Minireview

Fungal infection risks associated with the use of cytokine antagonists and immune checkpoint inhibitors

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Impact statement

The risk of opportunistic infections due to fungi is relatively less well addressed in patients receiving biologic agents, compared with other opportunistic bacterial and viral infections. There is a lack of consensus guideline on the screening, prophylaxis, and management of fungal infection in patients anticipated to receive or actively receiving biologic therapy. In addition, invasive mycosis in immunocompromised patients is associated with high mortality and morbidity. This review highlighted the risk of fungal infection in patients receiving cytokine antagonists and immune checkpoint inhibitors, two big categories of biologic agents that are widely used in the treatment of various autoimmune and malignant conditions, often in combination with other immunomodulatory or immunosuppressive agents but also as standalone therapy. The adverse outcomes of opportunistic fungal infection in these patients can be reduced by heightened awareness, active case finding, and prompt treatment.

Abstract

The revolutionary success of biologic agents in treating various malignant and autoimmune conditions has been met with increased risk of opportunistic infections due to perturbations in immunity. In patients receiving biologic-containing regimens, the risk of fungal infection is less well-understood, and there is a lack of established guideline on the standard of care in terms of screening and prophylaxis. In this article, we reviewed the risk of fungal infections associated with cytokine antagonists, including anti-tumor necrosis factor (TNF) agents and interleukin (IL) antagonists, and immune checkpoint inhibitors. The risk of fungal infection in this group of patients is drug-, pathogen-, host-, and context-dependent. Among the biologic agents reviewed, anti-TNF agents are associated with highest number of reported cases of fungal infection, especially histoplasmosis. In fact, infection due to all dimorphic fungi except *Talaromyces marneffei* have been reported in patients receiving TNF-α inhibitors, despite their widespread use in *T. marneffei*-endemic regions. The risk is higher with TNF-α inhibitors that block both the membrane-bound and soluble forms of TNF-α, i.e., infliximab and adalimumab, compared with etanercept which inhibits the soluble form only. In addition to the preferential suppression of Th1 pathway and granuloma formation leading to genuinely higher risk of infection, the longer history and extensive use of infliximab coupled with the endemicity of histoplasmosis in the United States lead to an apparent increase in reported cases. IL-17 antagonists lead to a moderate increase in mucocutaneous candidiasis, but not the risk of life-threatening mycosis, consistent with the essential role of Th17 cells in mucosal defense. Immune checkpoint inhibitors, on the other hand, do not significantly increase the risk of invasive fungal infections when used alone and may even be of therapeutic value in the treatment of severe and refractory mycosis.

Keywords: Fungal infection, biologic, cytokine antagonist, tumor necrosis factor, interleukin, immune checkpoint

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Introduction

In the first two decades in the new millennium, a large variety of biologic agents have been licensed for clinical use. They have revolutionized the management of many previously incurable cancers and difficult-to-treat autoimmune diseases. Broadly speaking, biologics can be classified into a few major categories based on their cellular targets. These include inhibitors against cell surface receptors and associated signaling pathways, immune checkpoint inhibitors, tyrosine kinase inhibitors, and cytokine antagonists, including anti-tumor necrosis factor (TNF) agents and soluble effector molecule inhibitors, such as antagonists to the interleukins (ILs). Since many of these

targets are major players in various host immune response pathways, therapeutic blockade confers increased susceptibility to infectious complications to different extent.

Although fungal infections have been associated with substantial mortality and morbidity, this group of disease is largely off the radar of global health programs. Opportunistic fungal pathogens associated with the use of biologics can be of global (e.g., *Candida*, *Cryptococcus*, *Aspergillus*, *Pneumocystis*) or local importance (e.g., *Histoplasma*, *Coccidioides*, *Talaromyces*). In this exercise, we attempt to review the epidemiology of major groups of fungal infections associated with specific groups of biologic agents. However, when inhibitors against cell surface receptors and associated signaling pathways or tyrosine kinase inhibitors are employed, they are often used together with other immunosuppressive agents, such as corticosteroids and cytotoxic drugs. Therefore, the relative contribution of these two categories of biologics to the corresponding fungal infections are often more difficult to gauge, except for fungal infections that were previously extremely rare in a particular group of patients, but the incidence of which has dramatically increased as a result of the use of these biologics, such as the emergence of *Talaromyces marneffei* infections in patients with underlying hematologic disorders.[1] Therefore, in this article, we will mainly focus on the epidemiology of opportunistic fungal infections that complicate the use of cytokine (TNF-α, IL-1, IL-2, IL-6, IL-17, IL-12, and IL-23) antagonists and immune checkpoint (PD-1, PD-L1, and CTLA-4) inhibitors.

TNF-α inhibitors

Overview of TNF-α inhibitors and risk of infection

TNF-α is synthesized, either as membrane-associated or soluble TNF, by activated macrophages, lymphocytes, and other immune cells in response to pro-inflammatory stimuli such as invading microbial pathogens. It exerts a wide range of biologic activities, including macrophage/monocytes activation, stimulation of chemotaxis and proliferation of inflammatory cells, and augmentation of cytotoxicity and intracellular killing by cytotoxic T lymphocytes and neutrophils.[2,3] Due to the prominent role of TNF-α in the inflammatory cascade, TNF-α blockade has been explored as a therapeutic means to counteract the dysregulated self-targeting immune system in various autoimmune conditions. The currently available TNF-α inhibitors, their mechanism of action, and licensed indications are summarized in Table 1. Off-label use of TNF-α inhibitors is often encountered in cases of refractory graft-versus-host disease (GVHD)[4] and sarcoidosis.[5]

Despite their revolutionary success in the treatment of various autoimmune conditions, the use of TNF-α inhibitors has been associated with increased risk of opportunistic infections. TNF-α is essential in the formation and maintenance of granulomas.[6] It primes macrophages for intracellular killing, and together with other cytokines and chemokines, induces the recruitment and organization of mononuclear cells into mature granulomas.[7] TNF blockade leads to a failure of containment of intracellular pathogens, which predisposes the host to opportunistic granulomatous infections. It has long been recognized that TNF-α inhibition confers an increased risk of tuberculosis. Other opportunistic infections reported to be associated with TNF-α inhibitors involve the intracellular pathogens *Listeria monocytogenes, Legionella pneumophila*, *Salmonella* species, *Nocardia* species, as well as fungal pathogens.

Histoplasmosis associated with TNF-α inhibition

Amongst all opportunistic fungal infections associated with TNF blockade, infections due to endemic fungi, especially *Histoplasma capsulatum*, is best characterized.[8] The risk of infection is increased by approximately five folds with the use of TNF-α inhibitors. Clinical symptoms and signs usually manifest one week to six months after the initial dose. Pulmonary infection occurs most frequently, although the spectrum of disease varies, including cutaneous, hepatic, intestinal, and disseminated forms. Mortality rate may be up to 20% in selected case series.[9] Whether the cases of histoplasmosis in patients receiving TNF-α inhibitors represent primary infection, reactivation, or re-infection remains a matter of debate. Based on data

Table 1. List of FDA-approved TNF-α inhibitors.

Agent	Mechanism of action	Half-life (days)	Route and interval of administration	Year of FDA approval	FDA-approved indication
Infliximab	Mouse chimeric mAb against both soluble and transmembrane TNF-α	7.7–9.5	IV every 4-8 weeks	1998	AS, CD, Ps, PsA, RA, UC
Etanercept	Human soluble TNF receptor fusion protein (TNFR2/p75 and Fc region of human IgG1), only TNF inhibitor that also binds TNF-β	3.0–5.5	SC once or twice weekly	1998	AS, JIA, Ps, PsA, RA
Adalimumab	Human mAb against both soluble and transmembrane TNF-α	10.0–20.0	SC every 1-2 weeks	2002	AS, CD, HS, JIA, Ps, PsA, RA, UC, UV
Certolizumab pegol	Pegylated humanized Fab' fragment against TNF-α	14.0	SC every 4 weeks	2008	AS, CD, PsA, RA
Golimumab	Human mAb against both soluble and transmembrane TNF-α	14.0	SC every 4 weeks	2009	AS, PsA, RA

AS: ankylosing spondylitis; CD: Crohn's disease; HS: hidradenitis suppurativa; IV: intravenous; JIA: juvenile idiopathic arthritis; mAb: monoclonal antibody; Ps: plaque psoriasis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SC: subcutaneous; UC: ulcerative colitis; UV: uveitis.

collected through the Adverse Event Reporting System (AERS) of the U.S. Food and Drug Administration (FDA) from 1998 to 2002, infectious adverse events were reported in ~129 per 100,000 infliximab-treated patients and ~60 per 100,000 etanercept-treated patients. Histoplasmosis was the second most common granulomatous infectious complication following *Mycobacterium tuberculosis*, occurring at a rate of 18.8/100,000 persons in the infliximab group and 2.7/100,000 in the etanercept group.[10] In view of this, the FDA has issued a black box warning on the increased risk of "*invasive fungal infections (such as histoplasmosis)*" for all TNF-α inhibitors.

However, unlike tuberculosis, there is no guideline on screening for histoplasmosis before commencing anti-TNF agents. Routine screening with serology or chest radiography is not recommended.[11] This is partly because that, unlike tuberculosis, the incidence of histoplasmosis associated with TNF-α blockade is low even in endemic regions where more than half of the population demonstrate evidence of past exposure by skin hypersensitivity test. Moreover, most infections likely represent recent/acute infection instead of reactivation. Patient counseling before and during treatment is of paramount importance in reducing the risk of exposure and early identification of infection. The use of screening tests, including serologic assays, histoplasmin skin tests, and chest radiography, may help to identify patients at higher risk of reactivation of histoplasmosis. However, their usefulness is not supported by robust clinical evidence. In addition, it is unclear whether a positive test contraindicates anti-TNF treatment or necessitates antifungal prophylaxis. The decision on initiation of antifungal prophylaxis should be individualized. The clinical practice guideline on the management of patients with histoplasmosis published by the Infectious Disease Society of America in 2007 stated that "active histoplasmosis during the past 2 years may be a basis for itraconazole prophylaxis during immunosuppression." However, the appropriate duration of antifungal prophylaxis is not defined.[12]

Other fungal infections associated with TNF-α inhibition

The risk of infection due to another dimorphic fungus, *Coccidioides* species, is also significantly increased by TNF-α blockade. In the above-mentioned review based on FDA data,[10] coccidioidomycosis was reported in 5.6/100,000 patients treated with infliximab and 0.9/100,000 patients treated with etanercept. Coccidioidomycosis can present with disseminated or even fatal disease in immunocompromised patients. The liver transplant center at Mayo Clinic Hospital in Arizona previously reported their strategy of pre- and post-transplant serologic monitoring of coccidioidomycosis and targeted prophylaxis with fluconazole.[13] However, given the relatively low incidence of coccidioidomycosis associated with TNF-α blockade and the fact that most cases likely represent acute infection rather than reactivation, the usefulness of pretreatment serological screening for coccidioidomycosis is doubtful.[3,14] Other commonly reported fungal agents responsible for opportunistic infection in patients receiving TNF-α inhibitors include *Aspergillus* species, *Cryptococcus neoformans*, *Candida* species, *Pneumocystis jiroveci*, and *Mucorales* (Table 2).

Invasive aspergillosis occurs more commonly in patients receiving TNF-α inhibitors as part of the treatment regimen for GVHD after hemopoietic stem cell transplant.[9] Most of these patients had also been receiving various other immunosuppressants, including high-dose corticosteroid, calcineurin inhibitors, mycophenolate mofetil, and other biologics such as anti-IL2, making assessment of the actual contribution of TNF-α inhibitors to the risk of invasive fungal infection difficult. Moreover, these patients are usually put on prophylactic antifungals such as azoles, echinocandins, or even amphotericin B, which will reduce the overall risk of opportunistic fungal infections but increase the relative risk of infections by fungal organisms that are resistant to the prophylactic antifungal given. Mortality can be up to 80% in this group of patients.[9] Similarly, most cases of *P. jiroveci* pneumonia (PJP) occurred in patients who were receiving concomitant immunosuppressants including corticosteroid, azathioprine, methotrexate etc.[15] Current guideline does not recommend routine PJP prophylaxis in patients on TNF-α inhibitors alone.[3,16] The risk assessment should be tailored to the overall degree of immunosuppression. The highest mortality was observed in patients who developed mucormycosis as a complication of advanced immunosuppression. Besides the infections listed above, there are also isolated case reports of *Trichosporon asahii* infection,[17] *Scedosporium apiospermum* infection,[18,19] paracoccidioidomycosis,[20,21] blastomycosis,[1] and protothecosis[22] associated with TNF-α inhibition. Interestingly, despite the wide use of TNF-α blockers, there is no reported case of *T. marneffei*

Table 2. Risk of fungal infection associated with TNF-α inhibitors.

	Infliximab	Etanercept	Adalimumab	Certolizumab	Golimumab
Histoplasmosis	+++++	+	+	0	0
Coccidioidomycosis	++	+	+	0	0
Aspergillosis	+++	+	+	0	+
Cryptococcosis	++	+	+	0	0
Mucormycosis	+	+	+	0	0
PJP	+++	++	+	0	0
Invasive candidiasis	+++	+	+	0	0

Note: Data derived from PubMed search of reported cases and case series of fungal infections complicating anti-TNF usage. The risks are assigned based on number of cases reported: +, <20 reported cases; ++, 20 to <40 reported cases; +++, 40 to <60 reported cases; ++++, 60 to <80 reported cases; +++++, 80 to < 100 reported cases. PJP: *Pneumocystis jiroveci* pneumonia.

infection associated with anti-TNF-α usage, even in endemic regions such as Hong Kong.

Risk assessment in patients receiving TNF-α inhibitors

The risk of opportunistic infection associated with TNF-α inhibitors is drug-, geographic location-, time-, and context-dependent. In contrast to infliximab which binds to both the soluble and membrane-bound TNF-α with high avidity, etanercept, which is a dimeric recombinant protein that contains the extracellular domain of the human TNF receptor TNFR2/p75 fused to the Fc portion of human IgG1,[23] binds primarily to the soluble form of TNF-α. This leads to a lack of activity by etanercept to fix complement and induce apoptosis in macrophages/monocytes and T cells expressing membrane-bound TNF-α.[7] As a result, etanercept does not demonstrate the same effectiveness as infliximab in treating granulomatous conditions such as Crohn's disease, sarcoidosis, and Wegener's granulomatosis,[24–26] likely due to inadequate suppression of granulomatous inflammation. This difference in pharmacology also underlines the lower risk of opportunistic infection conferred by etanercept compared antibody-mediated TNF-α neutralizers such as infliximab and adalimumab, as shown by the AERS data[10] mentioned above. In addition, patients who develop opportunistic fungal infections while on treatment with infliximab typically manifest earlier than those on etanercept.[27] Other proposed mechanisms underlying the difference in risks of infection include differential inhibition of TNF signaling, different binding kinetics to TNF molecules,[28] and the ability of infliximab and adalimumab, but not etanercept, to cause concentration-dependent suppression of interferon (IFN)-γ production.[29]

TNF-α blockade seems to confer a particular risk of infection by *H. capsulatum* not seen with other biologics. The preferential suppression of Th1-macrophage crosstalk and granuloma formation and relative sparing of extracellular immune pathways explain for the higher risk of infection by intracellular pathogens. In regions of the world where dimorphic fungi are endemic, the incidence of opportunistic systemic fungal infection could be even higher than that of *M. tuberculosis*.[11] It is no surprise that most cases of histoplasmosis associated with TNF-α inhibitor treatment were reported in the United States, since *H. capsulatum* is most prevalent in the Ohio, Missouri, and Mississippi river valleys. On the other hand, there seems to be more case reports on PJP related to TNF-α inhibitor use from Japan. Whether this represents a genuine genetic vulnerability to PJP or simply due to heightened awareness and increased diagnostic sensitivity with the use of molecular assays remains a matter of debate.[30] Infections by other fungal species, including *Aspergillus* spp., *Cryptococcus* spp., *Candida* spp., and *Mucorales*, reflect an overall state of immunosuppression, rather than opportunistic infection specific for TNF-α blockade and did not demonstrate geographic variation since these fungal pathogens are ubiquitously present.

Finally, the underlying disease which requires treatment by biologics may well contribute to impaired immunity, rendering the patient susceptible to opportunistic fungal infection even before the start of immunosuppressive treatment. For example, it has been shown that patients with higher disease activity of rheumatoid arthritis (RA) are more likely to develop infection, independent of the immunosuppressant regimen.[31] Concomitant immunosuppressive agents further increase the host susceptibility to infectious complications. This is reflected by the fact that the risk of serious infection is highest in the first year after initiation of TNF-α inhibitors among patients with RA.[32]

IL inhibitors

ILs comprise a big family of soluble effector molecules that are elaborated by immune cells of both innate and adaptive immunity. Some of the ILs play major roles in combating invading fungal pathogens. For example, IL-17, the signature cytokine of Th17 cells, has been shown to be crucial in host defense against extracellular fungi.[33] Table 3 summarizes the available IL-blocking agents, their mechanism of action, FDA-approved indications and overall risk of fungal infection. At present there is no FDA-approved IL-12-specific inhibitor for clinical use, thus agents blocking the p40 subunit shared by IL-12 and IL-23 will be discussed with other IL-23 antagonists. ILs involved in the Th2 response, including IL-4, IL-5, and IL-13, will not be covered in this review since the Th2 pathway is not typically involved in defense against fungal pathogens.

IL-1 inhibitors

IL-1 promotes the generation of acute phase reactants, endothelial cell activation, leukocyte recruitment and effector function, and orchestrates the differentiation and function of lymphoid cells.[34] IL-1β is predominantly produced by macrophages, monocytes, and dendritic cells in response to a wide array of stimuli known as "pathogen-associated molecular patterns" and "damage-associated molecular patterns," including microbial products such as lipopolysaccharides, nuclear debris from dead cells, and cytokines including TNF-α and IL-1 itself.[35,36] Activation of the IL-1 receptor complex activates the downstream signaling molecules myeloid differentiation primary response 88 (Myd88), IL-1 receptor-associated kinase, nuclear factor-κB, and subsequent inflammatory cascade. Therapeutic inhibition of the IL-1 pathway, especially IL-1β, has now been established as the standard of treatment for "autoinflammatory" conditions including cryopyrin-associated periotic syndrome, familial Mediterranean fever, etc., where dysfunctional macrophage/monocytes continuously drive inflammation.

In an international, multicenter, placebo-controlled trial of anakinra in patients with RA, the frequency of serious infection in the first six months was slightly higher in the anakinra group (2.1% vs. 0.4% in the placebo group, $p = 0.068$), but no infection due to opportunistic organism was observed.[37] When treatment by anakinra was extended to three years, the cumulative exposure-adjusted event rate of serious infection was 5.37 events/100 patient-years, which was three-fold higher than that observed in the placebo arm.[38] However, the analysis was likely skewed by concomitant use of corticosteroid in those with highest

Table 3. Summary of agents blocking interleukin pathways, their mechanism of action, indicated use and overall risk of fungal infection.

Category	Name	Mechanism of action	Year of FDA approval	FDA-approved indications	Risk of fungal infection
IL-1 inhibitor	Anakinra	IL-1 receptor antagonist	2001	CAPS, RA	Not significantly increased if used alone
	Rilonacept	Soluble decoy receptor that binds both IL-1β and IL-1α	2008	CAPS	
	Canakinumab	Human mAb against IL-1β	2009	CAPS, FMF, HID/MKD, JIA, TRAPS	
IL-2 receptor antagonist	Basiliximab	Mouse chimeric mAb against the α chain (CD25) of IL-2 receptor	1998	Prophylaxis against acute organ rejection	Not significantly raised if used alone
	Daclizumab	Humanized mAb against the α chain (CD25) of IL-2 receptor	2016	MS	
IL-6 receptor antagonist	Tocilizumab	Recombinant humanized mAb against IL-6 receptor	2010	CRS, GCA, JIA, RA	Dose-dependent mild increase if used alone
	Sarilumab	Human recombinant mAb against IL-6 receptor	2017	RA	
IL-17 pathway blocker	Secukinumab	Human recombinant mAb against IL-17A	2015	AS, Ps, PsA	Moderate increase in non-serious candida infection
	Ixekizumab	Humanized IgG4 mAb against IL-17A	2016	Ps, PsA	
	Brodalumab	Human mAb against IL-17 receptor IL-17RA	2017	Ps	
IL-12/IL-23 inhibitor	Ustekinumab	Human mAb against the p40 subunit of IL-12 and IL-23	2009	CD, Ps, PsA	Moderate increase in non-serious candida infection
IL-23 inhibitor	Guselkumab	Human mAb against the p19 subunit of IL-23	2017	Ps	Not significantly raised if used alone
	Tildrakizumab	Humanized mAb against p19 subunit of IL-23	2018	Ps	
	Risankizumab	Humanized mAb against the p19 subunit of IL-23	2019	Ps	

AS: ankylosing spondylitis; CAPS: cryopyrin-associated periotic syndrome; CRS: cytokine release syndrome; FMF: familial Mediterranean fever; GCA: giant cell arteritis; HID: hyperimmunoglobulin D syndrome; JIA: juvenile idiopathic arthritis; mAb: monoclonal antibody; MKD: mevalonate kinase deficiency; MS: multiple sclerosis; Ps: plaque psoriasis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; TRAPS: tumor necrosis factor receptor associated periodic syndrome.

risk of infection, since in patients without corticosteroid usage, the rate of serious infection was significantly reduced (2.87 events/100 patient-years). The infectious episodes mainly consisted of bacterial pneumonia and cellulitis but not opportunistic fungal infection. However, when anakinra was combined with etanercept for treatment of refractory RA, the risk of infection was increased compared with etanercept alone (3.7%–7.4% vs. 0%, p value not given).[39] Opportunistic fungal infection has not been reported in patients treated with other IL-1 blocking agents including canakinumab and rilonacept. From currently available evidence, IL-1 blockade per se is not associated with higher risk of fungal infection. However, when IL-1 inhibitors are used in conjunction with other immunosuppressant or biologics, the risk of opportunistic fungal infection is significantly increased, especially in patients with comorbid immunocompromising conditions.

IL-2 inhibitors

IL-2 is an essential molecule in adaptive immunity. It is mainly produced by activated CD4+ and to a lesser extent, CD8+ T lymphocytes. IL-2 drives the clonal expansion of activated T lymphocytes and enhances CD8+ T lymphocyte effector function. The upregulation of IL-2 signaling has also been shown to boost the cytolytic activity of natural killer (NK) cells, promote the development of T_{reg} cells, and regulate the differentiation and function of CD4+ T lymphocytes.[40] Basiliximab is approved for prophylaxis of acute rejection in renal transplantation in combination with other immunosuppressants including cyclosporine and corticosteroids. It is often used off-label for prophylaxis against acute rejection in other types of organ transplant including heart, liver and lung, and for treating refractory acute GVHD. Daclizumab shares similar function with basiliximab and is FDA-approved for treatment of relapsing forms of multiple sclerosis.

When used as induction treatment in solid organ transplantation, neither basiliximab nor daclizumab was shown to increase the risk of infective complications compared with placebo.[41,42] The risk of infection and mortality was only significantly raised when IL-2 antagonist was combined with T cell-depleting agents such as anti-CD3 or anti-thymocyte globulin.[43] When renal transplant recipients who received basiliximab-based induction treatment (followed by standard-dose tacrolimus, mycophenolate and prednisolone) were analyzed separately, invasive fungal infection occurred in 1% of patients during the first six months after transplantation.[44] Although there have been case reports of infection by *Aspergillus* spp., *Rhizopus* spp., and *Basidiobolus* spp., in transplant recipients treated with basiliximab,[45,46] due to its unique dosing schedule (typically with first dose given within 2 h prior to transplantation and second dose given 4 days after transplantation), the occurrence of opportunistic infection in

organ transplant recipients who are invariably receiving other immunosuppressants cannot be solely attributed to IL-2 blockade. Even in the cases of steroid-refractory acute GVHD, where patients typically receive more than one dose of basiliximab, the rate of fungal infection was not significantly increased compared with historical control.[47] In summary, the increased risk of fungal infection after treatment with IL-2 blocking agents, if any, is only significant when they are used in conjunction with other immunosuppressive agents.

IL-6 inhibitors

IL-6 is arguably one of the most multipotent cytokines discovered to date. It is able to modulate almost every aspect of the immune system, from leukocyte recruitment, activation, and survival, to the maturation of B cells, maintenance of plasma cells, and differentiation of T cells, culminating in the accumulation of specifically defined immune cell subpopulation within inflamed tissues.[48] Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody (mAb) licensed for the treatment of several autoimmune conditions including RA and cytokine release syndrome. It carries a black box warning on the FDA drug label for "invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis." In a meta-analysis conducted in 2011 comprising of five published randomized control trials and one open-label extension study, tocilizumab was not associated with increased risk of serious infection.[49] However, the analysis was done using data comparing standard dosing regimen (4 mg/kg every four-weeks) with control, a dosage that is at the lower end of recommended dose range by the FDA. In fact, tocilizumab at 8 mg/kg/dose but not 4 mg/kg/dose, when combined with disease-modifying anti-rheumatic drugs (DMARDs,) significantly increased the risk of infection by 1.3-fold compared with DMARDs alone,[50] suggesting a dose-depend increase in the risk of infectious complications. Nonetheless, the majority of infections reported were skin and subcutaneous tissue infections and respiratory tract infections, and fungal infections were not selectively reported. When RA patients enrolled in tocilizumab clinical trials were compared with age- and sex-matched controls treated with corticosteroids and DMARDs, the rate of serious respiratory infection was twice as high in the tocilizumab group, even after adjustment for corticosteroid use, pre-existing pulmonary involvement, and disease activity.[51] In an analysis of cumulative safety data till 2009, opportunistic infections were reported with a rate of 0.23/100 patient-years, including six cases of candidiasis (systemic, oesophageal, gastrointestinal, osteomyelitis), one case each of PJP and cryptococcal pneumonia, and three cases of unspecified fungal infections.[52]

IL-17 inhibitors

The IL-17 family consists of six members (IL-17A to IL-17F), among which IL-17A is a major pro-inflammatory mediator in the development of autoimmune diseases and key defense mechanism in immunity against extracellular bacteria and fungi.[53] IL-17 is mainly produced by the Th17 cells under the control of IL-23, IL-1β, IL-6, and transforming growth factor-β (TGF-β). By operating upstream of granulocyte-colony stimulating factor and various CXC chemokines such as CCR4 and CC46, IL-17 induces granulopoiesis and the recruitment and activation of neutrophils at the site of infection.[54,55] It has been shown that IL-17A receptor-knockout mice had a dose-dependent reduced survival when systemically challenge with *Candida albicans*,[56] and that both Th17-deficient (IL-23p19$^{-/-}$) and IL-17 receptor–deficient (IL-17RA$^{-/-}$) mice experienced severe oropharyngeal candidiasis,[57] suggesting an indispensable role of IL-17 in mucosal defense against candida. Further mechanistic study using mouse model revealed that susceptibility to oropharyngeal candidiasis correlated with IL-17-dependent expression of the antimicrobial peptide β-defensin 3 (BD3) by oral epithelial cells.[58] Consistent with findings in animal models, patients with autosomal dominant hyperimmunoglobulin E syndrome (Job's syndrome) due to underlying mutations in the signal transducer and activator of transcription 3 (STAT3) gene have absent IL-17 production, leading to particular vulnerability to mucocutaneous candidiasis and recurrent cutaneous and sinopulmonary infections.[59]

The infective complications of IL-17 blockade mirror the pathophysiology of Job's syndrome. Currently available IL-17 antagonists secukinumab and ixekizumab are both mAbs against IL-17A, while brodalumab binds to and inhibits the IL-17 receptor IL-17RA. In two phase 3, double-blinded trials on secukinumab for plaque psoriasis, it was associated with a dose-dependent increase in risk of candida infection during the entire treatment period of 52 weeks—4.7% in the 300-mg secukinumab group and 2.3% in the 150-mg secukinumab group experienced candida infection, mostly oral or genital, compared with 1.2% in the etanercept group.[60] All these candida infections were local and mild to moderate in severity, and none resulted in chronic mucocutaneous candidiasis or treatment discontinuation. Trials in patients with psoriatic arthritis,[61] ankylosing spondylitis,[62] and Crohn's disease[63] all demonstrated a similar moderate increase in the risk of non-serious candida infection. Similar observations have been made in clinical trials of ixekizumab and brodalumab.[64] In general, the frequency of candida infection in patients treated with IL-17 inhibitor was in the range of 1%–5%, and severe infection is rare.

IL-23 inhibitors

Ustekinumab is a fully human mAb targeting the p40 subunit shared by IL-12 and IL-23, both belonging to the heterodimeric IL-12 cytokine family. Both the IL-12 and IL-23 pathways will be affected upon exposure to ustekinumab, which leads to a disruption of both the Th1 and Th17 axes since IL-23 is a potent inducer of Th17 cell differentiation and IL-17 secretion. However, in two phase 3 studies comparing ustekinumab with brodalumab or placebo for treatment of psoriasis, the infection risk with ustekinumab was not higher than that with brodalumab. Candida infection, in particular, occurred more frequently with brodalumab than with ustekinumab,[65] reflecting an incomplete

blockade of the either IL-12 or IL-23 pathways with p40 inhibitor alone.[66] The overall risk of candida infection in patients receiving ustekinumab was 2.3%,[64] and severe infection was rarely reported.

Guselkumab, tildrakizumab, and risankizumab are all mAbs that bind to the p19 subunit of IL-23. Review of phase 2 and phase 3 clinical trials of guselkumab, tildrakizumab, and risankizumab in various clinical settings including plaque psoriasis and psoriatic arthritis did not demonstrate significant difference in rate of serious infection.[67–70] Most of the reported serious infective complications consisted of skin and soft tissue infections and respiratory tract infections. Most notably, the risk of mucocutaneous candidiasis was not particularly elevated with anti-IL23p19 agents, in contrast to IL-17 antagonists.[70] This is likely explained by the fact that IL-17 is also produced by other cells including neutrophils, dendritic cells, macrophages etc. independent of IL-23 stimulation, thus blocking IL-23 does not completely abolish IL-17 production.

Immune checkpoint inhibitors

Immune checkpoints are molecules that regulate the immune response to prevent indiscriminatory activity against self-signals. By binding to costimulatory receptors, they help to maintain the delicate balance between inflammatory cell activation and immune tolerance. Programmed cell death-1 (PD-1) and its ligands, PD-L1 and PD-L2 were identified in 1990s.[71–73] Signaling through the PD-1 pathway downregulates antigen receptor signaling, inhibits T cell activation, counteracts cell survival signals, and reduces the expression of transcription factors associated with effector cell function.[74] Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is a costimulatory molecule that binds to CD80 and CD86 on antigen presenting cells (APCs) with high affinity. Upon engagement, CTLA-4 delivers a negative second signal, leading to inhibition of CD28-dependent T cell activation, IL-2 production and accumulation, and cell cycle progression.[75,76]

Immune checkpoint inhibitors have received unparalleled attention as cancer therapeutics due to their potential application across different cancer types and relatively lower risk of serious infection compared with traditional cytotoxic chemotherapy. Pharmacologic blockade using mAbs against PD-1/PD-L1 or CTLA-4 restores anti-tumor immunity and opens up therapeutic options for various malignancies with limited treatment options in the past. To this end, James P Allison and Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine in 2018 "for their discovery of cancer therapy by inhibition of negative immune regulation." Currently FDA-approved immune checkpoint inhibitors are listed in Table 4.

Del Castillo et al. retrospectively reviewed 740 patients diagnosed with melanoma and treated with immune checkpoint inhibitors during a four-year period from 2010 to 2014.[77] Serious infection was reported in 54 patients (7.3%), including two cases of invasive pulmonary aspergillosis, three cases of PJP and one case of *Candida* bloodstream infection. Of note, 339 patients (46%) received corticosteroid, of whom 55 (16%) also received infliximab. The use of corticosteroid was associated with increased risk of serious infection with an odds ratio of 7.71 (95% confidence interval (CI), 3.71–16.18), and the odds ratio associated with the use of infliximab was 4.74 (95% CI, 2.27–9.45). Significantly increased risk of infection was also observed in patients receiving combination of nivolumab and ipilimumab, consistent with the higher incidence of immune-mediated reactions requiring immunosuppressive therapy.[78] In another retrospective review of non-small-cell lung cancer patients in Japan who received nivolumab, infectious complications were observed in 32 out of 167 patients (19.2%).[79] Only two cases of fungal infections were reported, including one case of invasive pulmonary aspergillosis and another case of candida oesophagitis.

Table 4. List of FDA-approved immune checkpoint inhibitors and risk of fungal infection.

Mechanism of action	Drug name	Year of FDA approval	FDA-approved indication	Route and interval of administration	Risk of fungal infection
PD-1 inhibitors	Pembrolizumab	2014	Cervical cancer, cHL, gastric cancer, HCC, HNSCC, MCC, melanoma, MSI-high cancer, NSCLC, PMBCL, urothelial carcinoma	IV 200 mg every 3 weeks	Not significantly increased if used alone. Significant increase in case of irAEs requiring corticosteroid or other biologics
	Nivolumab	2014	cHL, HCC, HCSCC, melanoma, MSI-high cancer, NSCLC, RCC, SCLC, urothelial carcinoma	IV 240 mg every 2 weeks or 480 mg every 4 weeks	
	Cemiplimab	2018	CSCC	IV 350 mg every 3 weeks	
PD-L1 inhibitors	Atezolizumab	2016	NSCLC, TNBC, urothelial carcinoma	IV 1200 mg every 3 weeks (840 mg every 2 weeks for TNBC)	
	Avelumab	2017	MCC, RCC, urothelial carcinoma	IV 800 mg every 2 weeks	
	Durvalumab	2017	NSCLC, urothelial carcinoma	IV 10 mg/kg every 2 weeks	
CTLA-4 inhibitors	Ipilimumab	2011	Melanoma, RCC	IV 3–10 mg/kg every 3 weeks	

cHL: classic Hodgkin lymphoma; CSCC: cutaneous squamous cell carcinoma; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous cell cancer; irAEs: immune-related adverse events; IV: intravenous; MCC: Merkel cell carcinoma; MSI: microsatellite instability; NSCLC: non-small cell lung cancer; PMBCL: primary mediastinal large B-cell lymphoma; RCC: renal cell carcinoma; SCLC: small cell lung cancer; TNBC: triple-negative breast cancer.

It is well-known that immune checkpoint inhibitors can cause a severe systemic immune-mediated reaction, including enterocolitis, hepatitis, dermatitis, pneumonitis, nephritis, pancreatitis, neuropathy, and endocrinopathy, collectively known as immune-related adverse events (irAEs), the treatment of which often involves high-dose corticosteroid. In several cases of invasive aspergillosis associated with the use of immune checkpoint inhibitors, the patients developed irAEs which necessitated the addition of high-dose systemic corticosteroid and other immunosuppressants including anti-TNF agents prior to the development of fungal infection.[80–82] In addition, immune reconstitution inflammatory syndrome may lead to more severe manifestation of chronic fungal infection, for example, chronic progressive pulmonary aspergillosis.[83] A third mechanism by which immune checkpoint inhibitor may lead to infectious disease risk is treatment-related cytopenia. Severe cytopenia has been reported as a complication of nivolumab use, which can cause severe bacterial and fungal infections and even mortality.[84]

Interestingly, despite case reports showing a possible correlation between immune checkpoint inhibitor exposure and infectious disease development, immune checkpoint inhibitors have been suggested as an adjunct treatment for some infections. Many microorganisms, similar to tumor cells, have been shown to be able to exploit the PD-1 pathway to attenuate host immune response. In a phase I trial in HIV-1-infected patients on antiviral therapy, a single dose of anti-PD-L1 antibody infusion resulted in a non-statistically significant increase in the number of HIV-1 Gag-specific CD8+ T cells expressing IFN-γ.[85] Likewise, immune checkpoint inhibition has been proposed as potential treatment strategy for chronic viral infection by hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus (CMV), JC virus (JCV), etc.[86] In infection by *H. capsulatum*, it has been shown in a mouse model that all PD-1 deficient mice survived the acute infection, while all wild-type mice died by day 25 after infection. Blockade of the PD-1 pathway with anti-mouse PD-1 mAb increased survival to 70%–90%.[87] *H. capsulatum* infection caused an upregulation of PD-L1 and PD-L2 expression on immune cells, and macrophage harvested from infected mice were able to suppress T cell activation *in vitro*.[87] Similarly, PD-1 and PD-L1 expression on T lymphocytes was upregulated in patients with candidaemia, indicating T cell exhaustion.[88] PD-1/PD-L1 and CTLA-4 blockade improved survival in mouse model of primary and secondary fungal sepsis through a reversal of sepsis-induced suppression of IFN-γ and increased expression of MHC II molecules on APCs.[89] Anti-PD-1 antibodies have also been tested in mouse models of cryptococcosis[90] and aspergillosis,[91] which showed promising results. Grimaldi et al. reported the first case of successful treatment of intractable mucormycosis with combination immunotherapy with nivolumab and IFN-γ.[92] Further clinical studies are needed to examine the clinical efficacy and safety profile of immune checkpoint blockade in the treatment of invasive fungal disease.

In conclusion, PD-1/PD-L1 inhibitors confer low risk for opportunistic fungal infection. However, when irAEs set in that require additional immunosuppressive therapy with high-dose corticosteroid and/or other biologic or non-biologic immunosuppressants, the risk of invasive fungal disease is significantly increased. Some authors have recommended routine pretreatment screening for latent/chronic infections such as latent tuberculosis and viral hepatitis,[93] but there is a lack of evidence support, and it is unclear whether the screening strategy should be generalized to involve opportunistic fungal infection, e.g., histoplasmosis. Apart from the established guideline on PJP prophylaxis in patients treated with prolonged high-dose corticosteroid, the role of antibacterial, antifungal, and/or antiviral prophylaxis in patients receiving immune checkpoint blocking agents requires further evaluation.

Conclusions

The degree of susceptibility to fungal infection conferred by each biologic agent varies. Among these, there is a well-established association between TNF-α inhibitors and the risk of dimorphic fungal infection such as histoplasmosis and coccidioidomycosis, even in the absence of concomitant cytotoxic chemotherapy or other immunosuppressive agents, implying a specific inhibition of intramacrophagic killing by TNF-α blockade. Other invasive fungal infections, such as aspergillosis, cryptococcosis, pneumocystis pneumonia, mucormycosis, and invasive candidiasis, are mainly observed in patients who received concomitant cytotoxic chemotherapy and/or high dose corticosteroid, which reflect the overall degree of immunosuppression. Interleukin antagonists as a group do not confer significantly increased risk of invasive mycosis when used alone with the exception of agents that block the IL-17 pathway, including IL-17 and IL-23 antagonists. They lead to a moderately increased risk of mucocutaneous candidiasis, although life-threatening infection has not been observed. Immune checkpoint inhibitors, including monoclonal antibodies against the PD-1:PD-L1 pathway and CTLA-4, represent a promising group of biologic agents that may be of therapeutic benefit in severe or refractory fungal infection. The risk of fungal infection in patients treated with immune checkpoint inhibitors as standalone therapy is not significantly raised. However, the frequent occurrence of immune-related adverse events which necessitate high-dose corticosteroid or even anti-TNF-α treatment mandate a careful search for fungal infection in these patients who develop infective complications.

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The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: PCYW has provided scientific advisory/laboratory services for Gilead Sciences, Incorporated; International Health Management Associates, Incorporated; Merck & Corporation, Incorporated; and Pfizer, Incorporated. The other authors report no conflicts of interest.

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