Has the Time Come for Routine Trimethoprim-Sulfamethoxazole Prophylaxis in Patients Taking Biologic Therapies?

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Patients with inflammatory diseases are treated with a variety of biologic agents. The association between use of biologics and tuberculosis is well known. Additionally, there are numerous case reports of infections in patients receiving biologics with organisms such as Pneumocystis, Listeria, Legionella, and Salmonella. Data from the US Food and Drug Administration Adverse Event Reporting System suggest that infection with these organisms in patients receiving infliximab is at least 5 times as frequent as would be expected if there was no association between use of the drug and the infection. Each of these organisms is typically susceptible to trimethoprim-sulfamethoxazole (TMP-SMZ), and this therefore represents a potentially attractive prophylaxis to prevent these infections in patients receiving biologics. A randomized controlled trial of TMP-SMZ prophylaxis in patients receiving biologics is necessary to prove that its utility outweighs risk, but may be best preceded by a multisite case-control study to determine which patients receiving biologics are at greatest risk.

Keywords. trimethoprim-sulfamethoxazole; biologics; prophylaxis; infection.

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, demyelinating syndromes, and inflammatory bowel disease are chronic and progressive inflammatory conditions associated with increased mortality and morbidity from a number of causes including infection. Infections are frequent in patients with inflammatory diseases (the incidence is almost double that observed in matched controls); this could be related to the disease itself, via altered immunologic function or the immunosuppressive drugs used to treat these conditions.

Patients with autoimmune diseases are increasingly treated with a variety of immunomodulatory and immunosuppressive medications, including biologic agents. Biologic agents approved for clinical use included tumor necrosis factor alpha inhibitors (anti-TNF-α) such as etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol; the interleukin 1 receptor antagonist anakinra; the T-cell costimulation inhibitor abatacept; and the humanized monoclonal antibody targeting the interleukin 6 receptor, tocilizumab. Other biologic therapies include rituximab, a monoclonal antibody against B-cell-specific CD20 antigen; belimumab, a fully human monoclonal antibody that binds to B-lymphocyte stimulator and inhibits its biologic activity; and natalizumab, a monoclonal antibody that binds to α4β1 integrin, a protein on the surface of lymphocytes, blocking their union to the endothelial receptor. Figure 1 shows potential targets of these biologic therapies.

There are no current guidelines for prevention of infection in patients receiving biologics, except for tuberculosis prevention. In this article we discuss the risk of opportunistic infections associated with biologic therapies, and advocate consideration of a simple prophylactic strategy using trimethoprim-sulfamethoxazole (TMP-SMZ). We base this strategy on the
known utility of TMP-SMZ as *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis in a variety of immunocompromised populations. Additionally, TMP-SMZ also has broad-spectrum antibiotic coverage against many other pathogens apart from *P. jirovecii* infection. These pathogens include causes of opportunistic infection such as *Listeria monocytogenes*, *Legionella* species, *Toxoplasma gondii*, *Isospora belli*, and *Nocardia* species. Additionally, common bacterial pathogens such as the Enterobacteriaceae, *Acinetobacter* species, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus* species, *Stenotrophomonas maltophilia*, and *Streptococcus* species may be susceptible to TMP-SMZ. Importantly, studies in other immunocompromised patient populations show that TMP-SMZ provides significant protection against many of these organisms, leading to significant reductions in morbidity and mortality (Table 1).

**METHODS**

We performed a PubMed search using the terms *trimethoprim-sulfamethoxazole* and *prophylaxis* to establish the use of TMP-SMZ as an agent to prevent infection in immunosuppressed patients. We then performed a PubMed search using the terms *biologic* and *infection* in order to provide data to answer the question, “Does use of biologics increase the risk of infections with TMP-SMZ–susceptible infections?” We therefore reviewed available data from randomized controlled trials (RCTs), registries, case reports, meta-analyses, and review articles. We also assessed guidelines on the use of biologics to determine whether TMP-SMZ is currently recommended as prophylaxis against infection in patients receiving biologics.

**HAS TMP-SMZ BEEN SHOWN TO PREVENT INFECTIONS IN OTHER IMMUNOCOMPROMISED SETTINGS?**

Trimethoprim-sulfamethoxazole is successfully used as PJP prophylaxis in immunocompromised populations, such as human immunodeficiency virus (HIV)–infected patients with decreased counts of CD4+ T lymphocytes and solid organ transplant recipients. In hematopoietic cell transplantation, allogenic recipients typically receive PJP prophylaxis from engraftment until at least 6 months after transplantation or as long as immunosuppressive therapy is given. Some authors have
suggested that patients with immune dysfunction induced by any inflammatory disease who received ≥20 mg/day of prednisolone for >2–3 weeks should receive PJP prophylaxis [1, 2].

TMP-SMZ has intrinsic in vitro activity against Acinetobacter species, Citrobacter species, Enterobacter species, Escherichia coli, Haemophilus influenzae, Klebsiella species, Legionella pneumophila, Listeria monocytogenes, Moraxella catarrhalis, Proteus mirabilis, Proteus vulgaris, Salmonella species, Serratia species, Staphylococcus species, Stenotrophomonas maltophilia, Streptococcus species, and Yersinia enterocolitica [3]. We performed a literature review in immunocompromised patients taking TMP-SMZ prophylaxis, in order to find additional coverage against infection apart from PJP protection. The main characteristics of the studies are summarized in Table 1.

Dworkin et al demonstrated in a large cohort of HIV-infected patients (CD4 <200 cells/µL) that, in addition to protection from PJP, receipt of TMP-SMZ was associated with significant protection from toxoplasmosis, salmonellosis, infection with Haemophilus species, and staphylococci [4]. Furthermore, 2 multicenter matched case-control studies of solid organ transplant recipients found that this drug gives protection against toxoplasmosis and listeriosis, respectively [5, 6]. Therefore, in addition to its protective effect against PJP, mortality differences might be observed among immunocompromised patients owing to the activity of TMP-SMZ against these other important pathogens. Two important studies performed in HIV-infected patients found a significant increased mortality among patients not receiving TMP-SMZ prophylaxis [7, 8].

Despite these positive reports, it is clear that TMP-SMZ prophylaxis is not completely effective in preventing infection with TMP-SMZ–susceptible organisms. For example, breakthrough Nocardia infections have been described in both solid organ and bone marrow transplant recipients receiving intermittent dosing of TMP-SMZ prophylaxis. Case reports have

<table>
<thead>
<tr>
<th>First Author [Reference]</th>
<th>Study Type</th>
<th>No. of Enrolled Patients</th>
<th>Patient Type</th>
<th>Infection Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anglaret [31]</td>
<td>Randomized controlled trial</td>
<td>545 (271T, 270C)</td>
<td>HIV</td>
<td>Bacterial pneumonia, isosporosis, and malaria</td>
</tr>
<tr>
<td>Wiktor [32]</td>
<td>Randomized controlled trial</td>
<td>771 (386T, 385C)</td>
<td>HIV-1</td>
<td>Enteritis (isosporiasis and nontyphoidal Salmonella spp), septicemia</td>
</tr>
<tr>
<td>Fox [33]</td>
<td>Prospective randomized double-blind study</td>
<td>132 (66T, 66C)</td>
<td>Kidney recipients</td>
<td>Bacterial infections</td>
</tr>
<tr>
<td>Green [34]</td>
<td>Meta-analysis of randomized trials</td>
<td>1155</td>
<td>Cancer pts, bone marrow and SOT recipients, corticosteroid-receiving pts and other immunosuppressive condition other than HIV</td>
<td>Bacterial infections</td>
</tr>
<tr>
<td>Dworkin [4]</td>
<td>Retrospective study</td>
<td>19,081 (13,518T, 9282C)</td>
<td>HIV &lt;200 CD4</td>
<td>Haemophilus spp, Salmonella spp, Toxoplasmosis, and Staphylococcus aureus infections</td>
</tr>
<tr>
<td>Fernandez-Sabe [5]</td>
<td>Multicenter matched case-control study</td>
<td>66 (22 cases, 44C)</td>
<td>SOT recipients</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Fernandez-Sabe [6]</td>
<td>Multicenter matched case-control study</td>
<td>90 (30 cases, 60C)</td>
<td>SOT recipients</td>
<td>Listeriosis</td>
</tr>
<tr>
<td>Edge [36]</td>
<td>Case-control and prospective study</td>
<td>171 (57 cases, 114C)</td>
<td>HIV</td>
<td>Community-acquired bacteremia</td>
</tr>
</tbody>
</table>

Abbreviations: C, patients not treated with trimethoprim-sulfamethoxazole (control or placebo patients); HIV, human immunodeficiency virus; HIV-1, HIV type 1; pts, patients; SOT, solid organ transplant; T, patients treated with trimethoprim-sulfamethoxazole prophylaxis.
described listeriosis and toxoplasmosis in cancer patients receiving TMP-SMZ prophylaxis. In some of these breakthroughs, TMP-SMZ was dosed twice or thrice weekly, and it is unclear whether administering a daily and/or higher dose of TMP-SMZ would have prevented these infections.

WHAT IS THE RISK OF INFECTION WITH TMP-SMZ-SUSCEPTIBLE ORGANISMS IN PATIENTS RECEIVING BIOLOGIC THERAPIES?

We reviewed 31 RCTs evaluating the efficacy of biologic therapies. Uniformly, TMP-SMZ use was not described in the methods of these studies. Unfortunately, reports of most RCTs use the term serious infection (SI) to quantify the risk of infection. SI is variously defined as infections that required hospitalization, infections that required intravenous antibiotic treatment, or life-threatening infections. The specific micro-organisms causing SI are not typically enunciated in the published reports of these RCTs. Furthermore, the RCTs which have been performed typically have follow-up periods of approximately 1 year. Finally, it should be noted that most RCTs performed for registration purposes exclude patients with increased infection risk. For these reasons, we are unable to quantify a risk of TMP-SMZ-preventable infections by analysis of RCTs.

Nevertheless, despite these shortcomings, infections that are potentially preventable by TMP-SMZ have been observed in RCTs. In the ATTEST study, which compared abatacept plus methotrexate (MTX) vs infliximab combined with MTX, opportunistic infection with PJP was observed in the infliximab group [9]. Two phase III trials that compared belimumab with placebo in systemic lupus erythematosus patients showed no overall increased infection risk, but 1 reported a case of Acinetobacter species pneumonia [9–11].

Outside the RCT setting, isolated case reports describing multiple infections in patients treated with anti-TNF-α included septic arthritis due to Salmonella enteritidis (4 reports), Legionella pneumophila infections (9 reports), listeriosis (9 reports), brucellosis reactivation (1 report), nocardiosis (6 reports), and PJP (12 reports). These reports have been supplemented by case series that have reported multiple patients with TMP-SMZ-susceptible infections. These patients were receiving anti-TNF-α and MTX (1 patient) [15]. The British Society for Rheumatology Biologics Register (BSRBR) found an increase in infections due to intracellular bacterial species in patients receiving biologics [16]. Specifically, 2 Legionella, 3 Listeria, and 3 Salmonella infections were observed in patients receiving biologics, in 1352 person-years of follow-up [16]. These intracellular organisms were not reported in patients in this registry who were not receiving biologics [16]. The Spanish BIODABASER cohort found an incidence of serious infection of 53 cases per 1000 person-years among patients treated with anti-TNF-α. Importantly, they identified 10 Salmonella species, 5 Legionella species, and 6 Listeria infections [17]. The French RATIO registry recorded opportunistic infections among patients receiving etanercept, infliximab, or adalimumab, including 10 legionellosis, 4 listeriosis, 4 nocardiosis, 3 nontyphoidal salmonellosis, and 5 PJP. Among these patients, 26% required hospitalization in an intensive care unit and 9% died from the opportunistic infection [18].

Perhaps the most revealing reports of the risk of infection during use of biologics come from the FDA Adverse Event Reporting System. This system identified 84 cases of PJP related to infliximab use from 1998 to 2003 [19]. In a review of reports in patients taking infliximab or etanercept from 1998 to 2002, a number of other TMP-SMZ-susceptible organisms were reported including listeriosis (38 cases), nocardiosis (11 cases), salmonellosis (11 cases), and toxoplasmosis (5 cases) [20]. In a separate report, the FDA identified 80 cases of Legionella pneumonia between the years 1999 and 2010 in patients treated with TNF-α blockers, with 14 reported deaths. In addition, the FDA identified fatal Listeria infections in a review of data regarding laboratory-confirmed infections that occurred in premarketing phase II and phase III clinical trials and from postmarketing surveillance. For this reason, Legionella species and Listeria species have been added to the FDA Boxed Warning for the entire class of anti–TNF-α therapies.
<table>
<thead>
<tr>
<th>First Author, Registry [Reference]</th>
<th>Type of Study (No. of Patients Treated With Biologic Therapies Included)</th>
<th>Type of Biologic Treatment</th>
<th>No. of Pneumocystis jirovecii Infections</th>
<th>No. of Listeria spp Infections</th>
<th>No. of Legionella spp Infections</th>
<th>No. of Salmonella spp Infections</th>
<th>No. of Toxoplasma Infections</th>
<th>No. of Nocardia Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon, BSRBB [16] Registry (7664)</td>
<td>Infliximab, etanercept, and adalimumab</td>
<td>NR</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Komano, REAL [37] Registry (646)</td>
<td>Infliximab and etanercept</td>
<td>3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Perez-Sola, BIOBADASER [17]</td>
<td>Infliximab, etanercept, and adalimumab</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ramos-Casals [27] Registry (1370)</td>
<td>Infliximab, etanercept, adalimumab, anakinra, and rituximab</td>
<td>NR</td>
<td>4</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Takeuchi [38] Postmarketing surveillance (5000)</td>
<td>Infliximab</td>
<td>22</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
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<tr>
<td>Koike [39] Postmarketing surveillance (7091)</td>
<td>Etanercept</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Tubach, RATIO [40] Registry (~24 000–30 000)</td>
<td>Infliximab, etanercept, and adalimumab</td>
<td>NR</td>
<td>NR</td>
<td>10</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Salmon-Ceron RATIO [18] Registry (~24 000–30 000)</td>
<td>Infliximab, etanercept, and adalimumab</td>
<td>5</td>
<td>4</td>
<td>NR</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>FDA AERS</td>
<td>Reported adverse effects Infliximab and etanercept</td>
<td>84&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38&lt;sup&gt;b&lt;/sup&gt;</td>
<td>80&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
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</table>

Abbreviations: AERS, Adverse Event Reporting System; FDA, Food and Drug Administration; NR, data not reported.

<sup>a</sup> Data recorded from 1998 to 2003 from patients taking infliximab.

<sup>b</sup> Data recorded from US patients receiving infliximab and etanercept from January 1998 to September 2002 (n = 346,000).

<sup>c</sup> Data recorded from 1999 to 2010 from patients taking anti–tumor necrosis factor alpha inhibitor therapies.
Unfortunately, the reports listed above do not include denominator data. However, the “risk” of developing certain infections has been assessed by use of a number of statistical methods. In a review of infliximab adverse events reported to the FDA up until 2005, a “signal” for an association between infliximab use and a variety of TMP-SMZ–susceptible infections was observed [21]. The excess risk of infection has been quantified by generating a statistic known as the empiric Bayes geometric mean (EBGM). An EBGM value of 5 is interpreted to mean that a drug–event pair has been reported 5 times as frequently as would be expected if reports involving the drug and reports of the event were independent (ie, no association). For purposes of signal detection, the authors determined the confidence intervals around the EBGM and used the lower 90% confidence bound (EB05) as their signal threshold. The EB05 for infections potentially preventable by using TMP-SMZ prophylaxis included Listeria (20.4), PJP (9.0), Legionella (8.7), Salmonella (5.8), Staphylococcus (3.6), Streptococcus pneumoniae (3.6), E. coli (3.4) and Enterobacter (2.4).

Are There Risks Associated With TMP-SMZ Prophylaxis in Patients Receiving Biologics?

The data presented above represent convincing evidence that TMP-SMZ–susceptible organisms do occur at increased rates in some patients receiving biologics. However, the potential benefit of using TMP-SMZ must be weighed against any specific risks of this prophylaxis. Known risks of TMP-SMZ include allergy and other side effects as cytopenias. These adverse effects may occur in as many as 21%–34% of HIV-positive patients or transplant recipients, respectively. The risks in patients with inflammatory diseases have not been specifically quantified.

Concomitant TMP-SMZ and MTX use may need to be avoided. This recommendation is based on several case reports and a retrospective case-control study, in which concomitant use of TMP-SMZ and MTX was associated with blood dyscrasias. The explanation of this phenomenon is that both MTX and TMP inhibit dihydrofolate reductase, and SMZ inhibits dihydrofolate synthesis, essential for erythroid and granulocyte-monocyte colony formation. Thus, TMP-SMZ administered with MTX may lead to a stronger inhibition of folate metabolism and thus induce blood dyscrasias. However, some suggest that low-dose TMP-SMZ prophylaxis may be used in patients receiving concurrent MTX treatment [22].

The potential for advent of antibiotic resistance in patients on prolonged TMP-SMZ is a significant concern. Some studies among HIV-infected patients have described development of TMP-SMZ resistance and cross-resistance to other drug classes. However, a review of the effect of TMP-SMZ prophylaxis in HIV patients concluded that TMP-SMZ may actually protect against development of bacterial resistance to other classes of antibiotics and to acquisition of certain drug-resistant bacteria, such as MRSA [23]. TMP-SMZ may directly protect against colonization with multiresistant organisms or indirectly benefit as a result of decreased hospitalization (which may be a risk factor for colonization with some drug-resistant bacteria).

Should TMP-SMZ Be Routinely Used as Prophylaxis in Patients Receiving Biologic Therapies?

It is estimated that the increased risk of tuberculosis reactivation is 4- to 7-fold when using an anti–TNF-α drug, being highest for infliximab and lowest for etanercept. Pretreatment screening for latent tuberculosis and preventive treatments is now a routine practice for all biologic therapies, and the implementation of these policies has coincided with a drastic decrease in tuberculosis incidence in patients receiving biologics. Could routine use of TMP-SMZ have the same impact in preventing PJP, listeriosis, and legionellosis in patients receiving biologics?

At this stage, it can be concluded that TMP-SMZ–susceptible organisms occur at a higher rate in patients receiving TNF-α blockers, and that TMP-SMZ prophylaxis can prevent PJP and some other TMP-SMZ–susceptible organisms in other immunocompromised patient populations. It is likely that routine TMP-SMZ prophylaxis in patients receiving biologics would prevent some life-threatening opportunistic infections. Furthermore, TMP-SMZ is low cost whereas admission to the hospital or intensive care unit with PJP, listeriosis, or legionellosis is likely to be extremely expensive. However, TMP-SMZ use is not likely to be 100% effective and may be accompanied by adverse effects. Do the potential benefits outweigh the potential risks?

Based on the BSRBR [16], we estimate that 1 TMP-SMZ susceptible infection occurs for every 1233 patient-years of follow-up (8 TMP-SMZ–susceptible infections were observed in 9868 person-years of follow-up in this registry). In contrast, in early studies of liver transplantation, 11% of transplant recipients developed PJP and 1% toxoplasmosis [24]. In early cohorts of HIV-infected individuals, 70%–80% with a CD4+ lymphocyte population <200 cells/mL developed PJP and 33% toxoplasmosis. Clearly, the rates of opportunistic infections with TMP-SMZ–susceptible organisms are much lower in patients receiving biologics than in other patient populations who benefit from TMP-SMZ.

Are there subgroups that may have higher infection risk? Unfortunately, this cannot be answered specifically with respect to TMP-SMZ–preventable infections. A subanalysis of the CORRONA database concluded that higher disease activity and previous history of infection were significantly associated with an increased rate for infections both managed as an outpatient or in hospital, with higher rates in patients treated...
with anti–TNF-α [25]. The difference of SI risk between drugs is an important issue to consider. A Dutch study found a significantly lower risk of SI in patients with rheumatoid arthritis treated with etanercept compared with both infliximab and adalimumab, whereas there was no difference between adalimumab and infliximab [26]. A large retrospective cohort of patients with autoimmune diseases found an increased risk of SI in infliximab regimens compared to other anti–TNF-α treatments [27]. The BIOBADASER registry showed that infliximab and adalimumab were considered risk factors for opportunistic infections compared to etanercept [17]. Finally, in a large series of granulomatous infections associated with TNF antagonists, the risk for patients receiving infliximab was significantly higher than that for patients receiving etanercept (239 vs 74 per 100 000 patients, P < .001) [20]. Furthermore, a report evaluating the risk comparing patients starting these agents with those who were switching from one biologic agent to another observed higher risks in patients undergoing a switch in therapy and those treated with infliximab [28].

The RABBIT study showed that there was a time-dependent decrease in infection risk profile, being highest in the first year after introducing anti–TNF-α treatment. Other studies have confirmed this association; for example, limiting follow-up to the first 90 days in the BSRBR registry revealed a significant adjusted infection incidence rate ratio of 4.6 (95% confidence interval, 1.8–11.9) [29, 30]. The authors hypothesized that subsequent decreases in serious infection risk could be explained by switching patients at increased risk of infection, improved clinical status of the patients, or reducing the concomitant use of glucocorticoid therapy.

We conclude that it is impossible with current data to predict which patients receiving biologics have the highest potential benefit from TMP-SMZ. Additionally, an RCT based on an entry point of “all patients receiving biologics” would likely need a sample size of several thousands of subjects to prove benefit of TMP-SMZ. We therefore propose that a multinationial case-control study be performed on incident patients with infections with TMP-SMZ–susceptible organisms occurring in patients receiving biologics. Such a study could identify high-risk patients who may benefit from TMP-SMZ prophylaxis. In our opinion, the increased risk of PJP, listeriosis, legionellosis, and potentially other infections in patients receiving biologics needs a greater response than simply a Boxed Warning in the drugs’ product information.

Notes

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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 content of the manuscript have been disclosed.

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