271 RA patients 1.8 (95% CI, 1.2–2.7) | Infliximab vs etanercept during first 3 mo of therapy |
| United States, Kaiser Permanente Northern California [25] | 2012 | 3485 patients with multiple disease indications 3.01 (95% CI, 1.49–6.07) | <65 y of age |
|                                 |                 |                 | 0.94 (95% CI, 0.41–2.13) | ≥65 y of age |
| Dutch, DREAM registry [26]      | 2013            | 2356 RA patients 0.49 (95% CI, 0.29–0.83) | Etanercept compared to infliximab |
|                                 |                 |                 | 0.55 (95% CI, 0.44–0.67) | Etanercept compared to adalimumab |
| Meta analysis                   | 2010            | 7 observational studies of RA patients 1.37 (95% CI, 1.18–1.60) |                   |

Abbreviations: ARTIS, Swedish Biologics Register; BSRBS, British Society for Rheumatology Biologics Register; CI, confidence interval; DMARD, disease-modifying anti-rheumatic drugs; DREAM, Dutch Rheumatoid Arthritis Monitoring registry; RA, rheumatoid arthritis; RABBIT, Rheumatoid Arthritis-Observation of Biologic Therapy; SABER, Safety Assessment of Biologic Therapy; TNF, tumor necrosis factor.

*a Indicates an infection requiring hospitalization.
depending upon which infections are considered “opportunistic” by investigators. In a US study, anti–TNF agent use was associated with an increased risk of opportunistic infections (OIs) (incidence rate ratio [IRR], 1.67 [95% CI, 0.95–2.94]) when compared to methotrexate [34]. However, they identified 10-fold higher rates of OIs than European studies primarily due to their inclusion of herpes zoster (whereas the European studies did not). While most of the literature focuses on RA, rates of OIs are clearly elevated in other IMIDs. A systematic review of RCTs of anti-TNF therapy in inflammatory bowel disease found the risk of OIs was significantly higher with anti-TNF therapy (RR, 2.05 [95% CI, 1.10–3.85]) [35]. A review of the TREAT (Crohn Therapy, Resource, Evaluation, and Assessment Tool) registry found 9 fungal and mycobacterial infections among 3420 subjects on infliximab vs 1 among 2853 individuals on other therapies [36]. A French study reported the incidence of nontuberculosis OIs across indications for anti-TNF therapy (33% bacterial, 40% viral, 22% fungal, 4% parasitic). Risk factors for OIs were treatment with infliximab (OR 17.6 [95% CI, 4.3–72.9]) or adalimumab (OR 10.0 [95% CI, 2.3–44.4]) vs etanercept [37]. In a US cohort of new anti-TNF users, there were 80 nonviral OIs with crude rates of 2.7 per 1000 person-years compared with 1.7 per 1000 person-years in those initiating nonbiological DMARD therapy (adjusted HR, 2.5; [95% CI, 1.5–4.0]) [38].

MYCOBACTERIAL DISEASE

TNF activates macrophages, leading them to phagocytose and kill mycobacteria. TNF inhibition was linked to progression of tuberculosis in early trials of infliximab [39]. This increased risk was subsequently established for other TNF antagonists, although rates have been shown to be 3- to 4-fold higher with adalimumab and infliximab compared to etanercept [40,41]. In a case-control analysis, exposure to infliximab or adalimumab vs etanercept was an independent risk factor for tuberculosis with an OR of 13.3 [95% CI, 2.6–69.0] and 17.1 [95% CI, 3.6–80.6], respectively [42]. Less is known about the risks of tuberculosis with certolizumab and golimumab given the lack of population-based data. Various mechanistic differences between drugs have been proposed to be responsible for the risk difference including differential granuloma penetration, downregulation of antigen-stimulated interferon-γ, and reduced antimicrobial-producing CD8 effector cells [43–46].

Rates of tuberculosis vary according to the background risk of the population and time period of the study. Later studies have shown decreased risk of tuberculosis after the implementation of recommendations for mandatory screening and treatment of latent tuberculosis prior to beginning biologic therapy. A Spanish registry found that after official recommendations were initiated, the active tuberculosis rates decreased by 78% (IRR, 0.22 [95% CI, 0.03–0.88]) [47]. Further analysis of this same registry has shown that the probability of developing active tuberculosis was 7 times higher when recommendations were not followed (IRR, 7.09 [95% CI, 1.60–64.69]) [48]. More recent studies show rates between 56 and 95 per 100 000 in the United Kingdom and the United States, respectively [40,49]. An analysis of psoriasis patients found that the lifetime risk of tuberculosis was as high as 17.1% in those on anti-TNF therapy compared to 0.3% in those not on anti-TNF therapy [50].

In areas of low tuberculosis prevalence such as the United States, NTM disease occurs more frequently than tuberculosis [31,51], with anti-TNF–associated rates of NTM and tuberculosis of 74 and 49 per 100 000 person-years, respectively [52]. Extrapulmonary manifestations of NTM appear to be more common in those on anti-TNF therapies, with nearly half of patients in one series having extrapulmonary disease [31].

LISTERIA AND LEGIONELLA

A Spanish registry found increased rates of listeriosis in RA patients treated with TNF inhibitors (0.265 vs 0.0034 per 1000 patient-years in the general European population) [53]. Slifman et al estimated the US annual incidence of Listeria to be 43 per million anti-TNF users compared with 13 per million in the general population ≥60 years of age [54]. The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database from 2004 to 2011 found 266 cases of Listeria associated with biologic therapy; 77.1% of patients were taking infliximab [55], and most were using steroids. Legionella risk is also elevated among anti-TNF users. In a French registry, the relative risk of anti–TNF–associated Legionella pneumonia was 16.5 to 21.0 compared with the general population of France [56]. A later review of the same registry calculated an age- and sex-adjusted annual incidence rate of legionellosis for patients receiving anti-TNF agents of 46.7 per 100 000 patient-years. The standardized incidence rate was higher for patients on infliximab (15.3 [95% CI, 8.5–27.6]) or adalimumab (37.7 [95% CI, 21.9–64.9]) than etanercept (3.0 [95% CI, 1.00–9.20]) [57].

FUNGAL/ENDEMIC MYCOSES

In 2008, the FDA issued a black box warning regarding endemic mycoses and reported 240 cases of histoplasmosis in patients mostly from endemic regions being treated with infliximab, etanercept, or adalimumab [58]. A recent US population-based study suggests that histoplasmosis occurs rarely, with only 9 infections found in a cohort of 33 324 new anti-TNF users [38], although this study included nonendemic areas in the United States. A case series of 19 anti–TNF–associated histoplasmosis cases suggested a high proportion of disseminated disease [59].
For other mycoses, less information is available, and the magnitude of risk increase is unclear. A large case-series of biologic-associated coccidioidomycosis (n = 44) was recently published and reported that at the time of diagnosis 36 patients were using a biologic, with infliximab being the most common [60]. Aspergillus has been reported with anti-TNF therapy, with invasive pulmonary aspergillosis being the most common clinical scenario [61]. Infections with nocardia have also been reported [35, 62, 63].

Infections characteristic of travel medicine could increase in clinical importance as more patients on biologics travel. One population-based study suggested the risk of leishmaniasis to be 8-fold more common among patients using anti-TNF therapy [64].

### VIRUSES

The reactivation of varicella virus (zoster) is of particular interest among IMID populations (Table 3), with risk elevated in the elderly and those with RA [66, 69]. Prednisone increases risk, but the data from population-based studies regarding TNF blockade is conflicting [70]. A German registry found a significantly increased risk of zoster with adalimumab and infliximab (HR, 1.82 [95% CI, 1.05–3.15]) but not for etanercept (HR, 1.36 [95% CI, .73–2.55]) [65], findings similar to those from the French registry [67]. However, a national study among US veterans with RA found a protective effect for adalimumab and etanercept [11]. Furthermore, a recent US-based study among new users of anti-TNF therapies across indications found high but similar rates of zoster in patients starting anti-TNF or nonbiologic DMARD therapies and no significant risk difference between TNF-blocking agents [68]. In general, steroid use patterns are different between European and US studies, perhaps complicating their comparison.

Anti-TNF agents have been associated with hepatitis B reactivation and progression and patients should be screened prior to starting therapy. Case series suggest that concomitant antiviral and anti-TNF therapy in patients with active hepatitis B virus (HBV) infection can be undertaken with careful monitoring for disease progression [71].

Reactivation of hepatitis C while on biologic therapy is rare. In a prospective study of 31 patients with RA and hepatitis C who were treated with anti-TNF agents, 19 patients were still on therapy, with stable liver enzymes and viral loads after 22 ± 11 months of follow-up [72]. Among 110 patients treated with etanercept, there was only 1 confirmed case of hepatitis C worsening [73].

For cytomegalovirus and Epstein-Barr virus, the risk of anti-TNF therapy is unclear with studies showing no evidence of reactivation [74, 75] and few case reports in the literature to suggest an association. Case reports indicate that the vast majority of patients are on therapy with other agents including steroids [76].

### BIOLOGICS WITH MECHANISMS BEYOND INHIBITION OF TNF-α

To date, biologics with targets other than TNF have generally been reserved for patients who have failed anti-TNF therapy.

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**Table 3. Selected Studies of Anti–Tumor Necrosis Factor Agents and Zoster Risk**

<table>
<thead>
<tr>
<th>Year Published</th>
<th>Source of Data</th>
<th>Crude Incidence Rate</th>
<th>Rate Ratio</th>
</tr>
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<tr>
<td>2009 German, RABBIT registry [65]</td>
<td>11.1 per 1000 person-years for monoclonal antibodies</td>
<td>1.63 (95% CI, 0.97–2.74) for anti-TNF as a class. 1.82 (95% CI, 1.05–3.15) for monoclonal antibodies.</td>
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<tr>
<td>2009 United States, Veterans Affairs [11]</td>
<td>10.6 per 1000 person-years for all TNF agents</td>
<td>1.38 (95% CI, 1.08–1.77) for all TNF agents. 0.62 (95% CI, 0.40–0.95) for etanercept. 0.53 (95% CI, 0.31–0.91) for adalimumab.</td>
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</tr>
<tr>
<td>2010 Spanish, BIOBADASER and national hospital discharge database [66]</td>
<td>0.32 per 1000 person-years for all TNF agents (hospitalized for infection)</td>
<td>3.49 (95% CI, 1.12–10.90) for adalimumab and infliximab compared to etanercept.</td>
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<tr>
<td>2012 French, RATIO registry [67]</td>
<td>10.9 per 1000 person-years for new users of TNF agents</td>
<td>1.09 (95% CI, 0.88–1.36) for all TNF agents (new users).</td>
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</tr>
<tr>
<td>2013 United States, 4 large databases [68]</td>
<td>16 per 1000 person-years</td>
<td>1.7 (95% CI, 1.1–2.7) for all TNF agents. 1.5 (95% CI, 0.9–2.4) for adalimumab. 2.2 (95% CI, 1.4–3.4) for infliximab.</td>
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</table>

**Abbreviations:** BIOBADASER, Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases; BSRBR, British Society for Rheumatology Biologics Register; CI, confidence interval; RABBIT, Rheumatoid Arthritis-Observation of Biologic Therapy; RATIO, Research Axed on Tolerance of Biotherapies; TNF, tumor necrosis factor.
This treatment paradigm is changing with some therapies now being used before TNF blockers. In the development programs of these molecules, infection rates similar to those seen within RCTs of anti-TNF agents have been observed. Few or no population-based observational studies have been conducted with these agents to date, limiting our understanding of their safety profiles [77].

**ABATACEPT**

Abatacept functions as a T-cell costimulation modulator. T cells require 2 signals for activation by antigen-presenting cells, with the second step being binding of costimulatory molecules to the cell surface. Abatacept mitigates CD4+ and CD8+ T-cell activation by blocking the binding of costimulatory molecules [78]. Abatacept carries a labeled warning regarding the risk of serious infections, particularly pulmonary infections in those with chronic obstructive pulmonary disease [79]. The risk of serious infection seems to be higher when abatacept is combined with anti-TNF therapy [80]. A meta-analysis of RCT data suggested a nonsignificant trend toward increase in serious infection when compared with placebo [81]. Data from 7 clinical trials of patients with RA found that the observed rates for infections requiring hospitalization was 2.72 per 100 patient-years for patients using abatacept, consistent with expected rates based on reference RA DMARD cohorts [82]. At 12 months of follow-up, those treated with abatacept had significantly fewer infections than those treated with infliximab (1.9% vs 8.5%), with a rate similar to the placebo group at 6 months (2.7%) [83].

An integrated safety analysis of abatacept RCT data, representing 10 366 patient-years of exposure, found that the risk for serious infections did not appear to increase over time. There were few OIs observed, including tuberculosis (60 events per 100 000 patient-years). Hospitalized infections were not increased for abatacept-treated patients compared with established RA patients [84]. A study of biologic-naive RA patients who were randomized to abatacept or adalimumab found fewer discontinuations due to serious infections (0/12 vs 9/19 patients) in the abatacept group [85]. An analysis of 5 clinical trials found a lower rate of serious infection with subcutaneous vs intravenous abatacept [86].

In 4 patients with chronic hepatitis B who received antiviral prophylaxis, there was no reactivation; however, among 4 patients who did not receive antiviral prophylaxis, all experienced reactivation [87].

**RITUXIMAB**

Rituximab is a chimeric murine/human anti-CD20 monoclonal antibody. CD20 is expressed on pre-B and mature B lymphocytes, and rituximab binding leads to depletion of circulating B cells [88]. RA clinical trials have not suggested a significantly increased risk of infection [81, 89]. Subgroups (approximately 5%) of people, however, can develop persistent hypogammaglobulinemia after rituximab treatment, thereby increasing infectious risk [90–92]. A study of patients starting or switching biologic therapies showed lower rates of hospitalized infections associated with rituximab (HR, 0.81[95% CI, .55–1.20]) compared with infliximab [93].

Hepatitis B reactivation and death have been reported, and rituximab use in persons with chronic hepatitis B is contraindicated [94, 95]. Progressive multifocal leukoencephalopathy (PML) is very rare in IMID patients without HIV (eg, 2 per 1 000 000) but has been reported to be associated with rituximab [96]. An analysis of 34 confirmed cases in the IMID setting revealed that 14 had received rituximab. Ten of 14, however, were using combination immunosuppressive therapies at the time of diagnosis and only 1 patient lacked other identifiable PML risk factors [97].

**TOCILIZUMAB**

Tocilizumab is a humanized monoclonal anti–interleukin 6 (IL-6) receptor antibody. IL-6 is secreted by T cells and macrophages and has a wide range of functions, from acute phase protein synthesis to B- and T-cell differentiation [98].

In general, RCT data suggest infection rates similar to other biologic agents, and rates may be dose dependent. Cumulative safety data from 8 trials showed an overall rate of serious infections of 4.9 per 100 patient-years in patients using the 8 mg/kg dose compared with rates of 3.5 per 100 patient-years in those using placebo or a low dose (4 mg/kg) [99]. The rate of OIs was 0.23 per 100 patient-years with all but 1 OI occurring in the 8 mg/kg dose group. A meta-analysis of RCT and extension data found increased infection risk in the group treated with 8 mg/kg tocilizumab and methotrexate compared with controls (OR, 1.30 [95% CI, 1.07–1.58]) [100].

A population-based postmarketing study from Japan (n = 3881 tocilizumab patients) showed overall infection rates of 9.09 per 100 patient-years, as well as rates of 0.22 per 100, 0.50 per 100, and 0.61 per 100 patient-years for tuberculosis, NTM, and zoster, respectively [101]. Tuberculosis rates were higher than the background Japanese population, but similar to those observed in anti-TNF–treated patients in Japan. In Japanese RA patients enrolled in tocilizumab monotherapy RCTs, the standardized incidence ratio of serious respiratory infections for tocilizumab was 2.35 (95% CI, 1.66–3.24) [102].

**USTEKINUMAB**

Ustekinumab is a human monoclonal antibody directed against the shared p40 subunit of interleukin 12 (IL-12) and interleukin
23. The importance of this subunit and of IL-12 to the development of Th1 responses and protection against mycobacterial and salmonella is well established in humans [103]. Interestingly, few such infections have been reported in patients using this compound.

A pooled analysis of psoriasis trials showed rates of serious infections of 0.6 and 1.4 per 100 patient-years in the ustekinumab 45-mg and 90-mg groups, respectively. However when compared to a psoriasis population treated with conventional systemic agents, the rates of serious infections in the long-term ustekinumab exposure groups were not increased [104, 105]. In an RCT of ustekinumab in patients with Crohn’s disease, 10 patients had serious infections [106]. No OIs or reactivation of tuberculosis were reported. Among 11 hepatitis B surface antigen–positive patients, 2 of 7 who did not receive antiviral prophylaxis had HBV reactivation. One patient had hepatitis C virus reactivation [107].

TOFACITINIB

Tofacitinib, a synthetic, oral nonbiologic DMARD, is the first Janus kinase (JAK) inhibitor approved for RA. JAK is a family of intracellular, nonreceptor tyrosine kinases that are involved in the signal transduction pathways of various cytokines including type 1 and 2 interferons [108].

There are limited data published regarding tofacitinib’s infectious risks. In 1 large RCT, rates of serious infection were higher in the 10 mg twice daily dosing group compared to the 5 mg twice daily and placebo groups (but still low at 1.3% at 0–3 months and 0.9% at 6–12 months). Four OIs occurred (disseminated herpes zoster, cryptococcal pneumonia, and tuberculosis) [109]. In clinical trial and extension studies, the rates of zoster and tuberculosis were elevated in tofacitinib-treated patients [110, 111].

CLINICAL MANAGEMENT AND PREVENTION OF INFECTIONS DURING BIOLOGIC THERAPY

Although a detailed discussion of prevention is beyond the scope of this article, the importance of this concept cannot be understated (Table 4). Screening for certain diseases such as tuberculosis and HBV prior to starting therapy is well defined, but for others is not possible or less clear. Vaccination remains a prime target as data suggest they are underutilized in IMID populations [121, 122].

Although much of the clinical management surrounding infection (ie, when to stop/restart biologic therapy) will be left to the discretion of the practicing clinician, some experience has been reported in the literature. Taroumian et al reported in the largest case series of coccidioidomycosis in the setting of TNF blockers (N = 44) that biologic modifiers (primarily anti-TNF agents) could be safely continued or resumed in patients with coccidioidomycosis who were treated with antifungals and presumed cured, and in selected cases during

<table>
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<th>Disease</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>Screen before starting any biologic, start prophylactic antibiotic therapy before beginning biologic therapy [112, 113]. False negatives are known to occur in immunosuppressed patients, and testing strategies that maximize screening sensitivity (ie, use of both TST and IGRA) in patients with tuberculosis risk factors should be considered [41, 47].</td>
</tr>
<tr>
<td>Nontuberculous mycobacterial disease</td>
<td>No screening recommendations [114].</td>
</tr>
<tr>
<td>Endemic mycoses</td>
<td>No screening recommendations [115].</td>
</tr>
<tr>
<td>Listeria</td>
<td>Avoid uncooked meats, unpasteurized milk products [115].</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Avoid uncooked meats, unpasteurized milk products [115].</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Screening prior to starting therapy, HBsAg positive should receive antiviral drugs concurrent with biologic therapy with close monitoring of viral load and liver enzymes during therapy. Patients who lack active infection (HBsAg negative) and immunity (HBsAb negative) but have prior exposure (HBcAb positive) should have close monitoring of viral load and liver enzymes during biologic therapy [17, 116].</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Screening prior to therapy, monitoring of viral load and liver enzymes during therapy [17].</td>
</tr>
<tr>
<td>Varicella</td>
<td>Use of Zostavax, prior to biologic therapy recommended [112, 117].</td>
</tr>
<tr>
<td>Pneumococcal pneumonia</td>
<td>Vaccination, consider 13-valent conjugate pneumococcal vaccine [118].</td>
</tr>
<tr>
<td>Influenza</td>
<td>Vaccination recommended during biologic therapy [112, 113, 119].</td>
</tr>
<tr>
<td>Other live vaccines</td>
<td>Other live vaccines are currently contraindicated in those who are receiving anti-TNF therapy and other biologic immune modulators given the lack of data confirming the safety of live vaccines in this population [120]. In general, one should wait at least 1 month after discontinuing therapy before vaccination with a live vaccine.</td>
</tr>
</tbody>
</table>

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; IGRA, interferon-γ release assay; TNF, tumor necrosis factor; TST, tuberculin skin test.
antifungal therapy [60]. After treatment of tuberculosis, anti-
TNF therapy can be reinstated [123]. Upon discontinuation
of anti-TNF therapy in patients with disseminated fungal dis-
ease (histoplasmosis) and mycobacterial infection, paradoxical
worsening can be seen and may be due to immune reconstitu-
tion inflammatory syndrome [31, 59, 124], with reported rates of
8 of 19 (42%) and 2 of 49 (4%), respectively. Tofacitinib is me-
tabolized by the cytochrome p450 3A4 system (CYP3A4)
whereas rifampin is a potent CYP3A4 inducer [125]; the com-
bination should not be used. Adverse events including new/
unusual infections thought to be associated with biologic therapy
should be reported to the FDA via the FAERS [126]. In addition,
information can be shared information via the Infectious Dis-
eases Society of America’s Emerging Infections Network [127].

CONCLUSIONS

Biologic therapies in IMID appear to carry increased infectious
risks, although our understanding of this risk is limited by a
lack of population-based observational studies for the newer
agents. The pipeline of development for agents with both similar
and differing mechanisms of action is large (Table 5), and these
therapies are spreading to areas of the world with a higher burden
of tuberculosis and other types of infections. The clinician treat-
ing these patients must maintain a high level of suspicion for in-
fected, acknowledging that the risk will vary between different
agents depending on the mechanisms of action and may also
be modified by individual patient risk factors. In addition to pop-
ulation-based studies of the newer biologic agents, consensus re-
garding the definition of “opportunistic” infection would be key
in guiding safety analyses of these future compounds.

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Both authors have submitted the ICMJE Form for Disclosure of Potential
Conflicts of Interest. Conflicts that the editors consider relevant to the con-
tent of the manuscript have been disclosed.

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