Infections in Children on Biologics

Lara Danziger-Isakov, MD, MPH

KEYWORDS

• Pediatrics • Infectious disease • Biologics • Opportunistic infection

KEY POINTS

- Biologics represent a wide range of products that often target immune system pathways resulting in unintended consequences, including infectious events.
- Tumor necrosis factor-α inhibitors in pediatric patients may have a differential infection risk based on the agent and underlying condition being treated.
- Emerging data on infections specific to biologic administration in pediatrics will be essential to determine the risks of these agents in the future.

INTRODUCTION

According to the US Food and Drug Administration, biologics represent a wide range of products, including vaccines, blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins (**Table 1**).[1] In the past decade, there has been an explosion of biologics, specifically recombinant therapeutic proteins, developed and approved to treat a broad range of immunologically mediated pediatric diseases, including rheumatologic diseases and inflammatory bowel disease (IBD), whereas other biologic products target pathways to disrupt cancer cell replication. Biologics aim to modify targeted pathways to interfere with the immunologic aberration creating the clinical disease either through dampening or upregulating responses (**Fig. 1**). However, alteration of the pathways results in selective deficits in the immune system potentially increasing the risk of infection. Risk for infection varies based not only on the biologic target but also on the intensity of dosing as evidenced by a recent meta-analysis of primarily adult studies that reported increased risk for infection in patients with rheumatoid arthritis (RA) who received standard or high-dose biologics compared with low-dose or traditional medications for the disease.[2] Although much has been reported in the adult literature regarding increased

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Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 7017, Cincinnati, OH 45229, USA
E-mail address: Lara.Danziger-Isakov@cchmc.org

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Table 1
Biologics and associated infectious events

Target	Agent	Pediatric Indications	Associated Infections in Pediatrics
TNF-α	—	—	URI, pneumonia, abscesses, varicella zoster, histoplasmosis
	Infliximab	CD, UC	Listeria meningitis, cutaneous blastomycosis,
	Adalimumab	JIA, CD, UC	*Mycobacterium avium*
	Etanercept	Polyarticular JIA, psoriasis	Purpura fulminans
IL-1	Anakinra	NOMID and CAPS, systemic JIA	Visceral leishmaniasis, varicella, labial herpes, URI
	Canakinumab	JIA, FMF, hyperimmunoglobulin D, TRAPS	URI, nasopharyngitis
IL-2	Basiliximab	Organ transplant rejection prophylaxis	—
IL-6	Tocilizumab	Polyarticular and systemic JIA	URI, pneumonia, bronchitis, cellulitis, varicella
IL-12/23	Ustekinumab	UC	—
CD28 blockade	Abatacept	JIA	—
a-4 Integrin	Vedolizumab	Off-label: refractory inflammatory bowel disease	URI, cellulitis
JAK	Tofacitinib	Off-label: GVHD, JAK/STAT pathway mutations, alopecia areata	Viral infection (BK, CMV, adenovirus), bacterial infection
CD20	Rituximab	Off-label: PTLD, EBV-related HLH, glomerular diseases, CNS-inflammatory diseases, Burkitt lymphoma	Viral infection (varicella, CMV, adenovirus), pneumonia, empyema, mastoiditis, *Salmonella enteritis*, candidiasis

Abbreviations: CAPS, cryopyrin-associated periodic syndromes; CD, Crohn disease; CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; FMF, familial Mediterranean fever; GVHD, graft-versus-host disease; HLH, hemophagocytic lymphohistiocytosis; JAK, Janus kinase; JIA, juvenile idiopathic arthritis; NOMID, neonatal-onset multisystem inflammatory disease; PTLD, posttransplant lymphoproliferative disease; STAT, signal transducers and activators of transcription; TRAPS, tumor necrosis factor receptor associated periodic syndrome; UC, ulcerative colitis; URI, upper respiratory infection.

infectious risk with these biologics, pediatric data are limited; but inference from prior experiences may be taken.

BIOLOGIC TARGETS AND ASSOCIATED INFECTIONS

Tumor Necrosis Factor-α Inhibitors

Tumor necrosis factor (TNF)-α, a cell-signaling protein produced acutely by macrophages and monocytes, activates the vascular endothelium and increases vascular permeability. TNF-α inhibitors block the signaling to reduce acute inflammation in patients with RA, juvenile idiopathic arthritis (JIA), various types of psoriasis, and IBD, such as Crohn disease (CD) and ulcerative colitis (UC). Infliximab (CD), adalimumab (CD, JIA), and etanercept (JIA, plaque psoriasis) currently have approved indications