Infectious Complications With the Use of Biologic Response Modifiers in Infants and Children

H. Dele Davies, MD, FAAP, COMMITTEE ON INFECTIOUS DISEASES

abstract

Biologic response modifiers (BRMs) are substances that interact with and modify the host immune system. BRMs that dampen the immune system are used to treat conditions such as juvenile idiopathic arthritis, psoriatic arthritis, or inflammatory bowel disease and often in combination with other immunosuppressive agents, such as methotrexate and corticosteroids. Cytokines that are targeted include tumor necrosis factor α; interleukins (ILs) 6, 12, and 23; and the receptors for IL-1α (IL-1A) and IL-1β (IL-1B) as well as other molecules. Although the risk varies with the class of BRM, patients receiving immune-dampening BRMs generally are at increased risk of infection or reactivation with mycobacterial infections (Mycobacterium tuberculosis and nontuberculous mycobacteria), some viral (herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, hepatitis B) and fungal (histoplasmosis, coccidioidomycosis) infections, as well as other opportunistic infections. The use of BRMs warrants careful determination of infectious risk on the basis of history (including exposure, residence, and travel and immunization history) and selected baseline screening test results. Routine immunizations should be given at least 2 weeks (inactivated or subunit vaccines) or 4 weeks (live vaccines) before initiation of BRMs whenever feasible, and inactivated influenza vaccine should be given annually. Inactivated and subunit vaccines should be given when needed while taking BRMs, but live vaccines should be avoided unless under special circumstances in consultation with an infectious diseases specialist. If the patient develops a febrile or serious respiratory illness during BRM therapy, consideration should be given to stopping the BRM while actively searching for and treating possible infectious causes.

INTRODUCTION

Biologic response modifiers (BRMs) refer to substances that interact with the host immune system and modify it. Several BRMs, such
as cytokines, chemokines, and antibodies, occur naturally in the body and help to protect against infections. Depending on the condition, synthetic BRMs mimicking natural cytokines or inhibitors, including humanized monoclonal antibodies against a cytokine or its receptor, have been used in treatment to restore, boost, or dampen the host immune response. The focus of this clinical report is on cytokine-inhibiting BRMs that dampen the immune response and treat immune-mediated conditions, such as juvenile idiopathic arthritis (JIA), inflammatory bowel disease, graft-versus-host disease associated with hematopoietic stem cell transplant (HSCT), and scleritis. Cytokines that have been targeted include tumor necrosis factor (TNF) α; interleukins (ILs) 6, 12, and 23; and the receptors for IL-1α (IL-1A) and IL-1β (IL-1B) as well as other molecules described below. These medications are increasingly being used in pediatric populations in combination with other immunosuppressive agents, such as methotrexate and corticosteroids. Although they have been very effective in treating the symptoms of the underlying immune-mediated conditions and lessening disability, the immunosuppressive effect of the cytokine-inhibiting BRMs can persist for weeks to months after the last dose. 1 There is strong evidence of an association of the use of these drugs with an elevated risk of infection with viral and mycobacterial pathogens and weaker evidence for fungal and other intracellular pathogens. 2–4

This clinical report aims to summarize the infectious disease complications associated with BRMs to guide subspecialists and to familiarize pediatricians, family physicians, and other primary care practitioners who may care for, diagnose, and manage infections in children treated with BRMs. A summary of key points for primary care providers is given in Table 1. It should be noted that experience with the use of BRMs varies by product, with infliximab having the most data available for its use. Data for children are mostly extrapolated from studies in adults. 5–9 with mostly small case series and cohort studies reported, and thus suggested practices are consensus driven on the basis of knowledge of the impact of BRMs on the immune system. Finally, patients are usually prescribed BRMs in conjunction with other immunosuppressive agents, such as methotrexate and prednisone, which also have immunomodulatory effects that must be considered when the data are being reviewed. In general, the combinations should be considered at least as immunosuppressive as the most immunosuppressive agent in the combination. Table 2 summarizes the BRMs that are currently approved by the US Food and Drug Administration (FDA) along with their mechanisms of action, route of administration, half-lives, and indications. Some currently licensed BRMs are being tested for new indications, and unlicensed BRMs are also being tested for various indications either as sole agents or in combinations.

**FDA-APPROVED BRMS**

**TNF-α Blockers**

Two classes of TNF-α blocking agents are currently used in managing rheumatologic conditions: (1) monoclonal anti-TNF antibodies (includes infliximab [Remicade; Janssen Biotech, Horsham, PA], adalimumab [Humira; AbbVie, North Chicago, IL], golimumab [Simponi; Janssen Biotech, Horsham, PA], and certolizumab pegol [Cimzia; UCB, Smyrna, GA]) and (2) soluble TNF receptors (etanercept [Enbrel; Immunex, Thousand Oaks, CA]).

Infliximab, the first to be licensed in its class, is a chimeric mouse/human protein, and the other monoclonal anti-TNF agents are fully composed of human amino acid sequences. Certolizumab pegol is unique in also being pegylated, which improves its pharmacokinetics and bioavailability. 48 Etanercept is composed of 2 extracellular domains of human TNF-R2 fused to the fragment-crystallizable (Fc) fragment of human immunoglobulin (Ig) G1 (Fig 1).

**Non–TNF-α Blockers**

The other classes of BRMs consist of monoclonal antibodies and other proteins that antagonize IL-1, IL-6, IL-12, and IL-23 or other molecules, which are important in the inflammatory cascade.

**Monoclonal Antibodies**

Tocilizumab (Actemra [IL-6]; Genentech, South San Francisco, CA), ustekinumab (Stelara [IL-12 and IL-23]; Janssen Biotech, Horsham, PA), and canakinumab (Ilaris [IL-1B]; Novartis Pharma, Basil, Switzerland) are all humanized monoclonal antibodies against the interleukins noted. Natalizumab (Tysabri, Biogen, Cambridge, MA) is a recombinant human monoclonal antibody against the cell adhesion molecule α-4-integrin, which acts by preventing the adhesion of leukocytes to endothelial cells. Rituximab (Rituxan; Genentech, South San Francisco, CA) is a chimeric monoclonal antibody against the CD20 protein, primarily found on the surface of B cells, which acts by inducing B-cell death through mechanisms that could include complement-dependent cytotoxicity, apoptosis, or antibody-dependent cytotoxicity. Belimumab (Benlysta; GlaxoSmithKline, Rockville, MD) is a human IgG1-λ.
monoclonal antibody against soluble human B lymphocyte stimulator protein (BLyS; also known as BAFF and TNFSF13B). It does not bind B cells directly but blocks the binding of soluble BLyS to its receptors on B cells, thereby inhibiting B-cell survival and differentiation into immunoglobulin-producing plasma cells. 34

Recombinant IL1 Antagonist

Anakinra (Kineret; Swedish Orphan Biovitrum AB, Stockholm, Sweden) is a recombinant, nonglycosylated human IL-1 receptor (IL-1R) antagonist that blocks the biologic activity of both IL-1A and IL-1B by competitively inhibiting IL-1 binding to the IL-1 type 1 receptor found in a wide range of organs and tissues.

Fusion Proteins

Abatacept (Orencia; Bristol Myers Squibb, Princeton, NJ) and rilonacept (Arcalyst; Regeneron Pharmaceuticals, Tarrytown, NY) are both fusion proteins composed of Fc regions of IgG1 fused with another molecule. Abatacept is a fusion protein of the Fc region of IgG1 fused to the extracellular domain of cytotoxic T-lymphocyte antigen 4. Abatacept has strong affinity and binds to the B7 protein on the antigen-presenting cells, which would normally bind to the CD28 protein on T cells, preventing the antigen-presenting cells from delivering the costimulatory signals needed to fully activate the T cells. Rilonacept (Arcalyst; Regeneron Pharmaceuticals, Tarrytown, NY) is a dimeric fusion protein made of the Fc region of human IgG1 that binds IL-1 linked to the ligand binding domains of the extracellular portions of human IL-1RI and the IL-1R accessory protein (IL-1RAcP).

Tofacitinib (Xeljanz; Pfizer, New York, NY) is an oral, small-molecule protein kinase inhibitor of the enzyme Janus kinase (JAK) 3 and 1 (JAK3 and JAK1, respectively) that interferes with the JAK-STAT signaling pathway, which transmits extracellular information into the cell nucleus, influencing DNA transcription. Functionally, tofacitinib affects both innate and adaptive immune responses by inhibiting pathogenic T helper (Th) 17 cells and Th-1 and Th-2 cell differentiation (Table 2). 49–52

INFECTIONS ASSOCIATED WITH THE USE OF BRMS

Overall Rate of Serious Infections

BRM use has been associated with an increased risk of developing certain infections. In addition to the immunosuppressive effects of these agents, concomitant use of other immunosuppressive agents, such as steroids and methotrexate, and the

<table>
<thead>
<tr>
<th>TABLE 1 Summary of Suggested Screening/Immunizations Before and After BRM Therapy</th>
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<tbody>
<tr>
<td><strong>Suggested screening/immunizations before BRM started</strong></td>
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<tr>
<td>Thorough history</td>
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<tr>
<td>Document previous vaccines, antibody testing when indicated (routine antibody testing not recommended for varicella)</td>
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<tr>
<td>Query about possible exposure and epidemiologic risk factors for histoplasmosis and coccidioidomycosis</td>
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<tr>
<td>Query about history of recurrent HSV</td>
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<tr>
<td>Consider serologic testing for EBV</td>
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<tr>
<td>Screen for past hepatitis B and determine need for vaccine (Table 3)</td>
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<tr>
<td>Routine immunizations</td>
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<tr>
<td>Follow current AAP, Centers for Disease Control and Prevention, and American Academy of Family Physicians guidelines16,17</td>
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<tr>
<td>Give recommended vaccines, inactivated, or subunit vaccines 2 weeks before initiation of BRM</td>
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<tr>
<td>Consider safety of giving live vaccine, if appropriate, give 4 weeks before initiating BRM18</td>
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<tr>
<td>TB</td>
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<tr>
<td>Test for latent TB and manage based on result (see ref 19 for algorithm)</td>
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<tr>
<td><strong>Suggested screening/immunizations after BRM started</strong></td>
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<tr>
<td>Routine immunizations</td>
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<tr>
<td>May still receive routine inactivated, polysaccharide, recombinant, or subunit vaccine{a}</td>
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<tr>
<td>Give annual inactivated influenza vaccine{a}</td>
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<tr>
<td>Avoid live vaccines, unless under special circumstances with help of infectious diseases specialist{a}</td>
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<tr>
<td>Immunizing immunocompetent household contacts (before or during treatment)?</td>
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<tr>
<td>Follow AAP guidelines for immunizing household contacts of immunocompromised patients{a}</td>
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<tr>
<td>Risk of listeriosis</td>
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<td>Avoid unpasteurized milk and milk products{a,b}</td>
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<tr>
<td>Febrile or serious respiratory illness during BRM therapy</td>
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<tr>
<td>Consider stopping BRM and actively search for infections including bacterial, mycobacterial, and opportunistic infections</td>
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<tr>
<td><strong>Suggested screening/immunizations after BRM stopped</strong></td>
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<tr>
<td>Routine immunizations</td>
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<tr>
<td>May still receive routine inactivated, polysaccharide, recombinant, or subunit vaccine{a}</td>
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<tr>
<td>Timing of giving live vaccines after stoppage of BRM + other immunosuppressive agents?</td>
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<tr>
<td>Consult infectious diseases specialist</td>
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<tr>
<td>These are suggestions only. Each situation should be guided by clinical scenario, and the help of an infectious diseases consultant may be sought.</td>
</tr>
<tr>
<td>{a} If receiving rituximab, may not respond.</td>
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If receiving rituximab, may not respond.
underlying inflammatory disease likely contribute to increased infectious risk.47,53,54 A 2011 Cochrane review examined adverse events identified in randomized controlled trials, controlled clinical trials, and open-label extension studies involving >60,000 participants (primarily adults) receiving 9 BRMs (adalimumab, certolizumab, etanercept, golimumab, infliximab, anakinra, tocilizumab, abatacept, and rituximab) for treatment of either rheumatoid arthritis (RA) or cancer.55 Serious infections were defined as infections associated with death, hospitalization, and/or use of intravenous antibiotics. The review identified an overall increased risk of serious infections (odds ratio [OR]: 1.37; 95% confidence interval [CI]: 1.04–1.82) among participants receiving BRMs compared with placebo recipients.55 The drugs most commonly associated with serious infection were certolizumab (OR: 4.75; 95% CI: 1.52–18.5) and anakinra (OR: 4.05; 95% CI: 1.22–16.8). Overall, patients receiving TNF-α inhibitors had a greater risk of developing a serious infection versus patients receiving other BRMs (OR: 1.4; 95% CI: 1.13–1.75). However, patients receiving any
of the other BRMs also had an increased overall risk of serious infection when compared with those receiving placebo. There was evidence of an increased risk of reactivation of tuberculosis (TB) among patients receiving BRMs compared with those receiving placebo (see section titled “TB”). Although the risk of serious infections is increased, there is no clear evidence of overall increased risk of bacterial infections, other than mycobacteria, with the use of BRMs. Before the BRM era, the rate of serious bacterial infections requiring hospitalization or parenteral antibiotics in patients with RA (primarily adults) was reported to be between 0.02 and 0.12 per patient-year.\textsuperscript{56,57} In contrast, the incidence of infection noted for patients with RA treated with etanercept has ranged from 0.017 to 0.050 per patient-year, a rate that is not significantly different from the general population.\textsuperscript{58} One hypothesis would be that even though BRMs temporarily increase the risk of serious infections, their profound positive effects on the underlying disease counterbalances this effect.

In head-to-head trials, the rates of upper respiratory infections (20%) were similar among recipients of etanercept and control patients with RA.\textsuperscript{47} Among studies involving children alone, etanercept has not been shown to increase the risk of serious nonmycobacterial infection compared with etanercept plus conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate,\textsuperscript{22,46,59-66} with rates ranging from 0.007 to 0.035 per patient-year. Children receiving infliximab\textsuperscript{12,23,61,67-70} and adalimumab\textsuperscript{58,42,43,64,71} had higher rates of serious nonmycobacterial infections, ranging from 0.027 to 0.086 per patient-year, but there were no data presented to suggest that these rates were higher than those observed for patients receiving DMARDs alone or DMARDs in combination with the BRMs. Infections related to these BRMs were primarily lower respiratory tract and gastrointestinal infections, sepsis, and abscesses. Although there is no clear increased risk compared with patients receiving DMARDs alone, case reports of sepsis and even death among patients receiving these drugs necessitate caution in instituting therapy in patients who have active infections.

Studies involving children treated with the other classes of BRMs (IL-1 [anakinra], IL-6 [tocilizumab], and T-cell costimulation [abatacept] inhibitors) are limited and generally showed few serious infections. Similarly, infection rates have been low in adult patients treated with ustekinumab, canakinumab, and rilonacept. When infections are identified, they have primarily been viral, gastrointestinal tract, or skin infections. However, there are no data to suggest that the overall incidence of infection is increased compared with the incidence in patients taking DMARDs alone. More studies are needed on the rates of infections for patients receiving these classes of BRMs.
Rituximab-Associated Neutropenia

Rituximab-associated neutropenia is prolonged neutropenia described during or after the completion of therapy, primarily in adult patients being treated for lymphomas. The incidence ranges mostly from 0.02% to 6%, although it has been described to be as high as 25% in 1 series and has involved admission to the hospital with fever and neutropenia and sometimes sepsis with bacterial pathogens including *Pseudomonas* species. The duration of the neutropenia has ranged from 4 days to 1 year. The mechanism is unknown, but circulating antibodies against neutrophils were postulated in 1 study. In 1 open-label cohort study in which rituximab was used to treat JIA in 55 children who had failed to respond to infliximab and other DMARDs, 8 serious infections, all lower respiratory tract infections including *Pneumocystis jirovecii* and *Mycoplasma pneumoniae*, were identified during a 96-week follow-up period. Of interest, neutropenia occurred in 17 (31%) of these patients between weeks 6 and 28 of treatment. The neutrophil count did not exceed 1500 per μL in 9 (16%) of the patients, was <1000 per μL in 5 (9%) of the patients, and was <500 per μL in 3 (6%) of the patients. All patients were treated with granulocyte-macrophage colony-stimulating factor (5 μg/kg), and no cases of sepsis or febrile neutropenia were described. Not surprisingly given the mechanism of action (anti-CD20 monoclonal antibody), 80% of the patients had a complete depletion of their B cells (CD20+ cells), which remained low throughout the 96 weeks of follow-up, but the level or duration of depletion did not correlate with any specific infection. Eleven (20%) patients also had a reduction in their serum immunoglobulin (IgM and IgG) levels below the age-related lower limits of normal. The most common (mild) infections noted were ear, nose, and throat (14%) as well as skin (11%) infections. Four cases of herpetic infections were also reported among the mild infections.

Specific Infections

**TB**

Reactivation infections caused by organisms in the *Mycobacterium tuberculosis* complex have been associated with use of TNF inhibitors. TNF-α has been shown in mouse models to contribute to granuloma formation and to induce and maintain latency of TB infection. In contrast, blockage of this cytokine results in failure to control bacillary growth and form protective granulomata. In the Cochrane review by Singh et al, the overall OR of TB reactivation was 4.7 (95% CI: 1.2–18.6) among patients receiving BRMs compared with those receiving placebo, with the absolute risk measured at 20 cases per 10 000 compared with 4 per 10 000 patients receiving placebo. However, there were insufficient data in that study to compare risk of TB activation in patients receiving 1 BRM versus another.

In other studies conducted in adults, the risk of TB reactivation appeared to be related to the class of TNF inhibitor. TNF antibodies (eg, infliximab and adalimumab) are associated with the highest risk, whereas soluble TNF receptor antibodies (eg, etanercept) appear to have the lowest risks. One study counted the rates of opportunistic infections associated with infliximab use by analysis of the Adverse Event Reporting System (AERS) of MedWatch, a spontaneous reporting system of the FDA. Although the baseline rate of TB in adults was estimated to be 6.2 per 100 000, the rate among the estimated 147 000 patients receiving infliximab was found to range from ~10 per 100 000 to 24.4 per 100 000. In contrast, there were many fewer cases of TB reported in relation to etanercept, with 9 cases identified among ~102 000 patients treated in the same database. Similar results were reported by Dixon et al, based on analysis of 10 712 patients treated with anti-TNF BRMs (3913 etanercept, 3295 infliximab, 3504 adalimumab). The rates of TB were much higher in patients receiving either of the monoclonal antibodies (adalimumab: 144 events per 100 000 person-years; infliximab: 136 per 100 000 person-years) versus those taking etanercept (39 per 100 000 person-years). Other data suggest that adalimumab is associated with TB in patients with RA in a dose-related manner, with higher doses associated with greater risk.

Although the risk appears to be lower with etanercept, since its approval many cases of TB have been described among patients receiving the drug. The estimated incidence noted in studies of 10 to 14.3 cases per 100 000 etanercept-treated patients is more than the Centers for Disease Control and Prevention–estimated rate of TB in the general US population of 6.2 per 100 000. Most cases have localized disease, although disseminated infections have been reported. Other cohort and case-control studies noted rates of 6 to 39 cases of TB for etanercept, compared with 71 to 100 cases for infliximab and adalimumab per 100 000 patient-years.

Risk of Extrapulmonary and Disseminated TB

Of note is the significant increase in the incidence of extrapulmonary and disseminated disease among the TB cases detected in adult patients receiving BRMs, with many cases requiring an invasive procedure for diagnosis. For example, in the Keane et al study, 56% of patients receiving infliximab who developed TB had...
extrapulmonary TB, and 24% had disseminated disease, compared with an expected background rate of 18% and 2%, respectively, in patients with non–HIV-related TB. Similarly, in the study by Dixon et al,62% of all cases were extrapulmonary TB, with 28% with disseminated disease. A high proportion of patients do not develop granulomas, which is consistent with diminished host response against the mycobacteria. In general, the median time to presentation is fastest with infliximab (12 weeks) versus adalimumab (30 weeks) and etanercept (46 weeks), suggesting different pharmacokinetics or pharmacodynamics or different levels of modulation of the immune system for each medication.94

Although there are fewer data available in children, the increased risk of TB reactivation with infliximab and etanercept has been corroborated in several case reports88,96,97 and at least 1 randomized controlled trial.31,68 However, it is important to note that the risk of TB reactivation associated with the underlying autoimmune/inflammatory conditions alone without medications has been estimated to be twice the baseline rate for the normal population.98

Screening to Reduce TB Infections During BRM Therapy There is fair evidence that screening for TB and treating before starting BRMs substantially reduces the risk of TB reactivation. In a small case series, 36 children from Turkey with JIA were treated with etanercept for a median duration of 11.5 months after careful screening with the use of chest radiography, tuberculin skin test (TST), clinical histories, family screening, and physical examination.99 It was noted that Turkey has a moderate baseline prevalence of TB of 27 per 100 000 population. Patients with TST results of >10 mm who had received bacille Calmette-Guérin (BCG) vaccine or those suspected of having latent TB for other reasons underwent computed tomography of the chest and/or had cultures performed if specimens were available. Those identified as having only latent TB (no evidence of abnormalities on computed tomography and/or sputum specimens) received 4 to 8 weeks of “treatment doses” of isoniazid followed by 9 months of “lower prophylactic doses.” The investigators did not indicate the actual doses used for either isoniazid treatment or prophylaxis, and North American authorities do not normally make a distinction between prophylaxis and treatment doses. Treatment with etanercept was started only during the “prophylaxis stage” of the treatment in 7 of the 36 children meeting the criteria, and none of the 36 developed active TB. Similarly, among 2210 adult patients with different rheumatologic conditions who were treated worldwide with golinumab, no cases of TB developed among the 317 who were assessed and treated for latent TB with isoniazid, whereas 5 cases developed in patients not assessed and treated by week 52.44

Nontuberculous Mycobacteria Although M tuberculosis has received the most attention, some reports suggest that nontuberculous mycobacteria (NTM) may be twice as common as TB in adult patients receiving BRMs.100–102 With the use of the FDA MedWatch database, 239 patients with NTM were identified among patients taking BRMs.102 Although pulmonary disease was most common (56%), a substantial number of presentations were extrapulmonary (44%), which is similar to the cases seen for patients developing TB while receiving BRMs. Most of the cases occurred during treatment with infliximab (75%), but this finding may be more indicative of the overall usage of this agent compared with the others. Mycobacterium avium was the organism most commonly isolated. Actual rates of disease could not be calculated from the data presented because the total numbers of patients in the database were not reported. Even though NTM may be common, there is no consensus on baseline screening, because there is no accurate (sensitive and specific) screening test.102 Furthermore, the treatment of NTM is not as clearly delineated as for TB.

Varicella and Herpes Zoster Infections Varicella-zoster virus (VZV) infections (primary or reactivated) are a frequently reported complication among patients receiving BRMs. For patients receiving anti–TNF-α BRMs, reactivation of VZV is the most common infection.2,60,63,103 However, primary VZV infections have also been reported. Varicella.

In a retrospective cohort study of etanercept use among 25 Italian children younger than 4 years treated for a mean period of 23 months, 2 unimmunized patients developed primary VZV infections at 40 and 24 months, respectively,60 with 1 case being complicated with necrotizing fascitis. Similarly, Lovell et al63 described 3 patients (ages 13, 10, and 8 years) with primary VZV among 58 children (ages 4–17 years) enrolled in a North American open-label trial of treatment of JIA with etanercept. Although there was no report of their immunization status, all 3 were antibody negative at the time of diagnosis and seroconverted after infection, suggesting that these were primary wild-type infections. One of these 3 patients’ courses was complicated by aseptic meningitis, but all 3 recovered with acyclovir therapy and discontinuation of etanercept. These data support the
importance of appropriate varicella immunization and the recognition of exposures in patients taking all BRMs.

**Herpes Zoster** There is mixed evidence of an increase in zoster infections with the use of BRMs. The data for this evidence are almost exclusively from adult patients. In a large German registry in which 5040 patients receiving anti-TNF-α BRMs or DMARDs were enrolled prospectively to monitor their outcomes, there was a significant increase in the risk of herpes zoster infections in patients treated with monoclonal antibodies (infliximab or adalimumab) but no increase noted for those receiving etanercept or DMARDs. Similarly, Smitten et al, Galloway et al, and Winthrop et al, analyzing large databases in the United States and United Kingdom, found an increased risk of VZV reactivation in patients receiving BRMs compared with those receiving DMARDs alone. In contrast, another study involving the National Data Bank for Rheumatic Diseases did not find an increased risk of zoster for infliximab, etanercept, or adalimumab. Encephalitis and meningitis attributable to herpes simplex virus (HSV) and VZV have also been described in postmarketing surveillance of patients receiving natalizumab.

**Herpes Simplex** Although uncommon, HSV encephalitis, disseminated cutaneous HSV, and localized disease have been described primarily in case series as a complication of treatment with TNF-α inhibitors. There is at least 1 case report in which infliximab was successfully used along with valacyclovir prophylaxis in a girl with Crohn disease who had relapsing peribuccal herpes labialis attributable to HSV type 1.

**Hepatitis B**

There have been reports of an increased risk of hepatitis B reactivation for patients receiving BRMs. As expected, the risk is greatest in patients who are hepatitis B surface antigen (HBsAg) positive. However, the presence of hepatitis B core antibody (HBCAb) in HBsAg-negative patients (indicating immunity on the basis of infection rather than vaccine) has been associated with HBV reactivation in some patients up to 2 years after immunosuppression with BRMs. In 1 study involving 257 patients infected with hepatitis B and treated with TNF inhibitors, 39% of patients who were HBsAg positive and 5% of those who were HBCAb positive had reactivation of hepatitis B. Increased risk of reactivation correlates with low levels of hepatitis B surface antibody (HbsAb) for patients taking rituximab or TNF-α antagonists, suggesting that reactivation is a direct result of the BRM decreasing antibody levels.

**Endemic Mycoses and Other Fungi**

Fungal infections (Aspergillus, Coccidioides, Histoplasma, Cryptococcus, Sporothrix, and Candida) have been noted, primarily in case reports or series during treatment with BRMs. Histoplasma is the most common invasive fungal organism identified and is especially important to diagnose, because the symptoms, signs, and chest radiography findings are virtually indistinguishable from those of acute TB (cough, fever, chills, night sweats, weight loss, and possible skin or mouth lesions). In at least 1 series, histoplasmosis was diagnosed 3 times more commonly than TB among recipients of BRMs. The presentation of histoplasmosis generally includes fever of unknown origin with disseminated disease in approximately three-fourths of patients, and pulmonary disease is less common. Because the signs and symptoms are nonspecific, diagnosis is usually more challenging. Furthermore, the case fatality rate of patients with disseminated disease receiving BRMs is very high (50%). Pancytopenia and liver dysfunction are often noted. Antigen detection in urine and serum is most useful for diagnosis, although culture of bone marrow could be considered.

Other fungi are less common. In an observational study of AERS data by Keane et al, although actual incidence rates were not given, there were 12 patients with P jirovecii pneumonia (PCP), 7 with histoplasmosis, 6 with aspergillosis, and 7 with severe Candida infections in association with infliximab treatment among the cohort of ~147 000 patients treated.

**HIV**

There have been no studies showing an increased rate of HIV infections among patients receiving BRMs.

**Progressive Multifocal Leukoencephalopathy**

Progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain associated with JC virus (a human polyomavirus named after the initials of the first patient in whom it was identified) infection in immunocompromised hosts, has been reported in adult patients receiving natalizumab, either as monotherapy or in conjunction with other immunomodulators or immunosuppressors. Risk factors associated with the development of PML include the duration of therapy, previous use of immunosuppressants, and presence of anti–JC virus antibodies. For this reason, natalizumab is only available...
through a restricted distribution program that also involves close monitoring known as the TOUCH prescribing program (https://www.touchprogram.com/TTP/).

Other Infections

Other opportunistic-type infections that have been noted (mostly case reports or case series) during treatment with BRMs used alone or with other immunosuppressive agents include viral (cytomegalovirus, Epstein-Barr virus [EBV]), protozoal (Pneumocystis), and bacterial (Listeria and Legionella) during postmarketing surveillance or in national or regional databases. In studies in which EBV or cytomegalovirus viral load was measured or polymerase chain reaction assay was performed before and during infliximab treatment over a period of 6 weeks to 5 years, there was no evidence of viral reactivation. In the adult US population older than 60 years, the annual risk of Listeria was identified as 43 per 1,000,000 among people receiving anti-TNF regimens versus 13 million in the general population. Similarly, a Spanish registry identified rates of 26.5 per 100,000 patient-years versus 0.34 per 100,000 patient-years in the general population.

P. jirovecii colonization has been identified in 16% to 29% of adult patients with systemic autoimmune inflammatory diseases. In mouse models, B cells play an antibody-independent role in clearing a murine form of Pneumocystis (Pneumocystis carinii f sp muris) by presenting antigen to CD4 T cells. Rituximab depletes B cells, and there have been reports of an increased risk of PCP in the population of patients receiving this BRM, primarily those patients receiving it for hematologic malignancies. Despite this report, the benefit of using induced sputum to screen for P. jirovecii or chemoprophylaxis for PCP in patients receiving rituximab is unclear. Although some experts have recommended PCP prophylaxis in the setting of rituximab therapy, there are concerns that the PCP risk is lower than the target of 3.5% for the benefits to outweigh the adverse effects of chemoprophylaxis in non–HIV-infected patients. PCP infections have also been identified in 84 patients receiving infliximab identified through the AERS database and in those receiving other BRMs. However, virtually all of the patients were also receiving concomitant immunosuppressive agents that included methotrexate, prednisone, azathioprine, 6-mercaptopurine, and cyclosporine. As a result, it is unclear whether there is an increased risk for PCP beyond that attributable to the underlying DMARDs.

Infectious Considerations for Patients Before Initiation and While Receiving BRMs

General Precautions

The indications for intervening with biologics are often to reverse a serious clinical condition. Thus, deferring BRMs to provide protection against vaccine-preventable diseases often involves trading risks. Although, at times, it is clearly appropriate to defer BRMs so the patient can receive an immunization, it may not always be the case, and deferral of BRMs should generally be undertaken in consultation with the relevant specialist managing the patient (eg, rheumatologist, gastroenterologist, dermatologist). However, some basic principles can be applied to reduce the risk of serious infections for patients taking BRMs. All patients with a newly diagnosed rheumatologic or immune-mediated condition, including Crohn disease and graft-versus-host disease after HSCT should be considered as a current or future candidate for a BRM and should be screened for potential opportunistic infections at the time of diagnosis before initiation of any immunosuppressive agents. Although the guidelines in this statement are applicable, patients with HSCT with or without graft-versus-host disease generally need to have several other considerations before and after their transplantation that are beyond the scope of this statement, and consultation with an infectious diseases specialist is warranted. These agents should not be given to any patients while they have clinically significant acute infections. Furthermore, restraint should be shown in prescribing BRMs to children who are being treated for chronic infections, those with a history of recurrent infections, or those with conditions (including HIV infection) that predispose them to such infections. For such children, it is prudent to involve an infectious diseases specialist to help guide and advocate that all risks are assessed and that appropriate screening tests before treatment and monitoring during and after treatment occur. Risks associated with potential opportunistic infections that are endemic in the area of residence (eg, histoplasmosis, coccidiodomycosis, etc) should be thoroughly considered before starting a BRM. Part of the consideration for such children will include the determination of underlying previous exposure to the infectious agent and associated risk of reactivation or infection during treatment with the BRM. If a decision is made to treat such children with a BRM, close monitoring will be required, ideally in conjunction with an infectious diseases specialist. Special consideration should always be given to the risk of TB. The development of symptoms suggestive of an opportunistic infection should lead to immediate cessation of the BRM pending confirmation of the infection, appropriate management of the infection, and resolution of
symptoms. Serum neutrophil counts should be monitored regularly (weekly) in patients receiving rituximab, and episodes of recurrent ear, nose, or throat infections in these patients should lead to measurement of serum immunoglobulin concentrations.

**Screening for and Facilitating Adequacy of Immunizations**

**Immunization Before a BRM Is Started**

Immunizations of children about to receive a BRM should follow the current recommendations of the American Academy of Pediatrics (AAP), Centers for Disease Control and Prevention, and American Academy of Family Physicians for persons 0 through 18 years of age (available at: http://aapredbook.aappublications.org/site/resources/IZSchedule.pdf). Before the initiation of BRM therapy, a thorough history should be taken for documentation of previous receipt of appropriate inactivated and live vaccines or history of having had the disease, with testing for specific antibody concentrations where documentation is inadequate. For varicella, if there is a reported history of vaccination but not confirmed by documentation, serologic testing is not indicated and vaccination is recommended if there is sufficient time to safely administer it (4 weeks minimum) before initiating the BRM (Table 2).

All recommended inactivated vaccines should be given at least 2 weeks before the initiation of BRMs to enhance immunogenicity. Live vaccines (rotavirus, live-attenuated influenza, varicella, measles, mumps, and rubella) should be given a minimum of 4 weeks in advance of beginning BRMs. The measles-mumps-rubella (MMR) vaccine can be given on the same day as a TST is administered. If the MMR vaccine is given before administering the TST, the latter should be delayed for 4 to 6 weeks because of temporary suppression of the TST test by the MMR vaccine. Inactivated vaccines, polysaccharide vaccines, and recombinant or subunit vaccines and toxoids do not interfere with TST interpretation. The determination of which vaccines are safe to give for patients receiving steroids should be made in concert with an infectious diseases specialist. The Committee on Infectious Diseases of the AAP recommends that children who have diseases such as systemic lupus erythematosus, which are, in themselves, considered to be suppressive of the immune system, and/or who are receiving immunosuppressive medications other than corticosteroids and who are receiving systemic or locally administered corticosteroids should not be given live-virus vaccines except in special circumstances. Patients receiving higher doses of steroids (≥2 mg/kg per day of prednisone or its equivalent or ≥20 mg/day for ≥14 days for those weighing >10 kg) should not receive any live-virus vaccines until corticosteroid therapy has been discontinued for at least 1 month.

**Immunization After a BRM Is Started**

If the patient is already receiving a BRM, he or she may still receive any inactivated, polysaccharide, recombinant, or subunit vaccine that is due. There is evidence that adult patients receiving BRM therapy develop a diminished but adequate response to such vaccines, including the annual inactivated influenza immunizations. A possible exception to this may be if the child is receiving rituximab, which has been shown to significantly impair antibody response, especially to pneumococcal vaccines. These impairments may persist for up to 6 months after the discontinuation of rituximab and highlight the importance of immunizing such patients who are to receive this or other BRMs before they begin BRM therapy. Where there is a test available for a known antibody correlate of protection in patients who are immunized while receiving a BRM, specific postimmunization serum antibody titers can be measured 4 to 6 weeks after immunization to assess immune response and to guide further immunization and management of future exposures. All children receiving BRMs should receive annual immunization with inactivated influenza vaccine. Live vaccines, including the live-attenuated influenza vaccines, should not be given to any patients receiving BRMs or other immunosuppressive drugs during treatment because of the risk of dissemination and adverse outcomes, except in special circumstances as recommended by an infectious diseases specialist.

**Immunization After a BRM is Stopped**

Because patients receiving BRMs may have prolonged periods of immunosuppression after the discontinuation of the agent, there are currently no clear data to guide how soon a live vaccine may be administered, and studies of duration of suppression are needed. Any consideration for giving a live vaccine after the cessation of a BRM should be made in consultation with an infectious diseases specialist.

**Immunizing Immunocompetent Household Contacts of Patients Receiving BRMs**

The immunization history of household members of patients receiving BRMs should also be assessed, because they may pose a risk of transmitting vaccine-preventable conditions. Household members should all be up to date with the recommended inactivated vaccines. The principles of vaccination of household contacts of patients receiving BRMs should follow the same
principles recommended by the AAP for household contacts of immunocompromised patients. All household contacts aged ≥6 months should also receive influenza immunization annually.

With regard to live vaccines, oral polio vaccine (no longer given in the United States) should not be administered to household contacts of persons receiving BRMs. However, susceptible household contacts can and should receive both MMR and rotavirus vaccines, because the vaccine-strain viruses are rarely transmitted. Similarly, varicella vaccine should be given to susceptible household contacts, because vaccine-strain virus is also rarely transmitted. In the event a household contact of a patient receiving a BRM who is thought to be susceptible to VZV develops a vesicular rash after receiving the varicella vaccine, efforts should be made to separate him or her from the person receiving a BRM for the duration of the rash. However, because the risk of transmission of the vaccine strain is very low and disease associated with the virus is expected to be mild, VariZIG (varicella-zoster immune globulin) is not indicated if contact does occur. For further guidance on immunizing parents and other household contacts in the pediatric office setting, including medico-legal, financial, and logistic considerations, please see the AAP’s technical report “Immunizing Parents and Other Households Contacts in the Pediatric Office Setting” (http://pediatrics.aappublications.org/content/129/1/e247.full; accessed September 10, 2015).

Screening and Treatment Recommendations for TB

As soon as a patient is diagnosed with a rheumatologic or inflammatory/autoimmune condition for which BRMs may be later needed for treatment, TB screening and appropriate treatment should be initiated using the principles outlined as follows:

- All patients, regardless of specific TB risk factors, who will be taking an immunomodulating biologic agent should be tested for latent TB infection (LTBI) before starting the therapy.

- There are 2 options that should be considered for screening, depending on the clinical scenario: either TST or use of an interferon-γ release assay (IGRA) or both. There are 2 choices for IGRA, the QuantiFERON-TB Gold In-Tube assay (Cellestis/Qiagen, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Abingdon, United Kingdom). Both are considered acceptable.

- For children without risk factors for LTBI (previous history of TB, previous history of positive TST result, history of exposure to someone with active TB, travel to an area with endemic TB in the past 12 months, or foreign-born patient or parents from area with endemic TB) and without any symptoms suggestive of TB, the decision as to which screening method to use at baseline should be based on age. Children younger than 5 years, in general, should be screened with TST, whereas an IGRA is preferred for children older than 5 years.

- For patients with any risk factor for LTBI (previous history of TB, previous history of positive TST result, history of exposure to someone with active TB, or travel to an area with endemic TB in the past 12 months) or any symptoms suggestive of TB, both the TST and an IGRA should be performed and appropriate treatment of LTBI should be started if either test result is positive once TB disease has been ruled out. Most experts do not currently use an IGRA when testing for LTBI for children younger than 2 years because of a lack of data for this age group and a high risk of progression to disease but will still use an IGRA in children 2 years or older, especially if they have received a bacille Calmette-Guérin vaccine. Although most of the data available are for children 5 years and older, there are increasing data also available for children 2 to 5 years of age.

- Patients with a positive TST or an IGRA result or any risk factor as stated previously for LTBI should also have chest radiography (postanterior and lateral) performed.

- Routine annual TST or IGRA is not recommended, but patients should be asked at least annually about TB symptoms and risk factors.

- If there is a change in risk or new symptoms suggestive of TB infection while receiving treatment, there should be further evaluation and risk assessment, including a repeat of both TST and IGRA (if the baseline result was negative) as well as chest radiography.

- If LTBI is diagnosed, the patient needs treatment to prevent TB disease.

- Patients suspected of having active TB should have their BRM and other immunosuppressive agents discontinued until TB is ruled out or under control. Guidance from an infectious diseases specialist is recommended in this setting for possible isolation precautions and management. Risk factors for drug-resistant TB (previous history of treatment of TB disease, contact with a patient with known drug-resistant TB, country of origin or current residence in geographic area with a high prevalence of drug-resistant TB, or contact with a source case who has positive smears for acid-fast bacilli or cultures after
2 months of appropriate anti-TB therapy) should be considered in formulating empirical therapy.\[^{158}\]

There will need to be an intensive investigation to examine for disseminated or extrapulmonary disease guided by an expert in TB management.

**NTM**

There are no recommendations or tests at the present time for screening for NTM. However, NTM should be considered in the differential diagnosis of patients receiving BRMs with febrile illnesses, cervical or unexplained lymphadenitis, or other focal infections or anytime TB is being considered.

**Screening for Histoplasmosis and Other Fungi**

All patients should be queried about possible exposure and epidemiologic risk factors for potentially invasive fungal infections, especially histoplasmosis and coccidioidomycosis, which have symptoms and signs that significantly overlap with TB. The main epidemiologic determinants of risk for histoplasmosis include the following:\[^{122,124,159-161}\] geographic location of residence near river beds (Mississippi River Valley, Ohio River Valley, Chesapeake Bay area, eastern Oklahoma, and eastern Texas). Anyone who lives in a histoplasmosis belt is potentially infected; estimates are that 90% of residents acquire histoplasmosis and self-resolve before adulthood; thus, routine laboratory screening is not indicated. Furthermore, negative serologic test results before the initiation of BRMs does not predict patients at risk of development of histoplasmosis, especially among patients already receiving DMARDs.\[^{122}\]

Imunosuppression and extremes of age are also major risk factors. Residence in geographic areas where coccidioidomycosis is endemic (eg, southwestern United States and southern California) is an epidemiologic risk factor for developing coccidioidomycosis,\[^{119,120,161-164}\] and Filipino, Hispanic, black, American Indian, and Asian persons and pregnant women during the third trimester and women in the immediate postpartum period are at risk for more severe disease. Any form of immunosuppression also leads to an increased risk of invasive and disseminated disease. Up to 2% of patients receiving BRMs will develop coccidioidomycosis if they reside in an at-risk region.

Patients suspected of having signs or symptoms compatible with acute histoplasmosis\[^{122,124,159,160}\] or coccidioidomycosis\[^{119-121,162-164}\] during therapy with BRMs should have the BRM discontinued immediately and require evaluation with a combination of chest radiography and serologic, antigen detection, and culture tests. These tests and treatment options are best conducted in consultation with an infectious diseases expert.

**Screening for HSV, VZV, EBV, Hepatitis B, and PML**

**VZV and HSV**

As noted previously in the immunization section, all patients should be screened by history, immunization, and possibly laboratory serologic records to facilitate documentation that they are either immune or have received the age-appropriate dose(s) of varicella vaccine at presentation. Routine testing for VZV is not recommended because of the variability in sensitivity of the assays, particularly in assessing immunity after VZV immunization; and where there is doubt about immunity on the basis of history or inadequacy of records, vaccination is recommended. If VZV vaccine is needed, because it is a live-virus vaccine it should be given at least 4 weeks before the initiation of BRM therapy.\[^{165}\]

Patients suspected of having VZV or HSV infection during BRM therapy should stop taking the BRM. Diagnosis should be sought by a combination of clinical, serologic, and polymerase chain reaction tests from skin lesions (ie, vesicles or papules), and acyclovir or valacyclovir therapy should be started pending confirmation of diagnosis. Patients with recurrent HSV who are being considered for BRM therapy should be given consideration for prophylaxis with valacyclovir or acyclovir.

**EBV**

Consideration should be given to baseline serologic testing for EBV at the time of diagnosis of the underlying rheumatologic condition. Further serologic testing should be considered if the patient develops signs or symptoms that have been associated with EBV, including mononucleosis-like illness or excessive fatigue.

**Hepatitis B**

Patients being considered for BRM therapy should be screened for past hepatitis B infection with both immunization records and serologic testing for HBsAg, HbcAb (total and IgM), and quantitative HbsAb\[^{166}\] (Table 3). It is advisable to obtain baseline liver function tests (LFTs) at the same time.\[^{167-172}\]

Patients who are negative for HBSAg, HbcAb, and HbsAb are considered uninfected and nonimmune. They should be immunized with the first dose of hepatitis B vaccine at least 2 weeks before initiation of the BRM.\[^{173}\]

Consideration of whether the full series of HBV vaccinations is given before initiation of the BRM should be made in conjunction with the specialist initiating the BRM, weighing the risks and benefit of delaying BRM therapy. Patients who are only HbsAb positive are likely immune and can be safely treated with BRMs. If their antibody
TABLE 3  Screening Tests for HBV Infection, Interpretation, and Recommendations Before BRM Therapy

<table>
<thead>
<tr>
<th>HBV Infection</th>
<th>HBsAg</th>
<th>HBsAb</th>
<th>HBcAb</th>
<th>HBcIgM</th>
<th>Abnormal LFTs and/or Symptoms</th>
<th>Additional Testing</th>
<th>Management</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected, nonimmune</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not needed</td>
<td>Safely treat with BRM</td>
<td>Administer hepatitis B vaccine before BRM therapy</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not needed</td>
<td>Safely treat with BRM</td>
<td>For HBsAb &lt; 10 mIU/mL, suggest HBV booster</td>
</tr>
<tr>
<td>Acute</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Not needed</td>
<td>Defer BRM therapy</td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+/-</td>
<td>HBeAg, HBeAb, HBV DNA</td>
<td>Treat with BRM in consultation with ID consultant or hepatologist</td>
<td></td>
</tr>
<tr>
<td>Resolved</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>HBV DNA</td>
<td>Treat with BRM in consultation with ID consultant or hepatologist</td>
<td></td>
</tr>
<tr>
<td>Occult</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>HBV DNA</td>
<td>Treat with BRM in consultation with ID consultant or hepatologist</td>
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Adapted with permission from ref 117. HBcIgM, hepatitis B core IgM antibody; HBsAg, hepatitis B core antigen; HBsAb, hepatitis B core antibody; HBcAb, hepatitis B core e antibody; HBeAg, hepatitis B core e antigen; ID, infectious diseases; –, negative; +, positive.

In the scenario of an occult HBV infection, it is advisable to first obtain a baseline HBV DNA quantitative level as well as LFTs that can be monitored in follow-up. Finally, some patients may only be positive for HBsAb and are generally considered to have "occult HBV," some of these patients may also have a false-positive test result or may have resolved infection. Most can be treated with the BRM under the guidance of an infectious diseases expert or a hepatologist.
Long-term Monitoring for HBV

All patients at risk of HBV reactivation (chronic, resolved, or occult) should have regular (every 1–3 months, depending on underlying HBV infection) monitoring of their LFTs, HBsAg, hepatitis B e antigen, and HBV DNA counts. This monitoring should continue for at least 6 months after termination of the BRM.

PML

All patients receiving natalizumab should be monitored regularly (3 and 6 months after the first infusion and every 6 months after and for at least 6 months after discontinuation) for PML, and the medication should be withheld immediately with any signs or symptoms of the condition. Diagnosis of PML involves a gadolinium-enhanced MRI brain scan and cerebrospinal fluid analysis for JC viral DNA when indicated. An algorithm has been proposed for risk profiling and management of PML for patients receiving natalizumab.

CONCLUSIONS

BRMs have become an important component of effective management of patients with a variety of autoimmune/inflammatory conditions. However, there is an increased risk of certain serious and opportunistic infections for patients receiving these biologic agents, especially the risks of TB and viral infections. It is important for pediatricians, family physicians, and other primary care practitioners managing patients who receive these important treatments to be aware of the potential infections complications and to practice anticipatory guidance between visits to reduce the risk of occurrence or of negative outcomes if the complications do occur. In most scenarios, a close working relationship among the pediatrician, the pediatric medical subspecialist prescribing the BRM, and an infectious diseases specialist is warranted.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
AERS: Adverse Event Reporting System
BRM: biologic response modifier
CI: confidence interval
DMARD: disease-modifying antirheumatic drug
EBV: Epstein-Barr virus
Fc: fragment-crystallizable
FDA: Food and Drug Administration
HBcAb: hepatitis B core antibody
HBsAb: hepatitis B surface antibody
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus
HSCT: hematopoietic stem cell transplant
HSV: herpes simplex virus
Ig: immunoglobulin
IGRA: interferon-γ release assay
IL: interleukin
JAK: Janus kinase
JIA: juvenile idiopathic arthritis
LFT: liver function test
LTBI: latent tuberculosis infection
MMR: measles-mumps-rubella
NTM: nontuberculous mycobacteria
OR: odds ratio
PCP: Pneumocystis jirovecii (previously carinii) pneumonia
PML: progressive multifocal leukoencephalopathy
RA: rheumatoid arthritis
TB: tuberculosis
Th: T helper
TNF: tumor necrosis factor
TST: tuberculin skin test
VZV: varicella-zoster virus
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