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REVIEW

Prevention Strategies to Minimize the Infection Risk Associated with Biologic and Targeted Immunomodulators

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Abstract: The introduction of biologic and targeted immunomodulators is a significant breakthrough in the therapeutic area of various fields of medicine. The occurrence of serious infections, a complication of secondary immunosuppression associated with these agents, leads to increased morbidity and mortality. Implementing preventive strategies could minimize infection-related complications and improve therapeutic outcomes. The purpose of this review is to focus on current evident approaches regarding screening, monitoring, preventing (immunization and chemoprophylaxis), and management of infections in patients who are candidates for about 70 biologic and targeted immunomodulators. Recommendations are based on relevant guidelines, especially the ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document series published in 2018.

Keywords: biologic immunomodulators, targeted immunomodulators, immunization, chemoprophylaxis

Introduction

Biologic immunomodulators are biosimilar medications synthesized by living organisms structurally related to antibodies, interleukins, and receptors that specifically target oncogenic cells or immune system pathways.[1] Targeted immunomodulators such as BCR-ABL tyrosine kinase inhibitors, phosphatidylinositol-3-kinase inhibitor, bruton tyrosine kinase inhibitors, and mammalian target of rapamycin (mTOR) inhibitors are small molecules which affect intracellular signaling cascades that eventually modulate protein expression.[2]

The availability of biologic and targeted immunomodulators has revolutionized pharmacotherapy of diseases in diverse aspects of medicine, including onco-hematology, rheumatology, nephrology, transplantation, neurology, pulmonology, and dermatology. Despite their therapeutic benefit, concerns regarding the potential risk of infections have been a challenge for using these agents in clinical practice.[3] Severe infection is a significant cause of morbidity and mortality in patients treated with immunosuppressants. Most patients on immunomodulator drugs require long term therapies; however, a significant number of these patients do not receive appropriate preventive care regarding infections.[4]

Biologic and targeted immunomodulators are categorized into several pharmacologic classes. Unlike traditional immunosuppressants, immune suppression associated with these agents is specific to certain signals in the immune system, occasionally

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causing profound immune suppression mimicking primary immunodeficiency disorders.[5–7] Depending on their mechanism of action and impact on the immune system, the infection risk associated with these therapies varies among pharmacologic classes; some affect intracellular signaling pathways, some bind to receptors of cellular immunity while some others inhibit the actions of cytokines (Table 1).

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts Consensus have reviewed articles and made recommendations to instruct clinicians on the strategies to prevent and manage infections associated with biologic and targeted immunomodulators.[8–13] In this review, we aim to focus on evidence-based strategies according to the latest guidelines to provide practitioners guidance regarding screening, chemoprophylaxis, vaccination, and management of infections in patients on biologic and targeted immunomodulators.

Methods

We conducted a literature search in databases including Scopus, Medline, Embase, Cochrane Database Systematic Reviews and Google Scholar from January 2007 to August 2019 using the search terms related to each of the agents along with "infection", "vaccination", "screening", "prophylaxis", "monitoring", "immunization", "immune response", "treatment", and "management". Polyclonal antibodies (e.g., anti-thymocyte globulin, rozrolimupab), and monoclonal antibodies that lack prominent immunosuppressive effects (e.g., trastuzumab) were beyond the scope of our review and are not considered here. We included articles and guidelines from the latest updates of ESCMID, The Infectious Diseases Society of America (IDSA), The European League Against Rheumatism (EULAR), National Comprehensive Cancer Network (NCCN), American College of Rheumatology (ACR), American College of Gastroenterology (ACG), The American Association for the Study of Liver Diseases (AASLD), The Canadian Dermatology Association (CDA), European Conference on Infections in Leukaemia (ECIL), The Advisory Committee on Immunization Practices (ACIP), The American Society of Transplantation (AST), European Conference on Infections in Leukaemia (ECIL), The German Society of Hematology and Medical Oncology and the International Consensus Guidelines on the Management of Cytomegalovirus.[8–29] We also included recommendations from Uptodate online, the relevant review articles, expert opinions, and European Medicines Agency (EMA) drug labels, especially on subjects that the guidelines do not offer an opinion. The recommendations regarding screening for infections, immunization, prevention, and monitoring of infections in patients candidates for biologic and targeted immunomodulators were finally categorized by the class of immunosuppressive agents.

Results

Of the relevant articles we found, data were obtained from 31 guidelines as well as consensus recommendations and 17 review papers. Comprehensive recommendations were not found on subjects such as prophylactic measures for prevention of pneumocystis pneumonia in biologic therapy of rheumatologic diseases, screening of infections for patients undergoing basiliximab induction, preventive measures to prevent infections associated with abatacept, immunization in patients undergoing treatment with new generations of anti-CD20 monoclonal antibodies and late onset neutropenia associated with anti-CD20 monoclonal antibodies. Such data were obtained from expert opinions, review articles, the EMA drug labels and clinical trials. The recommendations regarding screening, prophylaxis, monitoring, and immunization of infections associated with biologic and targeted immunomodulators are summarized in Tables 2–5.

Discussion

The growing number of approved biologic and targeted immunomodulators on the market and their various approved and off-label indications explain the necessity to guide health care professionals in the prevention and management of infections and define the relative risk of particular infections associated with these agents. This study reviewed and summarized prevention strategies, including screening, monitoring, immunization, prophylaxis, and management of infections associated with about 70 biologic and targeted therapies based on relevant guidelines, especially ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus document series published in 2018.[8–13]

The Risk of Hepatitis B Virus (HBV) Reactivation

Extensive studies have shown that the risk of HBV reactivation is highest with anti-CD20 targeted agents including rituximab, ofatumumab, obinutuzumab,[27,30] and probably ocrelizumab.[31] These agents are associated with a significant risk of HBV reactivation in both HBs Ag-positive and HBs Ag-negative/anti-HBc-positive patients. Studies have shown that tenofovir and entecavir are significantly more effective than lamivudine

Table 1 Biologic and Targeted Immunomodulators Classification and Their Impacts on the Immune System

Biologic and Targeted Immunomodulators	Effect on the Immune System	Risk of Infections
TNF inhibitors *Infliximab, Adalimumab, Golimumab, Certolizumab, Etanercept*	Inactivation of CD4+/CD 8+ T cells; neutropenia	TB, HBV
Co-stimulation modulator *Abatacept*	Inhibition of APC function; inhibition of T cell stimulation; inhibition of B cell response	Not associated with increased risk of infection
IL-1 targeted agents *Anakinra, Canakinumab, Rilonacept*	↓ IL-1	TB
CD19 targeted agents *Blinatumomab, Inebilizumab*	↓ CD19 B Cells; ↓ plasmablasts; hypogammaglobulinemia	Limited data
CD22 targeted agents *Epratuzumab, Inotuzumab Ozogamicin, Moxetumomab Pasudotox*	Inhibition of B cell proliferation	Not associated with increased risk of infection
CD30 targeted agents *Brentuximab Vedotin*	Antibody-dependent cellular cytotoxicity; neutropenia	HZ, PCP, CMV, PML
CD38 targeted agents *Daratumumab, Isatuximab*	Complement-dependent cytotoxicity	VZV (probably)
CD40 targeted agents *Dacetuzumab, Lucatumumab*	↓B Cells; impairment in T cell function	CMV, PCP Cryptococcus, Cryptosporidium
CD319-targeted agent *Elotuzumab*	Lymphopenia	VZV
CCR4 targeted agent *Mogamulizumab*	Lymphopenia	HBV, HZ, CMV
Anti-CD20 monoclonal antibodies *Rituximab, Ibritumomab Tiuxetan, Ofatumumab, Ocrelizumab*	↓ CD20 B Cells; neutropenia; hypogammaglobulinemia	HBV, HCV, VZV, PML, PCP, Enterovirus
Anti-CD52 monoclonal antibody *Alemtuzumab*	Inhibition of the action of CD4+ T Cells, B Cells epithelial cells, macrophages, and monocytes	HSV, PCP, TB, VZV, HPV
Component 5 (C5) targeted agent *Eculizumab*	Complement-mediated cytotoxicity	*Neisseria, H. influenzae, S. pneumonia,* Aspergillosis
BAFF inhibitor *Belimumab*	Reduction of B cell population	PML (Rare)
α4-integrin targeted agent *Natalizumab*	Targeting α4-integrin; inhibition of translocation of leukocytes in BBB	PML
α4-integrin targeted agent *Vedolizumab*	Targeting α4β7 integrin; inhibition of translocation of leukocytes in the mucosal membrane of the small intestine	Enteric bacterial infections (probably)
IgE targeted agent *Omalizumab*	Inhibition of the activity of mast cells, basophils, plasma cells, and eosinophils	Helminth infections
IL-5 targeted agent *Mepolizumab, Reslizumab*	↓ IL-5; inhibition of eosinophil differentiation	Not associated with increased risk of infection

(*Continued*)

Table 1 (Continued).

Biologic and Targeted Immunomodulators	Effect on the Immune System	Risk of Infections
IL-12 and IL-23 targeted agent *Ustekinumab*	Inhibition of action of NK Cells, Th17, Th1 CD4+ T-cells, ↓ IFNγ	TB, HBV (intracellular pathogens)
IL-17 targeted agents *Secukinumab, Ixekizumab, Brodalumab*	Inhibition of macrophage stimulation and neutrophil chemotaxis	Mucocutaneous candidiasis
Proteasome inhibitors *Bortezomib, Carfilzomib, Ixazomib*	Inhibition of the proteasome pathway Inhibition of the activity of T cell	HZ, VZV
BCR-ABL tyrosine kinase inhibitors *Imatinib, Dasatinib, Nilotinib, Ponatinib, Bosutinib*	Neutropenia; Impairment of B cell response; Reduced CD4+ and CD8+ T cell stimulation	HBV, CMV, EBV
mTOR inhibitors *Sirolimus, Everolimus, Temsirolimus*	Reduced neutrophil migration; Inhibition of dendritic cell differentiation; Inhibition of T cell stimulation	Bacterial infections TB, HBV, HZ
JAK inhibitors *Tofacitinib, Ruxolitinib*	Inhibition of differentiation of TH1 and TH17 cells	Bacterial infections, PCP, CMV, HZ, EBV Invasive fungal infections
Sphingosine 1-phosphate receptor modulator *Fingolimod*	Lymphopenia ↓ CD 4+ and CD8+ T Cells in CSF	HZ, PML, Cryptococcus
IL-6 targeted agents *Tocilizumab, Siltuximab*	Neutropenia	TB, NTM, HBV, PCP, invasive candidiasis
Agents targeting PD-1/PD-L1 *Nivolumab, Pembrolizumab*	Increase in activity of T cells	Not associated with increased risk of the infection itself
Agents targeting CTLA-4 *Atezolizumab, Ipilimumab, Tremelimumab*	Increase in activity of T cells	Not associated with increased risk of the infection itself
Phosphatidylinositol-3-kinase inhibitor *Idelalisib*	Reduced chemotaxis and cytokine production; neutropenia	PCP, CMV
Bruton Tyrosine kinase inhibitors *Ibrutinib, Acalabrutinib*	Inhibition of B cell proliferation; hypogammaglobulinemia	Bacterial infections
Monoclonal antibody targeting CD25 *Basiliximab*	Inhibition of the action of T cells	PCP, CMV

Abbreviations: APC, antigen-presenting cell; BAFF, B-cell activating factor, CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; *H. influenzae, Haemophilus influenzae*, HPV, human papillomavirus; HSV, *Herpes* simplex virus; HZ, herpes zoster; IFNγ, interferon-gamma; IL-1, interleukin-1; IL-5, interleukin-5; NTM, Nontuberculous mycobacteria; PCP, *Pneumocystis carinii* pneumonia; PML, progressive multifocal leukoencephalopathy; TNF, tumor necrosis factor; TB, tuberculosis; VZV, varicella-zoster virus.

in preventing HBV reactivation in patients on anti-CD20 monoclonal antibodies.[32,33] Therefore, ESCMID recommends either tenofovir or entecavir-based regimens for antiviral therapy in both active and occult hepatitis B patients who are candidates for anti-CD20 targeted agents.[10]

HBs Ag-positive patients are at high risk of HBV reactivation with alemtuzumab. Also, HBs Ag-negative/anti-HBc-positive patients are moderate to high risk for reactivation of hepatitis B; Therefore, ESCMID recommends that all patients with active hepatitis B should receive antiviral prophylaxis. Individuals with occult infection could either receive prophylaxis or be monitored for reactivation of HBV based on the indication of alemtuzumab and concomitant use of corticosteroids in certain clinical conditions (e.g., transplantation, multiple sclerosis)[10,30]

Anti-TNF monoclonal antibodies are considered as moderate to high risk for reactivation of hepatitis B in active infection and moderate risk for occult infection. The risk of

Table 2 Evidence and Recommendations on Screening of Infections in Patients Candidates for Biologic and Targeted Immunomodulatory Therapies

TNF inhibitors	Perform PPD and IGRA; Chest X-ray; smear and culture of the sputum.[13] Check HBs Ag and anti-HBc. Check anti-HBs for immunization status.[13] Screening pap smear abnormalities could be considered.[42]
IL-1-targeted agents	Perform PPD and IGRA; Chest X-ray; smear and culture of the sputum.[8]
CD19-targeted agents	Check baseline immunoglobulin levels.[10]
CD22-targeted agents	Check HBs Ag and anti-HBc; Check anti HBS Ab for immunization status; Check HBV viral load if necessary.[12]
CD30-targeted agent	Check HBs Ag and anti-HBc; Check anti HBS Ab for immunization status; Check HBV viral load if necessary.[12]
CD-38-targeted agents	Check VZV serology.[12] Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status. Check HBV viral load if necessary.[12]
CD-319-targeted agent	Check VZV serology.[12]
CCR4-targeted Agent	Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status. Check HBV viral load if necessary.[12]
Anti-CD20 monoclonal antibodies	Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status. Check HBV viral load if necessary.[10] Check baseline immunoglobulin levels.[22,83]
Anti-CD52 monoclonal antibody	Perform PPD and IGRA; Chest X-ray, smear, and culture of sputum.[10] Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status. Check HBV viral load if necessary.[10] Check HCV Ab.[10] Check VZV Serology.[10] Yearly screening of HPV is recommended in women.[10]
T-Cell Co-stimulation Blocker	Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status. Check HBV viral load if necessary.[30]
Monoclonal antibodies targeting α4-integrin and CD 11a	Brain MRI could be considered.[11] Checking Anti-JCV IgG is recommended.[11]
IgE targeted agent	Stool exam; Serologic test for *Strongyloides stercoralis* is recommended.[8]
IL-12 and IL-23-targeted agent	Perform PPD and IGRA; Chest X-ray; smear and culture of sputum.[8] Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status. Check HBV viral load if necessary.[8]
IL-17-targeted agents	Perform PPD and IGRA; Chest X-ray; smear and culture of the sputum.[8]
Component 5 (C5)-targeted agents	Real-time PCR for detection of *Neisseria gonorrhoeae* in highly sexually active patients[8]
IL-6-targeted agents	Perform PPD; IGRA; Chest X-ray; smear and culture of sputum.[8] Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status.[8]
Proteasome inhibitors	Check VZV serology.[11]
Agents targeting PD-1/PD-L1	Perform PPD and IGRA; Chest X-ray; smear and culture of sputum.[11] Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status.[11] Check HCV Ab.[11]
Monoclonal antibodies against CTLA-4	Perform PPD and IGRA; Chest X-ray; smear and culture of sputum.[11] Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status.[11] Check HCV Ab.[11]
BCR-ABL Tyrosine kinase inhibitors	Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status. Check HBV viral load if necessary.[9]
mTOR Inhibitors	Perform PPD and IGRA; Chest X-ray; smear and culture of sputum.[9] Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status.[9]

(*Continued*)

Table 2 (Continued).

JAK inhibitors	Perform PPD and IGRA; Chest X-ray; Smear and culture of sputum.[9] Check HBs Ag and anti-HBc. Check anti HBS Ab for immunization status.[9]
Sphingosine 1-phosphate receptor modulator	Check baseline CBC.[11] Check VZV serology.[11]
Monoclonal antibody targeting CD25	Perform PPD and IGRA; Chest X-ray or Chest CT scan; smear and culture of sputum.[29] Serologic test for CMV IgG, EBV antibody panel, HSV and VZV IgG, HBsAg, HBcAb, HBsAb, HCV IgG, HIV 1 and 2 antibodies, RPR or TP-PA test for syphilis is recommended according to transplantation protocols.[84]

Abbreviations: Ab, antibody; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HBs Ag, hepatitis B surface antigen; HIV, human immunodeficiency viruses; HPV, human papillomavirus; IGRA, interferon-gamma release assay; IL-1, interleukin-1; IL-5, interleukin-5; IL-6, interleukin-6; IL-12, interleukin-12; IL-17, interleukin-17; IL-23, interleukin-23; JAK, Janus kinase; JCV, John Cunningham virus; MRI, Magnetic resonance imaging; mTOR, mammalian target of rapamycin; PCR, Polymerase chain reaction; PD1, programmed death 1; PD-L 1Programmed death-ligand 1; PPD, purified protein derivative; PML, progressive multifocal leukoencephalopathy ; RPR, rapid plasma reagin; TNF, tumor necrosis factor; TP-PA, *Treponema pallidum* particle agglutination; VZV, varicella-zoster virus.

HBV reactivation in HBsAg-positive patients is moderate with etanercept, and HBsAg-negative/anti-HBc-positive patients are probably at low risk for seroconversion with etanercept. Accordingly, ESCMID recommends antiviral prophylaxis with either tenofovir or entecavir only for HBsAg-positive patients under TNF inhibitors.[13]

Tocilizumab, abatacept, ustekinumab, mogamulizumab, and BCR-ABL tyrosine kinase inhibitors are associated with a moderate risk of HBV reactivation.[30] Data on the risk of HBV reactivation with tofacitinib is limited; In a study, reactivation of hepatitis B occurred in 2 of 4 HBs Ag positive patients.[34] Reactivation of HBV did not occur in any of the HBs Ag-negative/anti-HBc-positive patients. Few case reports have demonstrated fatal HBV reactivation in HBs Ag-positive patients receiving 5–10 mg/day everolimus for renal cell carcinoma and breast cancer.[35,36] Therefore, ESCMID recommends antiviral prophylaxis only in HBs Ag-positive patients treated with mTOR inhibitors, janus kinase (JAK) inhibitors, BCR-ABL tyrosine kinase inhibitors, IL-6 targeted immunomodulators, ustekinumab, and mogamulizumab. Pre-emptive antiviral prophylaxis is reasonable in occult HBV infections during treatment with these agents.[8–13]

The Risk of *Pneumocystis Carinii* Pneumonia (PCP)

The greatest risk of PCP infection is attributed to alemtuzumab, and universal prophylaxis is required in solid organ transplant recipients and patients with hematologic diseases who have received this agent. Limited data suggest the risk of PCP with bortezomib in multiple myeloma patients treated with high dose corticosteroids; however, the overall risk is low.[37,38] The incidence of PCP with TNF inhibitors, tocilizumab, and rituximab is also low; however, several studies have demonstrated that the risk of infection is increased in particular conditions including age >65 years, concurrent long-term corticosteroid use (e.g., ≥ 15 mg/day prednisolone for more than four weeks), and co-existence of either pulmonary diseases or underlying granulomatosis with polyangiitis.[38,39] Comparative studies have shown a greater risk with TNF inhibitors, particularly infliximab than tocilizumab.[40] Eighteen cases of ibrutinib associated PCP have been published; in most of them, the patients were neutropenic.[41] Currently, trimethoprim/sulfamethoxazole is the drug of choice for the primary prophylaxis of PCP in different clinical conditions such as hematological malignancies and stem cell transplantation. Second-line choices for PCP prophylaxis in the case of trimethoprim/sulfamethoxazole intolerance include pentamidine inhalation, oral dapsone, and oral atovaquone.[26] These recommendations regarding PCP prophylaxis can be extrapolated to the setting of biologic and targeted immunomodulators.

The Risk of Progressive Multifocal Leukoencephalopathy (PML)

The incidence of PML appears to be greatest with monoclonal antibodies targeting α4-integrin. PML associated with efalizumab and natalizumab has been reported 1 in 300 patients and 1 in 1000 patients, respectively.[42,43] In contrast, to date, no case of PML has been reported with vedolizumab.[44] Fifteen case reports of PML have been reported in patients treated with fingolimod. Treatment duration, age, and JC virus (JCV) antibody titer could be associated with the occurrence of fingolimod-induced PML.[45,46] Cases of PML have been reported with anti-CD20 monoclonal antibodies (15 cases with rituximab and

Table 3 Evidence and Recommendations on the Prevention and Management of Infections in Patients Candidates for Biologic and Targeted Immunomodulatory Therapies

TNF Inhibitors	Treatment with TNF inhibitors should be started at least one month after initiation of the anti-TB regimen (isoniazid, rifampin, or the combination of isoniazid and rifampin). TNF inhibitors should be discontinued if active tuberculosis occurs.[13]
	Tenofovir or Entecavir is recommended for infected HBs Ag-positive patients at least two weeks before the initiation of TNF inhibitors. Antiviral agents should be continued for at least six months after the withdrawal of TNF inhibitors.[13,85] Antiviral prophylaxis is not recommended in HBs-Ag negative and anti-HBc-positive patients treated with TNF inhibitors.[13] Tenofovir or Entecavir is recommended in the case of HBV reactivation. TNF inhibitors are not recommended in the acute phase of hepatitis B, chronic untreated hepatitis B, and HBV infected patients with Child-Pugh B and C.[86]
	Some experts consider PCP prophylaxis for patients with rheumatologic diseases under TNF inhibitors who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
IL-1-targeted agents	In the case of latent tuberculosis, treatment with isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months is recommended.[8]
	Some experts consider PCP prophylaxis for patients with rheumatologic diseases under IL-1 targeted agents who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
CD22-targeted agents	Antiviral treatment is recommended in HBS-Ag positive patients who are candidates for CD-22 targeted agents.[12] Monitoring of HBV viral load is recommended in HBS-Ag negative and anti-HBc-positive patients.[12]
CD30-targeted agent	Both HBs Ag positive and HBs Ag negative anti-HBc positive patients should receive antiviral prophylaxis before the administration of brentuximab vedotin.[12]
	HSV prophylaxis is recommended in patients on brentuximab vedotin.[12]
	PCP prophylaxis is recommended in patients on brentuximab vedotin.[12]
	Secondary CMV prophylaxis is recommended in patients with a history of CMV disease who are candidates for brentuximab vedotin rechallenge.[12]
CD38-targeted agents	Antiviral treatment could be considered in HBS-Ag positive patients who are candidates for CD-38 targeted agents.[12] Monitoring of HBV viral load is recommended in HBS-Ag negative and HBV-Ab positive patients.[12]
	HSV prophylaxis is recommended in VZV seropositive patients at least one week before the administration of daratumumab and continued for 12 weeks after discontinuation[12]
	PCP prophylaxis is recommended in patients receiving concomitant glucocorticoids, and CD-38 targeted agents.[12]
CD40-targeted agents	PCP prophylaxis should be considered in patients on CD-40 targeted agents.[12]
	Regular monitoring of CMV PCR and signs, as well as symptoms of CMV disease, are recommended in patients on CD-40 targeted agents.[12]
CD319-targeted agents	HSV prophylaxis is recommended in VZV seropositive patients.[12]
	PCP prophylaxis is recommended in patients receiving concomitant glucocorticoids and elotuzumab.[12]
CCR4-targeted agent	PCP prophylaxis is recommended in patients on mogamulizumab.[12]
	HSV prophylaxis is recommended in patients on mogamulizumab.[12]
	Tenofovir or entecavir is recommended in HBs Ag positive patients who are candidates for treatment with mogamulizumab.[12] HBV viral load should be monitored in HBs Ag-negative/anti-HBc-positive patients who are candidates for treatment with mogamulizumab. Prophylaxis with lamivudine could be considered in HBs Ag negative and anti-HBc-positive patients.[12]

(*Continued*)

Table 3 (Continued).

Anti-CD20 monoclonal antibodies	HBs Ag-positive patients should receive antiviral prophylaxis (preferably tenofovir or entecavir) before the administration of anti-CD20 monoclonal antibodies. HBs Ag-negative/anti-HBc-positive patients should receive antiviral prophylaxis (could be lamivudine) before administration of anti-CD20 monoclonal antibodies. Antiviral agents should be continued for at least 12–18 months after the completion of anti-CD20 monoclonal antibody treatment and if viral load remains undetectable.[10,14] HBV viral load should be monitored for 12 months after discontinuation of antiviral prophylaxis.[10] Anti-CD20 monoclonal antibodies should be discontinued if reactivation of hepatitis B occurs. ECIL and ESCMID guidelines recommend PCP prophylaxis in patients receiving anti-CD20 monoclonal antibodies and corticosteroids equivalent to ≥ 20 mg prednisolone for more than four weeks.[10,26] ECIL and NCCN guidelines recommend PCP prophylaxis in CLL patients treated with Rituximab/Ofatumumab/Obinutuzumab, and purine analogs/high dose methylprednisolone; Fludarabine-Cyclophosphamide-Rituximab (FCR) and Pentostatin-Cyclophosphamide-Rituximab (PCR) regimens for ≥ six months after completion of treatment.[14,26] Some experts consider PCP prophylaxis for granulomatosis polyangiitis patients on rituximab and patients with rheumatologic diseases who have underlying pulmonary diseases.[39] PCP prophylaxis is optional for patients undergoing R-CHOP 14 regimen.[26]
	The third international consensus on CMV prophylaxis in solid organ transplant weakly recommends CMV prophylaxis in donor/recipient seropositive patients who are candidates for rituximab therapy during treatment of solid organ transplant rejection or desensitization protocol for up to 6 months.[15]
	Antiviral prophylaxis against HSV and VZV is recommended in CLL patients during therapy with Rituximab/Ofatumumab/Obinutuzumab, and fludarabine/high dose methylprednisolone; Fludarabine-Rituximab (FR), Fludarabine-Cyclophosphamide-Rituximab (FCR) and Pentostatin-Cyclophosphamide-Rituximab (PCR) for 6–12 months after discontinuation of the chemotherapy regimen.[87]
Anti-CD52 monoclonal antibody	In the case of latent tuberculosis patients undergoing alemtuzumab therapy, concomitant treatment with isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months is recommended.[10]
	In the case of latent tuberculosis, tenofovir or entecavir is recommended in all HBs Ag positive patients who are candidates for treatment with alemtuzumab. Antiviral agents should be continued for at least 6–12 months after the last dose of alemtuzumab.[10] HBV viral load should be monitored in HBs Ag-negative and anti-HBc positive patients who are candidates for treatment with alemtuzumab. Prophylaxis with lamivudine could be considered in HBs Ag negative and Anti HBc-positive patients.[10]
	PCP prophylaxis is recommended in patients treated with alemtuzumab for hematologic malignancies and indications other than multiple sclerosis for at least 2–6 months and should be continued until CD_4^+ ≥ 200 cells/μL.[26] PCP infection associated with alemtuzumab used in multiple sclerosis is extremely rare, and prophylaxis is not routinely recommended.[64] If alemtuzumab is administered for solid organ transplantation induction, the American Society of Transplant recommends PCP prophylaxis for at least 6–12 months after induction. Life long duration of PCP prophylaxis may be considered for lung and small bowel transplant or patients with chronic CMV infection or prior history of PCP infection.[17] If alemtuzumab is administered for conditioning of allogeneic hematopoietic stem cell transplantation, PCP prophylaxis is recommended for at least six months.[14]
	CMV prophylaxis should be considered in hematologic malignancies with the initiation of each cycle of alemtuzumab therapy and continued for at least two months until $CD4^+$≥200 cells/μL.[14] If alemtuzumab is administered for solid organ transplantation induction, the third international consensus on CMV in solid organ transplant recommends CMV prophylaxis for six months in CMV IgG Donor+/Recipients± for kidney transplants, 3–6 months for liver, heart, pancreas recipients and 6–12 months for lung recipients.[15] CMV prophylaxis is not currently required in multiple sclerosis patients; CMV DNAemia testing is recommended in the presence of signs and symptoms of mononucleosis. Some experts recommend weekly monitoring of CMV-DNAemia for the first month after initiating alemtuzumab.[64]

(*Continued*)

Table 3 (Continued).

	If alemtuzumab is administered for induction of allogeneic hematopoietic stem cell transplantation, VZV prophylaxis is recommended for one year.[14] HSV prophylaxis should be considered in hematologic malignancies and other off-label indications with the initiation of each cycle of alemtuzumab therapy and continued for at least two months until $CD4^+$≥200 cells/μL.[10,14] HSV prophylaxis should be considered in multiple sclerosis patients with the initiation of each cycle of alemtuzumab therapy and continued for at least two months until $CD4^+$≥200 cells/μL.[14,64] If alemtuzumab is administered for solid organ transplantation induction immunosuppressive therapy, HSV/VZV prophylaxis is recommended in CMV IgG Donor-/Recipient- (low-risk CMV) transplants.[15]
	Listeria- and toxoplasma-free diet should be recommended in patients under alemtuzumab therapy.[10]
T-Cell Co-stimulation Blocker	Antiviral treatment is recommended in HBs Ag- positive patients who are candidates for abatacept therapy.[30] Monitoring of HBV viral load is recommended in HBsAg-negative and anti-HBc- positive patients.[30]
	Some experts consider PCP prophylaxis for patients with rheumatologic diseases under abatacept who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
Agent targeting B-cell activating factor	Some experts consider PCP prophylaxis for patients with rheumatologic diseases under abatacept who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
IgE-targeted agent	In the case of parasitic infections, patients should be treated with a specific antiparasitic agent prior to omalizumab administration.[8]
IL-5-targeted agents	Some experts recommend PCP prophylaxis in Eosinophilic Granulomatosis with Polyangiitis (EGPA) patients on IL-5 targeted agents.[39]
IL-12 and IL-23-targeted agent	In the case of latent tuberculosis, treatment with isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months could be considered.[8]
	Antiviral treatment is recommended in HBS-Ag positive patients who are candidates for ustekinumab therapy.[8] Monitoring of HBV viral load is recommended in HBS-Ag negative and HBV-Ab positive patients.[8]
	Some experts consider PCP prophylaxis in rheumatologic disease patients on ustekinumab who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
IL-17-targeted agents	In the case of latent tuberculosis, treatment with isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months could be considered.[8]
	Some experts consider PCP prophylaxis in rheumatologic disease patients on secukinumab who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
Component 5 (C5)-targeted agents	Ciprofloxacin 500 mg Bid or penicillin V 250 mg Bid orally should be administered for at least four weeks after completion of vaccination preferably until antibody titer reaches protective.[8]
	The third international consensus on CMV in solid organ transplant weakly recommends CMV prophylaxis in donor/recipient seropositive patients who are candidates for eculizumab therapy during and up to 6 months after treatment of solid organ transplant rejection.[15]
IL-6-targeted agents	In the case of latent tuberculosis, treatment with isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months could be considered.[8]
	Antiviral treatment is recommended in HBsAg positive patients who are candidates for IL-6 targeted agents.[8] Monitoring of HBV viral load is recommended in HBs Ag-negative/anti-HBc positive patients.[8]
	Some experts recommend consideration of PCP prophylaxis in rheumatologic disease patients on tocilizumab who have underlying pulmonary diseases or receiving ≥ 15 mg/day prednisolone for more than four weeks.[39]
Proteasome inhibitors	HSV/VZV prophylaxis is recommended in VZV seropositive patients at least four weeks after discontinuation of therapy.[11]
	PCP prophylaxis could be considered in multiple myeloma patients treated with high dose corticosteroids.[11]

(*Continued*)

Table 3 (Continued).

	The third international consensus on CMV prophylaxis in solid organ transplant weakly recommends CMV prophylaxis in donor/recipient seropositive patients who are candidates for bortezomib therapy during treatment of solid organ transplant rejection or desensitization protocol and up to 6 months later.[15]
Agents targeting PD-1/PD-L1 and agents targeting CTLA-4	Autoimmune manifestations of PD-1/PD-L1 targeted and CTLA-4 blockade agents may require treatment with corticosteroids or TNF inhibitors. ECIL and ESCMID experts recommend PCP prophylaxis in patients treated with corticosteroids equivalent to ≥ 20 mg prednisolone for more than four weeks.[11,88] The Society for Immunotherapy of Cancer recommends PCP prophylaxis in patients treated with corticosteroids equivalent to ≥ 30 mg prednisolone for more than three weeks.[88]
	In the case of latent tuberculosis, treatment with isoniazid or rifampin is recommended in patients treated with anti-PD-1/CTLA-4 blocking agents and TNF inhibitors. Antiviral prophylaxis against hepatitis B is recommended if necessary in patients treated with anti-PD-1 and TNF inhibitors.[11]
	Antiviral prophylaxis against hepatitis B is recommended if necessary in patients treated with anti-PD-1/CTLA-4 blocking agents and TNF inhibitors.[11]
BCR-ABL Tyrosine kinase inhibitors	Antiviral agent against hepatitis B is recommended for HBV infected HBs Ag-positive before administration of BCR-ABL tyrosine kinase inhibitors.[9] HBV viral load should be monitored in HBs Ag-negative/anti-HBc-positive patients who are candidates for treatment with BCR-ABL tyrosine kinase inhibitors.[9]
mTOR inhibitors	In the case of latent tuberculosis, treatment with isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months could be considered.[9]
	Antiviral agents could be considered in chronic HBV–infected patients.[9]
JAK inhibitors	In the case of latent tuberculosis, treatment with isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months should be considered.[9]
	Antiviral prophylaxis is recommended in HBS-Ag positive patients.[9] Monitoring of viral load is recommended in HBsAg-negative/anti-HBc-positive patients.[9]
	PCP prophylaxis could be considered in patients receiving a high dose of JAK inhibitors, and concomitant corticosteroid therapy, and lymphopenic patients.[9]
Sphingosine 1-phosphate receptor modulator	Acyclovir/Valacyclovir prophylaxis could be considered for patients treated with corticosteroid pulse beyond 3–5 days and fingolimod.[63]
Bruton Tyrosine kinase inhibitors	PCP prophylaxis is recommended in CLL patients treated with ibrutinib in the presence of additional risk factors, including concomitant fludarabine or high dose corticosteroid therapy.[9,87]
Phosphatidylinositol-3-kinase inhibitors	PCP prophylaxis is recommended in CLL patients who are candidates for idelalisib therapy up to 2–6 months after discontinuation.[9]
Monoclonal antibody targeting CD25	In the case of latent tuberculosis, treatment with isoniazid for nine months is recommended. The recipients who have received an organ from donors with latent tuberculosis should be considered for treatment with isoniazid for nine months.[29] Recipients with active tuberculosis should be treated prior to transplantation.[29] PCP prophylaxis is recommended in transplant recipients who have received basiliximab induction for at least 6–12 months.[89] CMV prophylaxis/preemptive therapy is recommended in Donor+/Recipient- liver and all kidney transplant recipients for 3–6 months, respectively.[15]

Abbreviations: CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; ECIL, European conference on infections in leukemia; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IgE, Immunoglobulin E; IgG, Immunoglobulin G; IL-1, interleukin-1; IL-5, interleukin-5; IL-6, interleukin-6; IL-12, interleukin-12; IL-17, interleukin-17; IL-23, interleukin-23; HBs Ag, hepatitis B surface antigen; HBV, hepatitis B virus; HSV, Herpes simplex virus; JAK, Janus kinase; mTOR, mammalian target of rapamycin; NCCN, National Comprehensive Cancer Network, PCP, *Pneumocystis carinii* pneumonia; PCR, Polymerase chain reaction; PD1, programmed death 1; PD-L1, Programmed death-ligand 1; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride (doxorubicin hydrochloride), vincristine; TNF, tumor necrosis factor; VZV, varicella-zoster virus.

Table 4 Evidence and Recommendations on Monitoring of Patients on Biologic and Targeted Immunomodulatory Therapies

CD19-targeted agents	Risk of neutropenia: CBC monitoring is recommended[10] If neurologic or cognitive impairment occurred, MRI should be considered, and CSF for JC virus DNA PCR should be tested.[10] Monitoring for signs and symptoms of catheter-related infections should be considered in patients receiving blinatumomab.[10]
CD30-targeted agents	Risk of neutropenia: CBC monitoring is recommended.[12] If neurologic or cognitive impairment occurred, MRI should be considered and CSF for JC virus DNA PCR should be tested.[12] Regular monitoring of CMV PCR and signs and symptoms of CMV disease is recommended in patients on brentuximab vedotin.[12]
CD38-targeted agents	Risk of neutropenia: CBC monitoring is recommended.[12]
CD40-targeted agents	Risk of neutropenia: CBC monitoring is recommended.[12]
CD319-targeted agents	Risk of lymphopenia: CBC monitoring is recommended.[12]
CCR4-targeted agents	Monitoring of lymphocyte count is recommended.[12] Regular monitoring of CMV PCR and signs and symptoms of CMV disease is recommended in patients on mogamulizumab.[12]
Anti-CD20 monoclonal antibodies	If neurologic or cognitive impairment occurs, MRI should be considered, and CSF for JC virus DNA PCR should be tested. Monitor immunoglobulin levels during treatment with anti-CD20 monoclonal antibodies.[22,90] Immunoglobulin levels are best to be monitored every 6–12 months and at least up to 1 year after discontinuation of rituximab. Long term monitoring of IgG levels in patients with bronchiectasis or those treated with immunosuppressive agents is reasonable.[22] Immunoglobulin replacement therapy with 0.4g/kg/month (SC or IV) could be considered in case of persistent infections associated with low IgG level; in patients with low IgG level and concomitant comorbidities (neutropenia, bronchiectasis) or concomitant use of immunosuppressive agents, including corticosteroids.[22] Late-onset neutropenia episodes are mostly mild and do not predispose patients to infections as much as hypogammaglobulinemia.[91,92] The optimal approach in patients with a history of late-onset neutropenia is unclear; however, re-treatment with rituximab has been safe in most cases.[92] The role of GCSF in anti-CD20 associated neutropenia is not clearly defined; the decision should be made on a case-by-case basis.[91] Limited data have demonstrated the occurrence of late-onset neutropenia with other anti-CD20 therapies including obinutuzumab, ofatumumab, and ocrelizumab.[93]
T-Cell Co-stimulation blocker	Brain MRI and CSF analysis for JCV PCR should be obtained if neurologic impairment (visual disturbance, progressive paresis, cognitive impairment) occurs.[42]
Agent targeting B-cell activating factor (BAFF, BLyS)	Brain MRI and CSF analysis for JCV PCR should be obtained if neurologic impairment (visual disturbance, progressive paresis, cognitive impairment) occurs.[42]
Monoclonal antibody targeting α4-integrin and CD 11a	After the completion of the first year of therapy, JCV PCR should be tested every three months in JCV-seronegative patients treated with natalizumab.[11] JCV PCR should be tested every six months in JCV-seropositive patients with IgG antibody index ≤ 1.5.[11] The risks versus benefits of therapy should be considered in JCV seropositive patients with IgG antibody index ≥ 1.5 and JCV seropositive patients who have received natalizumab for more than 48 weeks.[11] For the early diagnosis of PML, the high sensitive assay should be utilized to detect JCV DNA. Negative CSF JCV PCR does not exclude PML even in repeated lumbar punctures.[44] Monitoring of signs and symptoms of PML (ataxia, dysarthria, motor weakness, and cognitive impairment) should be considered for at least six months after discontinuation of natalizumab.[11] Brain MRI and CSF analysis for JCV PCR should be obtained if neurologic impairment (visual disturbance, progressive paresis, cognitive impairment) occurs. Natalizumab should be discontinued if PML develops.[11] No cases of PML have been observed with vedolizumab in the clinical trials so far.[42]

(*Continued*)

Table 4 (Continued).

Component 5 (C5) targeted agent	Patients treated with eculizumab should be monitored for signs and symptoms of meningococcal disease (headache, nausea, vomiting, fever, rash, confusion, flu-like symptoms, photophobia, arthralgia, tenosynovitis).[8]
BCR-ABL tyrosine kinase Inhibitors	Weekly CMV PCR could be considered for HSCT patients on dasatinib.[9]
JAK inhibitors	Lymphocyte and neutrophil count should be monitored while treatment with tofacitinib; discontinue tofacitinib if lymphocyte count< 500 cells/mm^3 or ANC < 500 cells/mm^3.[94] Neutrophil count should be monitored while treatment with ruxolitinib. Interrupt treatment with ruxolitinib if ANC < 500 cells/mm^3.[95] Monitor for signs and symptoms of HSV infections. In case of mild Herpes Zoster infection in inflammatory bowel disease patients, some experts recommend holding tofacitinib until resolution of infection; in disseminated Herpes Zoster infections, alternative therapies could be considered.[96]
Sphingosine 1-phosphate receptor modulator	CBC should be monitored during therapy. Fingolimod should be interrupted in patients with absolute lymphocyte count < $0.2*10^9$ /l.[97] Cases of cryptococcal meningitis and PML have been reported in patients receiving fingolimod. Monitor for signs and symptoms (ataxia, dysarthria, motor weakness, cognitive impairment, headache, photosensitivity, and personality changes).[11] Screening for pap smear abnormalities could be considered during treatment with fingolimod.[97]
Bruton Tyrosine kinase inhibitors	If neurologic or cognitive impairment occurs during treatment with ibrutinib, MRI should be considered and CSF for JC virus DNA PCR should be tested.[9]
Phosphatidylinositol-3-kinase inhibitors	Monitoring for CMV PCR is recommended in seropositive patients on idelalisib. If signs and symptoms of CMV disease (leukopenia, thrombocytopenia, colitis, pneumonitis, nausea, vomiting, diarrhea, or abdominal pain) occurred during treatment with an idelalisib, check for CMV PCR. Idelalisib should be discontinued in case of severe diarrhea, significant elevations in hepatic enzymes, or pneumonitis.[9]

Abbreviations: ANC, absolute neutrophil count; BAFF, B-cell activating factor; BLyS, B Lymphocyte Stimulator; CBC, complete blood cells; CSF, cerebrospinal fluid; CMV, cytomegalvirus; GCSF, Granulocyte-colony stimulating factor; HSCT, Hematopoietic stem cell transplantation; MRI, magnetic resonance imaging; JCV, John Cunningham virus; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy.

5 cases with ocrelizumab); however, most of these cases could be attributed to previous natalizumab or fingolimod therapy. Therefore, it is reasonable to monitor MRI for signs and symptoms of PML (e.g., visual disturbance, progressive paresis, cognitive impairment) when switching from either natalizumab or fingolimod to anti-CD20 therapies.[47] Currently, there is no standard and specific therapy for PML. The offending agent should be discontinued permanently. Plasma exchange (e.g., 3–5 exchanges over 5 to 8 days) has been used for the reversal of natalizumab-associated PML. However, this modality often leads to immune reconstitution inflammatory syndrome (IRIS) phenomenon, which is a neurological deterioration associated with brain swelling and risk of herniation.[48]

The Risk of Latent Tuberculosis

Rheumatoid arthritis itself is associated with increased risk of tuberculosis reactivation up to 3.17 times. In patients with rheumatoid arthritis treated with TNF inhibitors, the risk is increased up to 17 fold than the general population.[49] When compared with etanercept, other anti-TNF monoclonal antibodies are associated with a statistically significant higher risk of tuberculosis reactivation. Ai et al. demonstrated that the risk of tuberculosis reactivation with adalimumab and infliximab is 3.88 and 2.78 times more than etanercept, respectively. The effect of anti-TNF monoclonal antibodies on inducing T-cell apoptosis, complement-dependent cytotoxicity, and pharmacokinetic properties could explain the higher potential of adalimumab and infliximab over etanercept in reactivating latent tuberculosis.[19,50] Statistical difference between infliximab and adalimumab has not been found; however, the risk of latent tuberculosis reactivation with infliximab was 1.28 times more than adalimumab.[49] Another meta-analysis showed that the incidence rate of

Table 5 Evidence and Recommendations on Immunization of Patients on Biologic and Targeted Immunomodulatory Therapies

TNF inhibitors	Immunization with inactivated vaccines during therapy with TNF inhibitors is recommended.[98] Non-immunized patients who were at risk should ideally complete the HBV vaccine series ≥ two weeks prior to the initiation of TNF inhibitors.[16] The EMA label of TNF inhibitors recommends that infants born from mothers on TNF inhibitors receive live vaccines after ≥ five months of last adalimumab injection,[99] ≥ four months of last etanercept injection,[100] ≥ six months of last golimumab injection,[101] ≥ five months after certolizumab injection[102] and ≥ six months after birth in infliximab treated mothers;[66] however, vaccine response to *Haemophilus influenzae* in infants born from mothers on biologic therapies including infliximab, adalimumab, certolizumab pegol, and golimumab is not impaired. The Canadian Dermatology Association strongly recommends routine immunization schedule for infants exposed to biologic agents during pregnancy and lactation.[103] EULAR recommends that live attenuated vaccines should be avoided during the first six months of life in newborns exposed to TNF inhibitors after 22 weeks of gestation.[98]
IL-1-targeted agents	In patients receiving IL-1 targeted agents, vaccination against *Pneumococcus* and *Haemophilus influenzae* type B should be considered. Infants born from mothers on canakinumab could receive live vaccines after ≥ 16 weeks of the last injection.[68] If a live vaccine is required; patients on rilonacept could be vaccinated ≥ six weeks of the last dose and ≥ six weeks before the next dose.[104]
CD19-targeted agents	The recommendations on vaccination with anti-CD20 therapies could be extrapolated to anti-CD19 targeted agents such as blinatumomab.[28] Live vaccines for infants born from mothers on CD19 targeted agents should be postponed until B cell recovery.[105]
Anti-CD20 monoclonal antibodies	Tetanus immunoglobulin should be administered in patients with contaminated wounds who have received anti-CD20 monoclonal antibodies in the past six months.[98,106] Live attenuated vaccines should not be received within six months of anti-CD20 monoclonal antibody administration.[10] For optimal immunization in patients on rituximab, vaccination should be deferred to at least 5–6 months after the last dose and at least one month before the next dose.[98,103] If the time window is not possible inactivated vaccines could be administered considering suboptimal response.[98] Administration of second booster dose of inactivated influenza vaccine is associated with superior immunity response.[28] Non-immunized patients who are candidates for R-CHOP therapy should complete HBV vaccines ≥ 4 weeks prior to the initiation of rituximab.[14] Patients should ideally complete the required vaccines ≥ six weeks prior to the initiation of ocrelizumab. Live vaccines are not recommended until B cell depletion in patients treated with ocrelizumab (may take up to 72 weeks).[106,107] Case reports have demonstrated that immunization of infants born from mothers on rituximab therapy up to the third trimester was not attenuated.[103] The Canadian Dermatology Association strongly recommends routine immunization schedule vaccines for infants exposed to rituximab during pregnancy and lactation;[103,108] however, EULAR recommends that Live-attenuated vaccines should be avoided during the first six months of life in newborns exposed to biologic agents in the second half of pregnancy.[98] The EMA label of ocrelizumab, obinutuzumab, and ofatumumab recommends that administration of live vaccines in neonates born from mothers receiving these agents during pregnancy should be postponed until B cell repletion.[106,109, 110]
Anti-CD52 monoclonal antibodies	Live vaccines should be avoided up to at least 12 months after discontinuation of MabCampath®.[111] Poor response to vaccination is observed in patients with hematologic malignancies who have received alemtuzumab in the previous six months.[77] Immunization requirements should be completed ≥ 6 weeks prior to the initiation of Lemtrada®. VZV seronegative patients should be immunized ≥ six weeks prior to the initiation of Lemtrada®.[76]
T-Cell Co-stimulation blockers	Live vaccines could be administered ≥ 3 months after discontinuation of abatacept.[112]

(*Continued*)

Table 5 (Continued).

Monoclonal antibodies targeting α4-integrin and CD 11a	The EMA label recommends discontinuation of efalizumab eight weeks prior to vaccination and resumption of therapy two weeks after vaccination.[78] Routine immunization schedule, including inactivated and live vaccines for infants exposed to natalizumab during pregnancy and lactation, could be considered.[103] Vaccine response to *Haemophilus influenzae* in infants born from mothers on natalizumab was not impaired.
IL-12 and IL-23-targeted agent	Live vaccines could be administered ≥ 15 weeks after discontinuation of ustekinumab.[113] Vaccine response to *Haemophilus influenzae* in infants born from mothers on ustekinumab was not impaired. The Canadian Dermatology Association strongly recommends routine immunization schedule, including both inactivated and live vaccines for infants exposed to ustekinumab during pregnancy and lactation.[103]
Component 5 (C5)-targeted agents	Unvaccinated patients should receive *S. pneumonia* and *H. influenzae* type b vaccine ≥ 2 weeks prior to treatment with eculizumab. Two-dose series with quadrivalent conjugate (MenACWY) at least two months apart and serogroup B (MenB) either two-dose series at least a month apart or three-dose series at 0,1, 2 and 6 months should be administered. Meningococcal immunization should be completed ≥ 2–4 weeks prior to eculizumab administration. Booster doses of tetravalent conjugate vaccine should be repeated every five years based on the duration of therapy.[8]
Proteasome Inhibitors	VZV seronegative patients should receive live attenuated vaccine ≥ 1 month prior to initiation of therapy.[11] HSV subunit vaccine could be considered for VZV seropositive patients ≥ 50 years.[11]
BCR-ABL Tyrosine kinase inhibitors	ECIL guidelines recommend yearly seasonal influenza vaccine and PCV followed by PPSV 23 (8 weeks later) in CML patients on BCR-ABL tyrosine kinase inhibitors.[23]
JAK inhibitors	Vaccination with Shingrix® should be considered ≥ 2 weeks or (Zostavax® ≥ 4 weeks) prior to the initiation of tofacitinib.[94]
Sphingosine 1-phosphate receptor modulators	Live vaccines are not recommended until at least two months after discontinuation of fingolimod.[97] The EMA label recommends vaccination against HPV prior to the initiation of fingolimod.[97] VZV seronegative, non-immunized patients should receive live attenuated (2 doses of Varivax® separated by four weeks) ≥ 1 month prior to initiation of therapy.[11,63] Adjuvant herpes zoster subunit (HZ/su) vaccine could be considered for VZV seropositive patients ≥ 50 years.[63] The vaccine should not be administered while the patient is on antiviral agents against VZV. An antiviral agent should be prescribed for vaccinated patients who develop rashes.[63] When treated with pulse dose corticosteroid, vaccination should be postponed for at least one month after the last dose of corticosteroid.[63]
Bruton Tyrosine kinase inhibitors	Pneumococcal vaccine and yearly inactivated influenza vaccine is recommended in CLL patients.[23]
Monoclonal antibody targeting CD25	Inactivated vaccines could be administered 3 months after induction of basiliximab. Inactivated influenza vaccine could be administered as early as one month after transplant.[114]

Abbreviations: CLL, Chronic lymphocytic leukemia; HBV, Hepatitis B virus; HPV, human papillomavirus; *H. influenzae*, *Haemophilus influenza*; ECIL, European Conference on Infections in Leukaemia; EMA, European medicines agency; EULAR; European league against rheumatism; IL-1, interleukin-1; *S. pneumonia*, *Streptococcus pneumonia*; TNF, tumor necrosis factor; VZV, varicella-zoster virus.

tuberculosis was highest with infliximab and certolizumab, followed by adalimumab, golimumab, tofacitinib, tocilizumab, etanercept, abatacept, and rituximab (44/9277; 13/4396; 30/12757; 4/3209; 11/6507; 9/12905; 3/7164; 2/7743; and 2/11962, respectively).[51] The incidence of tuberculosis reactivation was similar in adalimumab- and golimumab-treated patients.[51] It is noteworthy that the results could be affected by several confounding factors such as including patients from tuberculosis endemic areas in most of the certolizumab trials. The incidence rate of tuberculosis was 5–10 times more than the general population in North America and Western Europe (an incidence rate of 5–20 times were reported for anti-TNF therapies in

these areas). A cohort study demonstrated that the risk of tuberculosis is higher with infliximab- and anakinra-treated groups versus etanercept recipients (adjusted risk ratio: 1.6, 1.3, and 1.2, respectively).[52] Results of clinical trials have reported 10 cases of tuberculosis in 2588 ruxolitinib-treated patients.[53] Limited reports of tuberculosis following ustekinumab therapy exist; however, no case of latent tuberculosis reactivation has been reported with secukinumab so far.[54]

The incidence of tuberculosis in kidney transplant recipients and multiple sclerosis patients treated with alemtuzumab was found to be 0.67% and 0.3%, respectively;[55] however, in a small study conducted in a high endemic area, the incidence of tuberculosis in patients with hematologic malignancies and autoimmune cytopenias was 31–45%.[56] Few cases of tuberculosis reactivation have been reported in metastatic renal cell carcinoma patients receiving mTOR inhibitors,[57,58] and in one case report in lung transplantation, reactivation of latent tuberculosis has been attributed to mTOR inhibitors.[59]

In summary, available data indicate that the risk of tuberculosis is greatest with monoclonal antibodies against TNF and alemtuzumab (because of insufficient data and diversities in sample size, we could not compare the risk) followed by JAK inhibitors and IL-1 targeted agents. Limited cases of reactivation of tuberculosis exist on mTOR inhibitors used in chemotherapy. The risk of tuberculosis reactivation with rituximab and tocilizumab was not more than the general population and appeared to be negligible.[54] Accordingly, ESCMID recommends anti-TB prophylaxis in patients who are candidates to receive TNF inhibitors, alemtuzumab, JAK inhibitors, and mTOR inhibitors (used in chemotherapy regimens). Isoniazid for nine months, rifampin for four months, or the combination of isoniazid and rifampin for three months could be considered for the treatment of latent tuberculosis in the setting of biologic and targeted immunomodulators.

The Risk of Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV) Infections

Compared to the bortezomib-free regimens, the incidence of herpes zoster infection increased up to two-fold when bortezomib was added to the chemotherapeutic regimen of multiple myeloma patients (11% and 22.3%, respectively).[60] Tofacitinib-treated patients experienced HSV infection with an incidence rate of 4.4 per 100 patient-years and up to 7.7 per 100 patient-years in the Asian population versus 1.5 per 100 patient-years in rheumatoid arthritis patients receiving placebo.[42,61] The incidence rates of HSV infection in patients with rheumatoid arthritis receiving TNF inhibitors and rituximab were 1.6 (golimumab) to 2.4 (certolizumab) and 2.2 per 100 patient-years, respectively. Incidence rates and hazard ratios were not statistically significant among TNF inhibitors and rituximab; glucocorticoids were associated with increased risk of infection.[62]

The graph represented by Arvin et al. in 2015 demonstrates comparative incidence of VZV infections associated with disease-modifying therapy of multiple sclerosis; the incidence of VZV infection is greatest with alemtuzumab 12 mg/day (7–45 per 1000 patient-year) followed by fingolimod 0.5 mg/day (6–17.5 per 1000 patient-year), natalizumab (8–16 per 1000 patient-year), and rituximab (8–13 per 1000 patient-year).[63]

ESCMID recommends HSV/VZV prophylaxis for proteasome inhibitors- and alemtuzumab-treated patients (for all their indications) and also considers HSV prophylaxis in fingolimod-treated patients that concurrently receive corticosteroid pulse therapy. Acyclovir/Valacyclovir could be taken into account as prophylaxis of HSV/VZV in susceptible patients discussed above.[11]

The Risk of Cytomegalovirus (CMV) Infection

Alemtuzumab is associated with a remarkable risk of CMV infection, particularly in hematologic malignancies and solid organ transplant recipients, and CMV prophylaxis is recommended in these populations. However, the risk of CMV infection in patients with multiple sclerosis treated with alemtuzumab is less than 1 per 100 patient-years.[10] Therefore, ESCMID does not recommend CMV prophylaxis for multiple sclerosis patients on alemtuzumab.[10,64] Dasatinib has been associated with CMV reactivation, particularly in post-HSCT patients (adjusted hazard ratio, 7.65; 95% confidence interval, 1.84–31.7);[9,65] and ESCMID recommends monitoring of CMV infection in these individuals. Besides dasatinib, regular monitoring of CMV PCR and signs as well as symptoms of CMV disease is also recommended for patients receiving mogamulizumab.[12] Finally, the third international consensus on CMV in solid organ transplant weakly recommends CMV prophylaxis for donor/recipient seropositive patients who were candidates for either bortezomib or eculizumab therapy as treatment of solid organ transplant rejection or a part of desensitization

protocol.[15] Antiviral options for CMV prophylaxis include intravenous ganciclovir, oral valganciclovir, and high doses of oral valacyclovir.[15]

Immunization in Patients on Biologic and Targeted Immunomodulators

According to IDSA guidelines published in 2013, live vaccines, including measles, mumps, and rubella (MMR), live-attenuated influenza vaccine (LAIV), Bacillus Calmette–Guérin (BCG) vaccine, oral polio vaccine (OPV), live-attenuated HSV, and yellow fever should be avoided ≤ 2–4 weeks before initiation and during treatment with immunosuppressants.[16] The international guidelines recommend inactivated influenza, pneumococcal, toxoid tetanus, hepatitis A vaccine, hepatitis B, and human papillomavirus vaccines in patients with autoimmune rheumatologic diseases including those under biologic and targeted immunomodulators.[18,20,21]

The live-attenuated HSV vaccine should be preferably administered ≥ 4 weeks prior to the initiation of immunosuppressive agents for high risk individuals including those older than 50 years. ACIP does not make any recommendations on the administration of recombinant Zoster vaccine (Shingrix®) in highly-immunocompromised patients due to lack of data on efficacy and safety in this population;[24,25] however, recombinant zoster vaccine, has demonstrated greater efficacy than live-attenuated HSV vaccine (Zostavax®), decreases the risk of HZ in patients older than 70 years and also appears an interesting alternative to live-attenuated HSV vaccine in immunocompromised patients.

Humoral response to vaccine is generally not impaired in patients on TNF alpha inhibitors (except infliximab),[66] anakinra,[67] canakinumab,[68] abatacept,[69] belimumab,[70] natalizumab,[71] ustekinumab,[72] IL-17-targeted agents,[73] tocilizumab,[74] probably proteasome inhibitors[75] and alemtuzumab (in doses approved for multiple sclerosis).[76] Meanwhile, immune response to vaccines is significantly decreased in patients receiving rituximab[66] and alemtuzumab (used in hematologic malignancies).[77] No data exist for immunization in patients under CD19 and CD22 targeted therapies; based on their impact on humoral immunity vaccine response is probably diminished during treatment with these agents. Immune response to vaccine may be attenuated in patients on efalizumab,[78] BCR-ABL tyrosine kinase inhibitors,[79] tofacitinib[80] and ibrutinib.[81] Patients treated with vedolizumab have shown reduced response to oral vaccines but not injectable ones.[42] Interestingly, mTOR inhibitors have been shown to enhance immune response to certain vaccines.[82]

Conclusions

Biologic and targeted immunomodulators are associated with increased risk of particular bacterial, fungal, and viral infections based on their impact on the immune system. In order to minimize the potential infection risk, screening, immunization, monitoring, and prophylactic protocols should be implemented. Limited information exists on the risk of infections associated with the recently developed biologic agents including CD19, CD22; CD30; CD38; CD319; CD40; CCR4–targeted agents; second and third generation anti-CD20 monoclonal antibodies, second and third generations of BCR-ABL tyrosine kinase inhibitors; and their impact on patient response to immunization. Consequently, consensus guidelines do not make comprehensive recommendations regarding these agents. Further clinical research will guide us regarding the necessary safety measures to minimize the infection risk of these agents.

Disclosure

The authors report no conflicts of interest in this work.

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