doi: 10.30934/kusbed.1388668 **e-ISSN:** 2149-8571

Journal of Health Sciences of Kocaeli University

Review

http://dergipark.org.tr/kusbed

PREVENTION AND MANAGEMENT OF INFECTIOUS DISEASES IN CHILDREN USING BIOLOGICAL RESPONSE MODIFIERS

Sevgi Aslan Tuncay[1], Sevliya Öcal Demir[*1]

[1]Marmara University, Faculty of Medicine, Department of Pediatric Infectious Diseases, Istanbul, Türkiye

ORCID iD: Sevgi Aslan Tuncay: 0000-0002-2626-0316; Sevliya Ocal Demir: 0000-0002-7175-303X

***Corresponding Author:** Sevliya Ocal Demir **e-mail:** sevliyademir@gmail.com

Received: 09.11.2023 **Accepted:** 12.02.2025 **Published:** 27.05.2025

Abstract

In this manuscript, it is aimed to summarize the infectious diseases in children treated with biological response modifying agents, and to determine the protective measures and the conditions to be considered in follow-up.

Biological response modifying agents are medical molecules utilized in managing autoimmune and autoinflammatory diseases, exerting suppressive effects on the immune system through cytokines. The major targeted cytokines include tumor necrosis factor α; interleukin 6, 12, and 23; interleukin 1α and 1β receptors. Biological response modifying agents create a suppressive effect on these targets, making underlying disease remission more accessible. Patients using biological agents have an increased risk of opportunistic infections, particularly tuberculosis and viral infections. Although the risk varies by drug class, patients are generally at risk for mycobacterial (*Mycobacterium tuberculosis* and non-tuberculosis mycobacteria), viral (Herpes simplex virus, chickenpox virus, Epstein-Barr virus, Hepatitis B virus), and fungal (histoplasmozis, coccidioidomycosis*)* and other opportunistic infections. These infections can cause significant morbidity and mortality in immunosuppressive patients. Therefore, it is crucial for healthcare providers to closely monitor patients receiving biological agents for any signs or symptoms of infection. Additionally, appropriate prophylactic measures, such as vaccination against certain infectious agents or use of antimicrobial prophylaxis, may be considered to reduce the risk of opportunistic infections in these patients.

Overall, the management of patients using biological agents requires a careful balance between controlling the underlying disease and minimizing the risk of infections.

Keywords: *Cytokine, immunosuppression, tuberculosis, immunization.*

Introduction

Cytokines, chemokines, and antibodies are the natural part of the immune system, and they help protect the body against infections. Substances that mimic natural cytokines or are monoclonal antibodies against a cytokine or its receptor are known as biological response modifiers (BRMs). These agents have been utilized for various therapeutic purposes to restore, stimulate, or inhibit host immune response. They show their effects by disrupting cytokine functions, blocking the signals necessary for T cell activation or by decreasing the levels of B cells. Some of the BRMs are listed in Table 1.[1]
Immunosuppression is a well-known side effect of biological response modifiers (BRMs), and this characteristic is utilized to treat conditions associated with hyperinflammation, such as juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), and graft-versus-host disease (GVHD). However, the use of these agents may increase the risk of infections, including viral, bacterial, mycobacterial, and fungal infections. For instance, Rituximab has been associated with a heightened risk of serious lower respiratory tract infections in children, including pneumonia caused by *Pneumocystis jirovecii*.[2,3] Additionally, the inflammatory disease itself and concurrent use of other immunosuppressive medications, such as steroids and methotrexate also increase the risk of infections.[4] By closely monitoring patients for adverse reactions and taking proactive steps to manage these risks, healthcare providers can help ensure the best possible outcomes for their patients.

Table 1. Classification of biological response modifiers

Category	Drugs	Target/Function
Tumor Necrosis Factor α (TNF-α) Blockers	**Monoclonal Anti-Tumor Necrosis Factor (Anti-TNF) antibodies** Infliximab (mouse/human protein), Adalimumab, Golimumab, Certolizumab pegol (human amino acid)	Block TNF-α activity to reduce inflammation
	Soluble TNF receptors Etanercept	Mimic TNF receptors to neutralize TNF-α
Non-TNF-α Blockers	**Monoclonal antibodies** Tocilizumab (Interleukin [IL]-6) Ustekinumab (IL-12 and IL-23), Canakinumab (IL-1β), Natalizumab (α-4-integrin), Rituximab (Cluster of differentiation 20 [CD20]), Belimumab (Immunoglobulin G1 lambda [IgG1-λ])	Target specific cytokines or cell surface proteins
Recombinant IL-1 Antagonist	Anakinra	Recombinant human interleukin-1 receptor (IL-1R) antagonist that blocks IL-1 signaling.
Fusion Proteins	Abatacept, Rilonacept	Modulate immune response through receptor fusion proteins
Protein Kinase Inhibitors	Tofacitinib (Janus kinase [JAK] inhibitor), Baricitinib (JAK inhibitor)	Inhibit JAK enzymes to interfere with cytokine signaling
Complement 5 (C5) Inhibitor	Eculizumab	Inhibit complement protein C5 to prevent inflammation

1. Tuberculosis Infections

Tuberculosis (TB) incidence is 16 cases in 100.000 annually, patients who use anti-TNF have 10-20 times higher risk. The risk for extrapulmonary TB is much higher in who use BRMs. The immune system, which encounters the *Mycobacterium tuberculosis* complex, creates a response to microorganisms through TNF and other proinflammatory cytokines (IL-12 and Interferon gamma [IFN-γ]) and promotes the development of immunity. Medications used to treat autoimmune/autoinflammatory disease that block TNF, IL-12, or IFN-γ increase the risk of developing TB infection and disease. And anti-TNF treatment also increased risk of recurrence TB disease in people who previously treated for TB. In terms of risk, TNF antibodies (such as infliximab and adalimumab) have the highest risk, while soluble TNF receptor antibodies (such as etanercept) have the lowest.[5] Healthcare professionals should recommend regular TB screening and prophylactic treatment to mitigate the risk in high-risk individuals.[6] The rate of latent TB infection in children is lower than in adults. Therefore, the risk of developing TB in children is lower.[7]
Regardless of the risk factors for TB, all patients who will receive a BRM should be tested for latent tuberculosis infection (LTBI) before starting treatment (Table 2).[1] Even if they are asymptomatic after the biological agent treatment is started, a clinical evaluation should be performed every 6 months for screening for TB disease. After the biological agent treatment is discontinued, the risk of TB may continue. For this reason, patients should be followed for TB for at least 6 more months after the treatment is stopped.[7]
There are two methods that can be used in screening: Tuberculin Skin Test (TST) or interferon-γ release test (IGRA). There are two options for IGRA, Quantiferon (Cellestis/Qiagen®, Carnegie, Australia) and T-SPOT (Oxford Immunotec®, Abingdon, UK).[8] In LTBI screening, it is recommended to employ TST for children aged below 2 years and IGRA for those older than 2 years as an initial screening measure.[9-11] Approach to TB screening and the management of LTBI are summarized in the Figure 1.

For patients with a history of TB, checking the efficacy of past treatment (in terms of length, dosage, and compliance) is important. In these patients, IGRA or TST is not useful. If TB disease is detected during follow-up, treatment should be started immediately.[7] Patients suspected of having active TB should discontinue biological agents and other immunosuppressive agents until TB is ruled out or controlled. It is recommended to consult an infectious disease specialist for possible isolation measures and management.[1,7,14] It is crucial to prioritize completing the full course of treatment for TB before starting any BRM therapy in patients. Nonetheless, in exceptional scenarios, where the benefits of biological agent administration outweigh the potential hazards, it can be considered after starting TB treatment. It is important to carefully weigh the risks and benefits of any treatment plan in such cases to ensure the best possible outcome for the patient.

Risk factors for drug-resistant TB (previous history of treatment for tuberculosis, contact with a patient known to be drug-resistant tuberculosis, contact with a hospital or a source case in the geographical area with a high prevalence of drug-resistant TB, acid resistance bacilli (ARB) or culture positive cases after 2 months of appropriate anti-TB treatment) should be considered in the planning of empirical treatment regimen.[12]

Table 2. Summary of evaluation for infectious diseases before BRM treatment

<table>
<tr><td rowspan="2">Screening for TB[7,13]
• Symptom and contact history evaluation,
• Physical examination,
• TST or IGRA,
• Chest X-ray</td><td>• No symptoms/ contact history,
• Physical examination is normal,
• Chest X-ray is normal,
• TST or IGRA negative</td><td>LTBI is excluded in this group*
• Evaluate for symptom and contact history every 3 months,
• Perform chest X-ray every 6 months.
• Perform IGRA or TST annually.
Even if LTBI is excluded, the specialist physician may start prophylaxis, considering the risk situation of the patient.</td></tr>
<tr><td>• IGRA positive or
• TST in persons vaccinated with BCG >10 mm, in those without the BCG vaccine >5 mm[7] or
• Sequela lesion in chest X-ray
• Presence of symptoms or contact with a patient with TB</td><td>Investigate tuberculosis disease in this group (such as bacterial tests, thorax computed tomography)
1. If TB disease is detected, stop biological agent treatment, and treat TB disease.
2. TB excluded patient.
+
• IGRA positive or
• TST > 10 mm in those who are vaccinated against BCG, >5mm in those who are not vaccinated or
• Sequelae lesion in chest X-ray
-Give prophylaxis to these groups. Do not perform screening with TST/ IGRA anymore. Follow for sign and symptoms of disease.</td></tr>
<tr><td colspan="2">Perform blood count, kidney function tests, and liver function tests[13]</td><td>Perform at the beginning, if it is normal, repeat every 6 months</td></tr>
<tr><td colspan="3">Perform serological tests for VZV for immunity and EBV, CMV, Toxoplasma species, Histoplasma species and other intracellular pathogens for passed infection.[1,14]</td></tr>
<tr><td colspan="3">Evaluate for the history of recurrent HSV (prophylaxis may be given if necessary)</td></tr>
<tr><td colspan="3">Inform about food hygiene.
Inform about avoiding unpasteurized milk/ dairy products, and uncooked meats due to the risk of Listeriosis.
Inform about oral hygiene.</td></tr>
<tr><td colspan="2">Perform AntiHBs, HbsAg, AntiHBc (Total), and AntiHBc-IgM serological tests for a passed Hepatitis B infection and determine the vaccination need according to the immunity status
Perform serological tests for HIV (Anti-HIV), Hepatitis A (Anti-HAV IgM and Anti-HAV IgG), Hepatitis C (Anti-HCV) infection</td><td>• Plan vaccination scheme if unvaccinated and AntiHBs <10 mIU/mL.[1]
• Apply booster dose if fully-vaccinated and AntiHBs <10 mIU/mL.
• Follow Table 3 if there is a serology positivity of a passed or active HBV infection.
• If HAV, HCV, or HIV infection is detected, plan further examinations.
• If viral hepatitis serologies are negative, serology follow-up is not required. Liver function tests should be performed every 6 months. If liver enzymes are elevated, repeat serological tests for viral hepatitis factors.</td></tr>
</table>

* The American Academy of Pediatrics does not recommend chest X-ray or IGRA/TST routinely. They recommend only evaluation of risk factors and symptoms.

2. Non-tuberculosis Mycobacteria Infections

Non-tuberculous mycobacteria (NTM) have been observed to have an impact on patients utilizing BRMs. Although the actual rate of NTMs is unknown, *Mycobacterium avium* was the most isolated organism. There are no recommendations for screening NTMs. It is imperative to consider the presence of NTMs in patients using BRM in circumstances involving febrile illnesses, cervical or unexplained lymphadenitis, other localized infections, or any scenario where TB disease is being evaluated.[7,15]

3. Varicella Zoster and Herpes Zoster Infections

Varicella-zoster virus (VZV) infections are typically regarded as primary or reactivation. It's essential to assess the patient's immunity to varicella or the history of chickenpox infection before beginning treatment with BRMs. The vaccination certificate of the child must be obtained for the age-appropriate varicella vaccine status or past serological tests should be screened for the immunity status. If the vaccine records have not been reached and the past serological tests are negative, vaccination is recommended at least 4 weeks before the biological agent treatment is started. Although Herpes Simplex Virus (HSV) infections are rare, HSV encephalitis, disseminated cutaneous HSV, and localized disease have been identified as a complication of treatment with TNF-α inhibitors, primarily in case series. Treatment should be discontinued in patients suspected of having VZV or HSV infection during biological agent therapy. For diagnosis, clinical evaluation, serologic tests, and polymerase chain reaction tests from skin lesions (i.e., vesicles or papules) should be used together.[16] Acyclovir or valacyclovir treatment should be started while performing diagnostic examinations. Prophylaxis with valacyclovir or acyclovir should be considered for patients with recurrent HSV.[1,16]

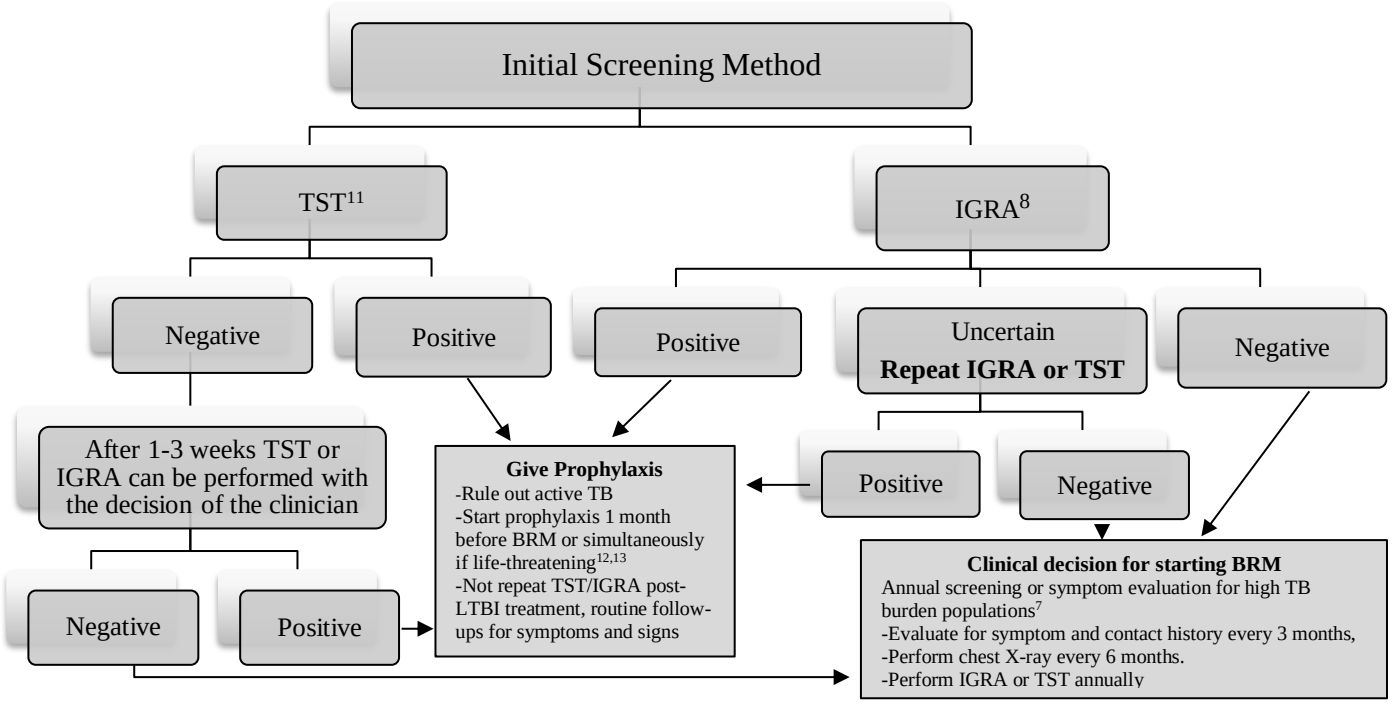

Figure 1. Algorithm for Tuberculosis Screening and Management of Latent TB Infection (LTBI)

4. Epstein-Barr Virus Infections

Initial serological tests should be performed for Epstein-Barr Virus (EBV) at the diagnosis of primary diseases. Further serological testing should be considered if the patient develops signs or symptoms associated with EBV, including mononucleosis-like disease or extreme fatigue during the treatment with BRMs.

5. Hepatitis B and Hepatitis C Viruses Infections

Hepatitis B virus (HBV) reactivation may develop in patients receiving BRM.[4,17] The vaccination records of patients should be questioned before biological agent treatment; patients should be screened with serological tests including Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (Anti-HBc, total and IgM), and quantitative Hepatitis B surface antibody (Anti-HBs) for past HBV infection. Also, it is recommended to perform liver function tests (Table 3).[18]

The positivity of Anti-HBc in HBsAg-negative patients indicates infection-related immunity. In general, the risk for HBV reactivation is much higher in the HBsAg-positive and anti-HBc positive patients than in HBsAg-negative patients. In these patients, using B-cell-depleting treatments, such as rituximab, natalizumab, and alemtuzumab carries the highest risk of reactivation and could require preemptive therapy.[19] Co-infection of HBV with Hepatitis C virus (HCV), Hepatitis D virus (HDV) or Human immunodeficiency virus (HIV) may increase the risk for HBV reactivation.[1]

All patients at risk of HBV reactivation (chronic, recovered, or occult) should be monitored regularly (every 1-3 months, depending on underlying HBV infection) with liver function tests, HBsAg, Anti-HBe, and HBV DNA levels. This monitoring should continue for at least 6 months after the end of biological agent therapy. As a general approach, biologic therapy is not likely to have a detrimental effect on HCV

infection. However, it should be used with caution, and only after a thorough risk-benefit analysis has been conducted in consultation with a hepatologist.[13]

6. Histoplasmosis and Other Fungal Infections

Aspergillus, Coccidioides, Histoplasma (most often), Cryptococcus, Sporothrix, and Candida species are fungal infections that can occur in patients receiving BRM.[20] All patients should be evaluated for exposure to invasive fungal infections and epidemiological risk factors, especially histoplasmosis and coccidioidomycosis which have similar clinical signs to tuberculosis. Routine laboratory screening is not recommended

Table 3. Evaluation of patients who are being planned/on biological agent therapy for Hepatitis B infection[18]

Non-infected, non-immune	• HBsAg, AntiHBc, and AntiHBs negative patients • The first dose of the hepatitis B vaccine should be administered at least 2 weeks before the start of treatment. In order to start BRM treatment, the decision to wait for the completion of the series should be made considering the benefit/harm situation due to the delay of the treatment.
Non-infected, immune	• Patients with HbsAg negative, AntiHBc negative, AntiHBs positive • BRM treatment can be started • If the antibody titer is low (<10 mIU/mL), a booster dose of the hepatitis B vaccine should be administered before starting treatment.[1]
Acute HBV infection	• HbsAg positive, AntiHBc positive, AntiHBc-IgM positive, and high liver function tests. • Biological agent therapy should not be started for these patients.
Recovered HBV infection	• Patients with HbsAg negative, AntiHBs positive and AntiHBc positive • HBV DNA should be performed • BRM treatment can be started by closely monitoring by a pediatric gastroenterology/ hepatology and infectious diseases specialist.
Chronic HBV infection High risk of reactivation • B-cell depleting agents as rituximab, natalizumab, alemtuzumab, • High-dose corticosteroids • Potent TNF-α inhibitors including infliximab, adalimumab, certolizumab, and golimumab	• HbsAg positive, AntiHBc positive, AntiHBc-IgM negative and persistently or intermittently high liver function tests. • Antiviral prophylaxis may be considered in patients at high risk for reactivation.[14,19] • HBV DNA, HbeAg, AntiHBe, and HBV DNA tests should be performed. • Patients with high viral load (HBV DNA >105 duplication/mL) and abnormal liver function tests may need to be treated with antiviral agents. Starting biological agent treatment should be decided by consultation with pediatric gastroenterology/ hepatology and infectious diseases specialists.
Occult HBV infection High risk of reactivation • Patients who are receiving B-cell depleting therapies.	• HbsAg negative, AntiHBs negative, AntiHBc positive. • They might be at risk of HBV reactivation. • Antiviral prophylaxis may be considered in patients with a high-risk group.[14,19] • HBV DNA test should be performed. • BRM treatment can be started by close monitoring by a pediatric gastroenterology/ hepatology and infectious diseases specialist.

7. Other Infections

Other opportunistic infections during the use of biological agents alone or with other immunosuppressive agents include viral (eg. Cytomegalovirus, EBV), protozoal (eg. Pneumocystis), and bacterial (eg. Listeria, Legionella).[1] Routine laboratory screening is not recommended for these agents.

8. Immunization of Children Using Biological Response Modifiers

8.1. Recommended Screenings/immunizations Before Starting the BRMs

The vaccination card should be checked, and the missing vaccinations should be completed. Inactive vaccines (including annual inactivated influenza vaccine) should be applied at least 2 weeks before treatment begins.[21] Live vaccines (rotavirus, live attenuated influenza, chickenpox, measles, mumps, and rubella) should be administered at least 4 weeks before the start of biological agent therapy, if not contraindicated due to other treatments or a different disease. The pneumococcal vaccination schedule recommended by the Turkish Ministry of Health for high-risk pediatric populations is outlined in Table 4.[22] According to the American Academy of Pediatrics (AAP), children at increased risk for invasive pneumococcal disease (IPD) who have completed the routine immunization series with PCV13, PCV15, or PCV20, and who have not previously received PCV20, should receive a single dose of either PPSV23 or PCV20 at least 8 weeks after the final dose of PCV13 or PCV15. A second dose of PPSV23, or the first dose of PCV20 (if not previously administered), is recommended five years after the initial PPSV23 dose.[23]

8.2. Recommended Screening/immunizations After Biological Agent Initiation

Live vaccines, including live attenuated influenza vaccines, should not be administered to any patient taking a biological agent or other immunosuppressive medication due to the risk of dissemination. Inactivated, polysaccharide, recombinant, and subunit vaccines can be administered. İnactivated influenza vaccine is recommended annually. In children, rituximab can cause a reduction in antibody response, especially against pneumococcal vaccines. This condition can continue up to 6 months after discontinuation of rituximab. The effectiveness of inactivated vaccines during BRM treatment can be evaluated by analyzing the antibody response 4-6 weeks post-vaccination.[1]

Table 4. Recommendations for pneumococcal immunization with PCV13 and/or PPSV23 vaccine for children at high risk or presumed high risk of pneumococcal disease [22]

Age (month)	Previous Vaccination Status*	Application Diagram
<23 months	Unvaccinated	Administer 2–4 age-appropriate doses of PCV13 PSV23 is not administered to children < 2 years of age
24-71 months	Fully vaccinated for age with ≥2 doses of PCV13	Administer 1 dose of PPSV23**, ≥8 weeks after the last PCV13 dose
	Unvaccinated or received ≤3 doses of PCV7 (regardless of whether 1 dose was PCV13)	Administer 2 doses of PCV13 at intervals of ≥8 weeks, followed by 1 dose of PPSV23** ≥8 weeks after the last PCV13 dose
	Completed age-appropriate 4 doses of PCV7 series	Administer 1 dose of PCV13 ≥8 weeks after last PCV7 dose, followed by 1 dose of PPSV23** ≥8 weeks after PCV13
72 months-18 years	Not vaccinated with PCV13 or PPSV23	Administer 1 dose of PCV13, followed by 1 dose of PPSV23** ≥8 weeks later
	Vaccination with 1 dose of PCV13	Administer 1 dose of PPSV23** ≥8 weeks after the last PCV13 dose
	Vaccination with PPSV23	Administer 1 dose of PCV13 ≥8 weeks after the last PPSV23** dose

* If the vaccination status is unknown, it should be evaluated as if it has never been vaccinated with pneumococcal vaccine.
** If PPSV23 was administered before the 8-week break, PPSV23 is administered once again 12 months after PCV13, as it cannot be sure of the effectiveness of the vaccine. It is recommended to administer an additional dose of PPSV23 to children older than 24 months with hemoglobinopathies, functional/ anatomical asplenia, cochlear implants, congenital/ acquired immunodeficiency, HIV infection, chronic renal failure, and malignancy. Second PPSV23 should be applied 5 years after the first dose.

8.3. Recommended Screening/immunizations After Discontinuation of BRM Therapy

Patients may have long-term immunosuppression after discontinuation of biological agents ± other immunosuppressive agents. After stopping BRM therapy, live vaccinations cannot be administered immediately and the exact time frame for their administration remains unclear. [21]

8.4. Immunization of Immunocompetent Household Contacts of Patients Receiving BRMs

Household members should have up-to-date recommended inactivated vaccinations. The annual influenza vaccine should be recommended to all households older than 6 months. Oral polio vaccine should not be administered to the household members of the patients receiving BRMs. Since the chance of transmitting the vaccine strain is very low, household members can receive vaccines for Measles, Mumps, Rubella, Rotavirus, and Varicella. If a household member receiving Varicella vaccine develops a rash, they should avoid contact with the patient receiving BRM. Varicella-zoster immune globulin is not needed if contact occurs since the risk of transmission of the vaccine strain is low and the associated disease is mild. [21]

9. Special Conditions for Children Using BRM

9.1. Approach to the Baby of the Mother Using Biological Agents During Pregnancy

Infants exposed to in-utero maternal BRMs may develop immunosuppression, and immunosuppression can last up to 12 months from the last maternal dose. Certolizumab is not transferred across the placenta, likely infliximab, although the data are sparser for it. Rotavirus vaccination of infants can be considered when either of these BRMs were administered during pregnancy. These recommendations might not apply in other countries, where the risk of natural infections may be different and where other live vaccines like BCG or OPV are given early in life. So, consultation with an immunologist or a pediatric infectious diseases physician is recommended. [21]

9.2. Anti-TNF BRMs in Breast Milk

Current evidence indicates that anti-TNF medications have not been shown to transfer significantly into human milk. It is appropriate to counsel women undergoing anti-TNF medication therapy to continue nursing. Breastfed children whose mothers are using anti-TNF drugs should receive routine immunizations, including live virus vaccines, according to the recommended schedule, unless vaccination is being withheld due to in-utero exposure to the biologic response modifier. [24]

9.3. Infection Risk During Eculizumab Therapy

Eculizumab is a monoclonal antibody that binds to complement protein C5, blocking its cleavage into C5a and C5b, hence inhibiting terminal complement activation. It is approved by the FDA for treating atypical hemolytic uremic syndrome, myasthenia gravis, and paroxysmal nocturnal hemoglobinuria (PNH). Complement blockage at C5 diminishes opsonophagocytic killing of the immune system.[25] Complement inhibitor use, such as eculizumab and rovelizumab, has been linked to an approximately 2000-fold higher risk of aspergillus infections, as well as infections from encapsulated bacteria like *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Streptococcus pneumoniae*, and *Hemophilus influenzae*.[26] Complement inhibitor recipients should receive both meningococcal ACWY and meningococcal B vaccines. Although vaccination, patients may be at risk of invasive meningococcal disease. Antimicrobial prophylaxis (with amoxicillin or penicillin) could be considered for the duration of complement inhibitor therapy, and until immunocompetence is restored. All inactivated and live-virus vaccines can be administered. Meningococcal vaccination should be applied at least 2 weeks before treatment, if it has been less than 2 weeks, penicillin prophylaxis should be given. Patients treated with eculizumab are at increased risk of invasive and recurrent meningococcal disease.[27]

Conflict of Interest

The authors declare no conflict of interest.

Financial Disclosure

No funding was utilized for this manuscript.

Author Contributions

S.Ö.D and S.A.T designed the article; S.A.T research the literature, wrote the manuscript; S.Ö.D made critical review of manuscript. All authors read and approved the final manuscript. All authors meet the ICMJE authorship criteria.

References

1. Davies HD; Committee on Infectious Diseases. Infectious complications with the use of biologic response modifiers in infants and children. *Pediatrics*. 2016;138(2):e20161209. doi:10.1542/peds.2016-1209.
2. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*. 2008;59(6):762-784. doi:10.1002/art.23721.
3. Alexeeva EI, Valieva SI, Bzarova TM, et al. Efficacy and safety of repeat courses of rituximab treatment in patients with severe refractory juvenile idiopathic arthritis. *Clin Rheumatol*. 2011;30(9):1163-1172. doi: 10.1007/s10067-011-1720-7.
4. Askling J, Fored CM, Brandt L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum*. 2005;52(7):1986-1992. doi:10.1002/art.21137.
5. Salgado E, Gómez-Reino JJ. The risk of tuberculosis in patients treated with TNF antagonists. *Expert Rev Clin Immunol*. 2011;7(3):329-340. doi:10.1586/eci.11.6
6. Ayaz NA, Demirkaya E, Bilginer Y, et al. Preventing tuberculosis in children receiving anti-TNF treatment. *Clin Rheumatol*. 2010;29(4):389-392. doi:10.1007/s10067-009-1334-5.
7. Tüberküloz Saha Rehberi. Sağlık Bakanlığı, Ankara-2019. Available at: https://hsgm.saglik.gov.tr/depo/birimler/tuberkuloz-db/Dokumanlar/Rehberler/Tuberkuloz_Tani_ve_Tedavi_Rehberi.pdf. Accessed September 25, 2023.
8. Starke JR; Committee on Infectious Diseases. Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children. *Pediatrics*. 2014;134(6):e1763-e1773. doi:10.1542/peds.2014-2983.
9. Debord C, De Lauzanne A, Gourgouillon N, et al. Interferon-gamma release assay performance for diagnosing tuberculosis disease in 0- to 5-year-old children. *Pediatr Infect Dis J*. 2011;30(11):995-997. doi: 10.1097/INF.0b013e3182272227.
10. Moyo S, Isaacs F, Gelderbloem S, et al. Tuberculin skin test and QuantiFERON® assay in young children investigated for tuberculosis in South Africa. *Int J Tuberc Lung Dis*. 2011;15(9):1176-1181. doi: 10.5588/ijtld.10.0770.
11. American Academy of Pediatrics. Summaries of Infectious Diseases. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:786-814.
12. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of tuberculosis in adults and children. *Clin Infect Dis*. 2017;64(2):e1-e33. doi: 10.1093/cid/ciw778.
13. Holroyd CR, Seth R, Bukhari M, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis-Executive summary. *Rheumatology (Oxford)*. 2019;58(2):220-226. doi:10.1093/rheumatology/key207.
14. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2021;73(7):1108-1123. doi:10.1002/art.41752.
15. Winthrop KL, Chang E, Yamashita S, Iademarco MF, LoBue PA. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy. *Emerg Infect Dis*. 2009;15(10):1556-1560. doi: 10.3201/eid1510.090310.
16. American Academy of Pediatrics. Summaries of Infectious Diseases. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:831-843.
17. Carroll MB. The impact of biologic response modifiers on hepatitis B virus infection. *Expert Opin Biol Ther*. 2011;11(4):533-544. doi: 10.1517/14712598.2011.554810.
18. Motaparthi K, Stanisic V, Van Voorhees AS, Lebwohl MG, Hsu S. From the Medical Board of the National Psoriasis Foundation: recommendations for screening for hepatitis B infection prior to initiating anti-tumor necrosis factor-alpha inhibitors or other immunosuppressive agents in patients with psoriasis. *J Am Acad Dermatol*. 2014;70(1):178-186. doi: 10.1016/j.jaad.2013.08.049.
19. Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. *Gastroenterology*. 2017;152(6):1297-1309. doi:10.1053/j.gastro.2017.02.009.
20. Gundacker ND, Baddley JW. Fungal infections in the era of biologic therapies. *Curr Clin Micro Rpt*. 2015;2:76-83. doi:10.1007/s40588-015-0018-y.
21. American Academy of Pediatrics. Summaries of Infectious Diseases. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:527-532.
22. Risk Grubu Aşılamaları, Sağlık Bakanlığı, Türkiye Halk Sağlığı Kurumu, 2016. Available at: https://istanbul.saglik.gov.tr/Eklenti/83243/0/risk-grubu-asilamalari-ekdoc.doc. Accessed October 1, 2023.
23. American Academy of Pediatrics. Summaries of Infectious Diseases. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2024 Report of the Committee on Infectious Diseases*. 33rd ed. Itasca, IL: American Academy of Pediatrics; 2024:819-820

24. American Academy of Pediatrics. Summaries of Infectious Diseases. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2024 Report of the Committee on Infectious Diseases*. 33rd ed. Itasca, IL: American Academy of Pediatrics; 2024:114.
25. Crew PE, Abara WE, McCulley L, et al. Disseminated gonococcal infections in patients receiving eculizumab: a case series. *Clin Infect Dis*. 2019;69(4):596-600. doi: 10.1093/cid/ciy958.
26. Rondeau E, Cataland SR, Al-Dakkak I, Miller B, Webb NJ, Landau D. Eculizumab safety: five-year experience from the global atypical hemolytic uremic syndrome registry. *Kidney Int Rep*. 2019;4(11):1568-1576. doi: 10.1016/j.ekir.2019.07.016.
27. American Academy of Pediatrics. Summaries of Infectious Diseases. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:527-532.