European Society of Clinical Microbiology and Infectious Diseases Study Group for Infections in Compromised Hosts: Guidelines for Infectious and Immunological Complications of Targeted and Biological Therapies

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Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

REFERENCE

Aguado JM, Manuel O. Editorial for ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective. Clin Microbiol Infect 2018;24(Suppl 2):S1.

BACKGROUND

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts (ESGICH) recently published a series of guidelines in *Clinical Microbiology and Infection* in June 2018 detailing the safety of targeted and biological therapies.[1-9] By specifically targeting the immune system, these therapies treat various disorders of the immune system and malignancies. However, there are often negative immunologic consequences when using these agents—infectious susceptibility and immune dysfunction. Preventing and treating the complications from these therapies is challenging, and the ESCMID ESGICH guidelines provide a practical framework for immunologists and infectious disease specialists.

METHODS

ESCMID developed the ESGICH by choosing a group of clinical and scientific experts within various subspecialties. Although the guidelines are predominantly based on high-quality evidence gathered by computer-based Medline searches, the study group used expert opinion based on personal experience when there was a lack of high-quality evidence. Where reliant on study data, the study data may be limited by the lack of infections within the limited scope of the trial, lack of comparison groups during postmarketing surveillance, and poor granularity in the clinical trial data. The guidelines are grouped into the following: antitumor necrosis factor-α agents[3]; agents targeting interleukins, immunoglobulins, and complement factors[4]; cell surface receptors and associated signaling pathways[5]; tyrosine kinase and mammalian target of rapamycin (mTOR) inhibitors[6]; agents targeting lymphoid cell surface antigens[7]; agents targeting lymphoid or myeloid cell surface antigens[8]; immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators, and proteasome inhibitors.[9] These guidelines describe the mechanism of action, approved indications, supportive evidence, and expected and actual impact on the immune system for each class of medication. Figure 1 summarizes these guidelines but is only an overview.

RESULTS

There are many agents described by these guidelines that mimic a primary immunodeficiency, such as the agents targeting B-cell surface antigens.[7] Agents that target lymphocytes early in maturation cause more profound hypogammaglobulinemia than those that target more mature lymphocytes. For instance, CD19 is expressed on plasmablasts, whereas CD20 is not and CD52 in addition to CD22 is limited to mature lymphocytes. This causes anti-CD19 agents to cause more profound hypogammaglobulinemia than anti-CD20 causes. Anti-CD52 and anti-CD22 agents do not significantly affect immunoglobulin levels. Also, interestingly, IgM levels fall more significantly than IgG with CD20 targeted therapy, and often there is a selective effect on autoantibody secretion with CD20 targeted therapy that preserves humoral immunity. CD40 is commonly found on B cells, and targets for CD40 are expected to cause effects similar to hyper-IgM syndrome with impaired class switching of immunoglobulin.[8] And lastly, when an agent targets Bruton TK, the defect in X-linked agammaglobulinemia, hypogammaglobulinemia results.[6]

In addition, there are several examples that increase the risk for unusual infections that might mimic a primary immunodeficiency. For instance, TNF-α is particularly important for the formation of tuberculosis granulomas by activating and recruiting lymphocytes and monocytes to the site of the infection.

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Therapy Target or Inhibitor	Viral Reactivation Risk				Bacterial Infection Risk		Fungal Infection Risk		Other Immunologic Complications
	HSV/VZV	HBV	CMV	PML	Neutro-penia	PCP	TB	IFI	
TNF-α	Likely yes	Possible	Yes	Likely no	No	No	Yes	Likely no	Granulomatous conditions
IL-1	Likely no	No	No	Likely no	No	No	Possible	No	None
IL-4, IL-13	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
IL-5	Likely no	Likely no	Likely no	Likely no	No	Likely no	No	No	None
IL-6, IL-6R	Likely yes	Likely yes	Likely yes	Likely no	No	Possible	Yes	No	None
IL-12, IL-23	Possible	No	Possible	Likely no	No	No	Possible	No	None
IL-17	No	No	No	Likely no	No	No	Yes	Unknown	CAND
IgE	No	No	No	Likely no	No	No	No	No	Geohelminths
C5	Possible	No	No	Likely no	Likely no	Likely no	No	Likely no	*Neisseria* and encapsulated bacteria
VEGF	Likely no	Yes	Likely no	Likely no	No	Likely no	No	No	Gastrointestinal perforation
VEGFR	Likely no	Likely yes / No	Likely no	Likely no	No	Likely no	No	No	None
EGFR	Likely no	Yes	Likely no	Likely no	No	Likely no	No	Likely no	Infected papulopustular rash
ErbB2, HER2	Likely no	No	Likely no	Likely no	No	Likely no	No	No	None
ErbBR TK	Likely no	No	Likely no	Likely no	No	Likely no	No	No	None
BCR-ABL, Src TK	Yes	Yes	Yes	Yes	No	No	Yes	Yes	None
B-Raf, MEK	No	No	No	No	No	No	No	No	None
Bruton TK	Unknown	Likely yes	No	Unknown	Yes	Yes	No	Yes	HGG
PI3K	Unknown	Likely yes	No	Yes	Yes	Yes	No	Yes	Colitis, pneumonitis
Bcl-2	No	Likely no	No	No	No	No	No	No	Likely none
JAK	Yes	Unknown	Yes	Yes	Yes	Yes	Yes	Yes	EBV
mTOR	Yes	Unknown	Yes	Unknown	No	No	Yes	No	None
CD19	Yes / Unknown	No / Unknown	Yes / Unknown	Unknown	Yes	Yes / Unknown	No	Yes	HGG, enterovirus
CD20	No / Unknown	Yes / Unknown	Yes / Unknown	Unknown	Yes	Probably No / Unknown	No	No	HGG, HCV, enterovirus
CD52	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	BKV, HPV, TOX, LIS,
									CAND
CD22	No / Unknown	No / Unknown	Unknown	No / Unknown	No	Possible / Unknown	No	No	None
CD30	Unknown	Yes	Yes	Yes	Yes	Unknown	No	No	None
CD33	Unknown	Yes	Unknown	Unknown	Likely no	Unknown	No	No	None
CD38	Yes / Unknown	Yes / Unknown	Possible / Unknown	No / Unknown	No No	Possible / Unknown	No No	No No	None
CD40	Possible	Yes / Unknown	Unknown	Possible	No	Possible	No	Yes	Protozoa
CD319	Yes	Yes	Unknown	No	No	Possible	No	No	None
CCR4	Unknown	Possible	Yes	Yes	No	Unknown	No	No	Unknown
CTLA-4	No	Likely no	Likely yes	Possible	No	Possible	Yes	No / Possible	IRIS
PD-1, PD-L1	No	Likely no	Likely yes	Possible / Unknown	No	Possible	Yes	No / Possible	
LFA-3	No	Likely no	Unknown	Unknown	No	Possible	No	No	None
Integrins	No	Likely no	Unknown	Unknown	Likely yes	No	No	No	None
S1PR	Yes	Likely no	Unknown	Unknown	Likely no	Possible	No	No	None
Proteasome	Yes	Likely no	Likely no	Likely no	No	No	No	No	Pneumonia

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FIGURE 1. Infectious risk and immunologic complications of biologic agents. ANG, angiogenesis related pathways; Bcl-2, B-cell lymphoma-2; BKV, BK virus; C, complement; CAND, candida; CKPT, checkpoint; CMV, cytomegalovirus; CTAL-4, cytotoxic T-lymphocyte-associated protein 4; EBV, Epstein-Barr virus; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HBV, hepatitis B virus; HCV, hepatitis C virus; HER2, human epidermal growth factor receptor 2; HGG, hypogammaglobulinemia; HPV, human papillomavirus; HSV, herpes simplex virus; IFI, invasive fungal infection; IRIS, immune reconstitution inflammatory syndrome; JAK, janus kinase; LFA-3, leukocyte function-associated antigen 3; LIS, listeriosis; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PCP, *Pneumocystis* pneumonia; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase; PML, progressive multifocal leukoencephalopathy; R, receptor; S1PR, sphingosine-1-phosphate receptor; TB, tuberculosis; TK, tyrosine kinase; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; TOX, toxoplasmosis; VEGFR, vascular endothelial growth factor receptor; VZV, varicella zoster virus.

Therefore, TNF-α blockade can cause tuberculosis reactivation or dissemination.[3]

There are also many new biologic agents for allergic diseases that target IgE, IL4, IL5, and IL13. IgE and IL5 are involved in activation of eosinophils and eosinophils are important for antiparasitic immune responses. Although an increase in parasites has not been universally seen for these agents, there remains a theoretical risk for anti-IgE and anti-IL5 therapy.[4]

Anti-IL1 therapy is a common approach to autoinflammatory syndromes. However, there is an overall mild-to-moderate increased risk of infection with anti-IL1 therapy. In addition, primary immunodeficiencies such as common variable immunodeficiency can mimic autoinflammatory syndromes. Therefore, a basic immune evaluation is warranted before commencing ant-IL1 therapy.[4]

Targets for angiogenesis and endothelial growth can impair cellular immunity. Inhibiting vascular endothelial growth factor (VEGF) signaling affects T-cell function but likely only within the tumor microenvironment and not for other T cells in the body. Actually, some studies in mouse models suggest that inhibiting VEGF enhances the immunogenicity of T cells.[5]

Furthermore, targeted biologic agents can be used to treat specific immunodeficiencies, but the clinical consequence of these therapies is compounded by the treatment effects. For instance, mTOR inhibitors can be used to treat autoimmune lymphoproliferative syndrome but with the negative consequence of impaired neutrophil migration and increased risk for bacterial infection.[6] Phosphoinositide 3-kinase (PI3K) inhibitors are currently being studied as a treatment for activated PI3K delta syndrome, and there are many successful reports using janus kinase inhibitors for signal transducer and activator of transcription gain-of-function syndromes.[6] Anti-CD20 biologics can also be used for refractory autoimmune manifestations and granulomatous-lymphocytic interstitial lung disease in common variable immunodeficiency patients.[7] Lastly, there are trials underway using proteasome inhibitors in refractory immune cytopenias associated with primary immunodeficiencies and patients with autoantibodies to IFN-ϒ.[9]

CRITICAL APPRAISAL

There are several limitations to the ESCMID ESGICH guidelines.[1-9] First, a few recently approved biologic agents, such as dupilumab and benralizumab, are not covered. Secondly, many of these therapies are typically used with other immunosuppressive agents. Therefore, the immunological consequences of the biologic agent are not always clear. Thirdly, the infectious risk assessments described in Figure 1 are an incomplete but useful starting point for the evaluation of infectious susceptibilities. When there is high-quality evidence, such as data from randomized control trials or postmarketing surveillance, the risk assessment detailed in Figure 1 is marked in green or red. When there is low-quality evidence, such as expert opinion or theorized conclusions, the risk assessment is marked in orange. In addition, the risk assessment for *Pneumocystis* pneumonia is largely based on using the agent by itself without other immunosuppressive agents; however, the threshold for prophylaxis should be lowered when steroids are used concurrently. Fourthly, although these guidelines were developed by a European society, there are no current equivalent guidelines published by a North American society. Some of these medications have different indications in Europe than in the United States. Also, the European population is very different from the North American population and these guidelines were developed for a European population.

RECOMMENDATION

These guidelines should change the practice of immunologists. These guidelines can be referenced when starting a patient on one of these therapies in order to better evaluate, monitor, and manage infectious and immunologic complications of the therapy. However, with the widening use of biologics, these lists of infectious susceptibilities and immunologic consequences will need to be updated and revised periodically. These guidelines can also be referenced when evaluating a patient for immunodeficiency who is on one of these therapies. The ESCMID ESGICH guidelines for infectious and immunological complications of targeted and biological therapies provide immunologists with a valuable framework for managing patients on these treatments.[1-9]

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