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Fungal Infections and New Biologic Therapies

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Abstract The development of biologic therapies targeting pro-inflammatory mediators has led to significant advances in the treatment of immune-mediated inflammatory diseases (IMIDs). Blocking undesired inflammatory effects also has the potential to disrupt the body's immune response and increase the risk for infections, including fungal infections. This review summarizes the published data on the frequency and risk for fungal infections among patients treated with biologics, with a focus on the newer therapies approved for use with IMIDs in the last 10 years. The use of biologics is associated with a small but important risk of fungal infections. *Pneumocystis jirovecii* pneumonia, histoplasmosis, and candidiasis are some of the most common fungal infections associated with biologics. Providers should be vigilant for fungal infection among patients taking biologics, be aware that biologic agents may alter the typical presentation of fungal infections, and take timely steps to diagnose and treat fungal infection to reduce resultant morbidity and mortality.

Keywords Biologics · TNF-alpha inhibitors · Anakinra · Abatacept · Rituximab · Ustekinumab · Tocilizumab · Tofacitinib · Vedolizumab · Secukinumab · Ixekizumab · Fungal infections · Histoplasmosis · Candidiasis · Cryptococcosis · Coccidioidomycosis · Aspergillosis · Incidence · Risk · Prevention

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Introduction

In the last decade, significant advances have been made in the development of biologic therapies targeting pro-inflammatory mediators to treat immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis, psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Tumor necrosis factor-alpha (TNF-α) inhibitors were among the first biologics developed with infliximab and etanercept, gaining FDA approval in 1998. Since then, three other TNF-α inhibitors and several more biologic therapies that target other proinflammatory mediators, including interleukin (IL)-1, IL-6, IL-12, IL-23, and janus kinase (JAK) have been approved for use, and many more are under development [1•]. These biologic therapies have two things in common: they block the undesired inflammatory effects of a dysregulated immune system, but they also have the potential to disrupt the body's immune response that would normally be mounted against pathogens. Therefore, some patients who are on biologic therapies may be at increased risk for infections, including those caused by fungi.

The objective of this review is to summarize the published data on the frequency and risk for fungal infections among patients taking biologics, with a focus on the newer agents approved for use with IMIDs in the last 10 years. This is challenging for several reasons. First, many patients taking biologics have underlying immune dysregulation that already predispose them to fungal infections [2] and biologics are often used in combination with other immunosuppressive agents such as corticosteroids and non-biologic disease-modifying antirheumatic drugs (DMARDs), which also contribute to increased risk of

fungal infections [3]. Second, many studies that evaluate the safety profile of biologics only report on the risk of serious infections or opportunistic infections (OIs), which is an aggregate measure of multiple types of infections including viral, bacterial, mycobacterial, fungal, and parasitic. Fungal infections, especially invasive fungal infections (IFIs), are relatively rare and account for a very small proportion of serious infections or OIs, making it difficult to assess if findings indicating an increased risk of serious infection or OIs apply specifically to fungal infections. Because not all studies include the same infections in calculations of serious infection risk, it is challenging to compare risks across different studies and different biologic agents. Third, some fungal diseases, such as histoplasmosis, coccidioidomycosis, and blastomycosis are generally restricted to certain geographic regions of the world and studies where a majority of participants are recruited from non-endemic areas (e.g., a substantial number of studies evaluating the safety of biologics among patients with RA have been done in Japan where these diseases are not endemic) cannot evaluate the risks of infections by these geographically restricted pathogens. Finally, unlike etanercept and infliximab, which have been in use for nearly two decades, many of the newer agents have not been in use for more than a few years and data on fungal infection occurrence are simply not available.

In a 2014 meta-analysis of 70 randomized controlled trials (RCTs) that included over 30,000 RA patients receiving a variety of biologics, there were fewer than 100 OIs in the treatment and control groups combined. While there was significant increase in risk of all OIs and specific infections such as tuberculosis and viral infections for those receiving biologic treatments compared with placebo, there were no significant differences between the groups for superficial fungal infection (RR 1.31; 95 % CI, 0.46–3.72), any IFI (2.85; 0.68–11.91), or *Pneumocystis jirovecii* pneumonia (PJP) (1.77; 0.42–7.47) [4••]. There were a total of 14 fungal infection (6 PJP, 5 invasive aspergillosis, 2 histoplasmosis, and 1 coccidioidomycosis) reported in this study. In another large study of patients with IMIDs, there were more non-viral OIs (includes IFIs) among patients treated with TNF-α inhibitors than among those treated with non-biologic DMARDs, but this difference was not statistically significant [5•]. The lack of statistical significance in these studies should not be interpreted as proof of no association between biologic therapies and fungal infection risk. Despite the rarity of fungal infections, they do occur among patients taking biologic therapies, they have the potential to cause significant morbidity and mortality, and they are important to understand, recognize, treat, and prevent when possible. In this review, we first describe specific biologic agents then discuss specific fungal infections.

TNF-α Inhibitors

Infliximab, Etanercept, and Adalimumab

The possible influence of biologics on patients' susceptibility to opportunistic fungal infection became a prominent issue when the Food and Drug Administration (FDA) issued a black box warning about the risk of histoplasmosis with TNF-α inhibitors in 2001 following the reporting of 240 cases of histoplasmosis among patients receiving these medications [6]. TNF-α plays a crucial role in the host immune response to pathogens because it is involved in the recruitment of inflammatory cells to the site of infection and formation and maintenance of granulomas to contain the infection and prevent dissemination. The three older TNF-α inhibitors (infliximab, etanercept, and adalimumab) have been best studied. These three TNF-α inhibitors have been associated with a small but significant increase in risk of serious infections including viral and non-viral OIs [5•, 7–9] when compared with treatment with non-biologic DMARDs. The monoclonal TNF-α inhibitors (infliximab and adalimumab) may be associated with a higher risk of OIs, including fungal OIs like histoplasmosis, coccidioidomycosis, candidiasis, and aspergillosis, than soluble TNF receptor agents (etanercept) [10–14] (Table 1). IFIs seem to also occur earlier during infliximab therapy compared with etanercept therapy (median of 55 versus 144 days) [11]. In a recent study using administrative claims data of more than 30,000 patients prescribed a TNF-alpha inhibitors during 2007–2009, 158 patients (0.51 %) developed fungal or mycobacterial disease [15••]; approximately half of these infections were fungal, including PJP, cryptococcosis, histoplasmosis, coccidioidomycosis, and blastomycosis. Similarly, in another meta-analysis of the safety of TNF-α inhibitors among more than 7000 patients with IBD, less than 1 % experienced an OI and oral or esophageal candidiasis was the most common fungal OI [8].

Certolizumab

Certolizumab is a TNF-α inhibitor that was approved for use in 2008 for RA, Crohn's disease, PsA, and AS. Certolizumab neutralizes both soluble and membrane TNF-α. In contrast to the other TNF-α inhibitors, certolizumab does not activate antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity. In a pooled safety analysis of over 4000 RA patients enrolled in RCTs or open-label extensions (OLEs) studies, patients on certolizumab had 4 times higher odds of having a serious infection than those in the placebo groups during a mean drug exposure duration of 2.1 years. There were 13 fungal infections in the treatment group (7 esophageal or oral candidiasis, 3 bronchopulmonary aspergillosis, 2 disseminated histoplasmosis, and 1 PJP) and no reported fungal infections in the more than 1000 patients

Table 1 Biologic agent, mechanism of action, date of approval, indication, and comments about fungal infections

Agent	Mechanism	Date of FDA approval	Indication	Notes about fungal infections	Reference
TNF-α inhibitors					
Infliximab	Monoclonal Ab against TNF-α	1998	RA, Crohn's disease, UC psoriasis, AS	Carry black box warning for histoplasmosis and other endemic fungi. Infliximab and adalimumab may be associated with higher risk of some fungal infections than compared with etanercept	[6, 10–14]
Etanercept	Receptor fusion protein	1998	RA psoriasis, AS, JIA		
Adalimumab	Monoclonal Ab against TNF-α	2008	RA, Crohn's disease, UC, psoriasis, AS, JIA		
Certolizumab	Monoclonal Ab against TNF-α	2008	RA, Crohn's psoriasis, AS	Multiple fungal infections reported, including candidiasis, PJP, histoplasmosis	[16, 17]
Golimumab	Monoclonal Ab against TNF-α	2009	RA, psoriasis, AS, UC	Multiple fungal infections reported, including candidiasis, PJP, histoplasmosis, coccidioidomycosis	[20, 21]
Other agents					
Anakinra	IL-1 receptor antagonist	2001	RA	Increased risk of serious infection compared to placebo but no fungal infections; limited data	[24, 27]
Abatacept	Selective T-cell co-stimulation modulator	2005	RA, JIA	Small number of fungal infections reported including histoplasmosis, blastomycosis, aspergillosis, and systemic candidiasis	[23, 25]
Rituximab	Monoclonal Ab against CD20, affects B cells	2006 (approved in 1997 for NHL)	RA	Small number of fungal infections reported including candidemia, *Scedosporium* lung infection, and *PJP*	[32]
Ustekinumab	Monoclonal Ab against IL-12 and IL-23	2009	Psoriasis, PsA; being studied for Crohn's disease	Lowest risk of any serious infection in the patients with psoriasis when compared with infliximab and other biologics. No fungal infections reported	[34–36]
Tocilizumab	Monoclonal Ab IL-6 receptor	2010	RA, JIA	Small number of fungal infections including invasive candidiasis, PJP, and cryptococcal pneumonia	[42]
Tofacitinib	Janus kinase inhibitor (oral)	2012	RA	Esophageal candidiasis and cryptococcal infection reported	[44, 45]
Vedolizumab	Monoclonal Ab against integrin	2014	Crohn's disease, UC	No signal for increased risk for fungal infections	[48]
Secukinumab	Monoclonal Ab against IL-17A	2015	Psoriasis, PsA, AS	Two to 5 % of patients of secukinumab developed candidiasis; most was oral, esophageal, skin, or vaginal	[49–51]
Ixekizumab	Monoclonal Ab against IL-17A	Under investigation	Psoriasis	Twice as many skin, oral, esophageal, and vaginal *Candida* infections in ixekizumab given every 2 weeks compared with placebo	[52]

included in the control groups [16]. In a 7-year OLE study of certolizumab in Crohn's disease with nearly 600 patients and 2000 patient-years of follow-up, there were 13 fungal infections reported, though the type of fungal infection was not specified [17]. There were no reports of any OIs including fungal infections in a 24-week study of certolizumab among 409 patients with PsA [18]. Whether certolizumab is associated with a lower incidence of OIs than other TNF-α inhibitors because of its different mechanism of action is unclear since head-to-head trials have not been conducted. In a meta-analysis of TNF-α inhibitors used in IBD patients, there was no difference in risk of OIs when stratified by the different TNF-α inhibitors compared with placebo [8]. Evidence is insufficient to assess comparative risk of infection between TNF-α inhibitors [19].

Golimumab

Golimumab is a newer TNF-α inhibitor approved in 2009 and indicated for use in moderate to severe RA, PsA, AS, and ulcerative colitis (UC). In a pooled safety analysis of RCTs evaluating the use of 50 and 100 mg of golimumab versus placebo in over 2000 patients with RA, PsA, and AS for up to 3 years, there were 11 OIs reported (included histoplasmosis, PJP, esophageal candidiasis, and coccidioidomycosis), all of which were among the treatment groups [20]. The incidence of OIs was higher in the group treated with 100 mg of golimumab. In an RCT of golimumab among more than 1000 UC patients followed for 54 weeks, there was one fungal infection reported, esophageal candidiasis in a patient in the treatment arm [21, 22].

Other Biologic Therapies

A number of non-TNF-α-based biologic therapies that are have been approved for use in treating IMIDs. In general, these agents have been found to have a risk of serious infections similar to or less than that of TNF-α inhibitors [4••, 23–25]. But whether this difference in risk is due to differences intrinsic to the biologic therapies themselves or because of better selection and screening of patients in trials conducted more recently with newer non-TNF-α-based biologic therapies is unclear. A network analysis of several non-TNF-α-based biologics used in RA found no difference in safety between individual agents [26]. Use of these non-TNF-α-based biologics in combination with TNF-α inhibitors or with each other has been found to be associated with an unacceptably high risk of infection and is usually not recommended. The section below provides detail about the fungal infections associated with currently approved non-TNF-α-based agents.

Anakinra

Anakinra is an IL-1 receptor antagonist used for treatment of RA in 2001. In pooled studies of nearly 2800 RA patients, there was an increased risk of serious infection with higher doses (≥100 mg/day) of anakinra treatment compared with placebo, but no cases of fungal infections were reported in either the treatment or placebo groups [24, 27].

Abatacept

Abatacept, approved for use with RA in 2005, and later for JIA, is a soluble receptor IgG fusion protein that interferes with T-cell co-stimulation. In an integrated safety analysis of over 4000 patients with over 10,000 patient-years (PY) of exposure to abatacept, treatment with abatacept was associated with a slightly higher risk of serious infections; several fungal infections were reported including aspergillosis (0.02/100PY), blastomycosis (0.01/100PY), and systemic *Candida* (0.01/100PY) in the treatment arms [23]. In a 2-year head-to-head trial of subcutaneous abatacept versus adalimumab among over 600 RA patients, there were four OIs, all fungal infections in the abatacept arm (1 disseminated histoplasmosis and 3 oral candidiasis) and four OIs in the adalimumab arm (1 disseminated histoplasmosis, 1 oral candidiasis, and 2 tuberculosis) [25]. There are several other abatacept trials with several thousand patient-years of follow-up that did not report occurrence of any fungal infections [28–31].

Rituximab

Rituximab is a selective monoclonal antibody targeting CD20+ B cells and leads to depletion of these cells in the peripheral blood. B cells can contribute to the initiation and maintenance of the inflammation in RA by acting on antigen presentation by T cells and through production of proinflammatory cytokines and auto-antibodies. Rituximab was initially approved for use in non-Hodgkin's lymphoma in 1997 and later approved for use in RA in 2006. The overall risk of serious infection in RA patients does not appear to be elevated with rituximab treatment compared with placebo [24], and incidence of any OI is low at 0.05/100PY [32]. In a 10-year follow-up study of RA patients treated with rituximab reporting on nearly 12,000 patient-years of observation, there were 7 OIs reported, of which three were fungal: candidemia, *Scedosporium* lung infection, and PJP [32]. Rituximab is one of the few biologic agents that are sometimes used in combination with TNF-α inhibitors among individuals who do not respond to TNF-α inhibitor therapy alone. A safety study of 51 patients with RA were stratified to receive, in addition to methotrexate and a TNF-α inhibitor, either rituximab or placebo; there were non-statistically significant more overall infections with the rituximab group compared with the placebo

group, but none were invasive IFIs; only one patient in the rituximab group had vaginal candidiasis [33].

Ustekinumab

Ustekinumab is an IL-12 and IL-23 blocker that was approved for use in moderate to severe plaque psoriasis in 2009 and for PsA in 2013. Among patients with psoriasis treatment with ustekinumab had a lower frequency of serious infection than was observed for treatment with infliximab and other biologics [34]. In a pooled safety analysis of ustekinumab among 3000 patients with psoriasis, no IFIs were reported during 1.7 years of follow-up time [35, 36]. In an RCT of 312 adults with PsA, there were no cases of invasive fungal infections in the ustekinumab arm [37]. Because of the lower risk of infection with ustekinumab, it might be preferred over etanercept in patients with PsA who are at higher risk for OIs (e.g., patients with latent tuberculosis infection) [38]. No fungal infections were observed among patients with Crohn's disease and AS treated with ustekinumab, though it is not FDA approved for these indications yet [39, 40].

Tocilizumab

Tocilizumab, approved in 2010 for use in RA, is a monoclonal antibody that binds to IL-6 receptor and blocks IL-6 mediated proinflammatory signaling. The odds of serious infections was almost twice as high among those treated with higher dose (8 mg as opposed to 4 mg) of tocilizumab plus methotrexate compared with those treated with methotrexate alone [41]. In a combined analysis over 4000 patients RA exposed to tocilizumab with a mean treatment duration of 2.4 years, 11 cases of invasive fungal infections were reported (including 6 cases of invasive candidiasis, and one case each of PJP and cryptococcal pneumonia). All of these infections, with the exception of PJP, occurred among patients taking the higher dose of tocilizumab. There were no OIs reported in the 1555 patients in the placebo arms of these studies [42]. In another study comparing 600 RA patients treated with tocilizumab monotherapy and an equal number of age- and gender-matched patients being treated with other therapies including non-biologic DMARDS, the risk of serious respiratory infection was two times higher in the tocilizumab group. However, most of the difference in risk was attributable to bacterial pneumonia and there was no substantial difference in the number of respiratory fungal infections between the two groups [43].

Tofacitinib

Tofacitinib is a novel, oral JAK inhibitor used for the treatment of RA and PsA in 2012 and is under investigation for psoriasis and IBD. In an RCT of 10 and 5 mg of tofacitinib used in combination with other DMARDS (primarily methotrexate) versus DMARDs alone, rates of serious infection were higher in the higher dose tofacitinib compared with low-dose and placebo groups. One of 391 patients in the 10 mg tofacitinib arm presented with cryptococcal pneumonia after 6 months of taking study drug. There were no other fungal infections reported in any of the other arms of the study [44]. In a combined safety analysis of tofacitinib that included over 5000 patients, there were 0.21 non-TB-OIs per 100 patient-years, and those on concurrent corticosteroids had a higher rate of these OIs than those not on steroids. Fungal infections recorded in this study included esophageal candidiasis ($n=9$), PJP ($n=4$), and cryptococccal infection ($n=3$) [45].

Vedolizumab

Vedolizumab is a biologic agent which was FDA approved in 2014 for use in IBD among patients who are not responsive to or have lost response to TNF-α inhibitors. It is anti-integrin monoclonal antibody that acts by inhibiting leukocyte adhesion and subsequent migration into the brain and gut. Although some individual trials found increased risk of serious infection with vedolizumab [46], in a meta-analysis of six RCTs of vedolizumab, there was no significant increase in serious infection compared with placebo [47]. Although there is evidence that vedolizumab may increase the rate of *Clostridium difficile* and cytomegalovirus colitis [48], there was no signal for increase in risk of fungal infections.

Secukinumab

Secukinumab is an anti-interleukin-17A monoclonal antibody which was approved for use in patients with moderate to severe plaque psoriasis in 2015. In two 3-arm RCTs of secukinumab versus etanercept versus placebo among 1200 patients with psoriasis, infection risk was higher in the secukinumab arms than the etanercept or placebo arms. *Candida* infections were more common with secukinumab than with etanercept and placebo, with 2–5 % of patients on the secukinumab treatment arms developing *Candida* infections at some point during the trial; none of the infections resulted in chronic mucocutaneous candidiasis or discontinuation of the study drug, and all were either self-limited or resolved with standard therapy [49]. The same finding of increased risk of superficial *Candida* infection was confirmed by another RCT of secukinumab used in PsA and AS patients [50, 51]. More data is needed on long-term infection risk of this agent as most published studies have been of RCTs with relatively short follow-up periods.

Ixekizumab

Ixekizumab is a monoclonal antibody against IL-17A under investigation for use in psoriasis. In a combined report of 2400 patients comparing various doses of ixekizumab to etanercept or placebo, there were twice as many skin, oral, esophageal, and vaginal *Candida* infections in the ixekizumab given every 2 weeks (12 infections, 1.6 % of patients) than placebo (2, 0.6 %), etanercept (5, 0.6 %), or ixekizumab arms every 4 weeks (4, 0.5 %) [52]. All but one of these infections resolved with standard oral, local, or topical treatments, and none of the patients' biologic treatment was discontinued. There were no other fungal infections reported. In a 64-week OLE study of ixekizumab among 300 patients with RA, there were no reports of invasive fungal infections [53].

Specific Fungal Diseases

Candidiasis

The incidence of *Candida* infections among patients treated with TNF-α inhibitors is between 5 and 10 cases/100,000 persons [14]. As mentioned above, other biologic agents such as secukinumab and ixekizumab also have had a notable number of *Candida* infections (mostly the skin and mucous membrane as opposed to invasive disease) reported. *Candida* infections do not often require discontinuation of biologics and are easily treated. When invasive candidiasis does occur, mortality may be as high as 50 % [11].

PJP

The incidence of PJP among patients on TNF-α inhibitors varies widely between <0.01/1000 PYs in North America to 8.8/1000 PYs in Japan [54]. The difference in incidence has been attributed to the use of different testing modalities as well as difference in the actual distribution of disease. Up to a quarter of patients with RA have been reported to be asymptomatically colonized with PJP; risk factors for colonization include methotrexate and corticosteroid use and infliximab treatment for >3 years [56]. When presenting with PJP, patients with IMIDs tend to have a shorter duration of symptoms (~1 week as opposed to ~1 month in HIV-infected persons) and lower beta-D glucan and higher C-reactive protein levels [55]. Because of the wide variation in incidence, there is no universal recommendation for prophylaxis for PJP; given the low incidence among patients in North America and Europe, routine prophylaxis is likely unnecessary in these settings. Studies in Japan have shown some benefit with trimethoprim/sulfamethoxazole prophylaxis. Patients treated with both high-dose corticosteroids and TNF-alpha inhibitors may be at higher risk for PCP, and prophylaxis may be considered [54].

Aspergillosis

Invasive aspergillosis (IA) is an opportunistic infection most commonly seen in patients with prolonged neutropenia. TNF-alpha inhibition and other changes in the inflammatory pathways caused by biologic agents can interfere with neutrophil function. The majority of cases of aspergillosis reported in patients taking biologics agent have been reported in patients with concomitant solid or bone marrow transplants, but a few cases have been reported among patients with IMIDs, especially those with IBD and RA [56, 57]. There is no indication for prophylaxis against IA among patients with IMIDs being treatment with biologics.

Cryptococcus

Cryptococcal infections are rare among patients with IMIDs treated with biologics. In one case series of 28 patients on TNF-α inhibitors with cryptococcal infection, most patients had cryptococcal pneumonia and responded to azoles or amphotericin treatment; none died [11].

Dermatophytosis

TNF-α may play a role in the skin cell's cytokine cascade and defense against superficial fungal infections and inhibition of this cascade may result in skin infections with *Tinea, Pityriasis*, and *Trichophyton* [58, 59]. One study that systematically conducted surveillance for *Pityriasis versicolor* over a 1-year period among psoriasis patients given TNF-α inhibitors reported an incidence of 4 % [59]. Nearly all of the infections occurred within 12 months of initiating therapy. Dermatophytosis may occur more frequently than reported because the diagnosis is often missed during routine care of patients with IMIDs. Whether superficial fungal infections increase risk of IFI is unknown.

Endemic Mycoses

The incidence of endemic mycoses among patients taking biologics is hard to obtain because of the small numbers of infections and lack of region-specific denominators in many cases. Interestingly, one study found that residence in the Western census region of the USA was associated with an increased odds (OR 1.77; 95 % CI 1.05–2.98) of seeking healthcare for a mycobacterial or fungal disease compared with living in the South. This may, in part, be due to regional variations in exposure to various endemic fungi such as coccidioidomycosis [15••].

Histoplasmosis

Histoplasmosis is the one of the most common IFIs among patients taking TNF-α inhibitors [60] and histoplasmosis-associated hospitalizations have increased by nearly 15 % per year in the last decade [61]; mortality rate in this population has been reported at 20 % [11, 62]. Unlike otherwise healthy patients who develop histoplasmosis, a majority of patients on TNF-α antagonists who develop histoplasmosis present with progressive disseminated histoplasmosis and diagnosis is often missed [63]. In one case series of 26 patients with RA who developed histoplasmosis, median time between initiation of biologic agents and diagnosis was 15 months, suggesting new exposure and not reactivation as the cause of disease [64]. Notably, half of these patients were on concurrent steroids. Clinicians should maintain a low threshold for suspicion of histoplasmosis among persons on biologic therapy residing in endemic areas or with recent travel to endemic areas. Biologic agents are usually discontinued during treatment of infection. Treatment may involve amphotericin and itraconazole; itraconazole treatment may be required for 12 months, even for cases with pulmonary histoplasmosis [64]. Resuming biologic therapy needs to be done cautiously.

Coccidioidomycosis

Studies of coccidioidomycosis among patients on biologics is largely limited to those taking TNF-α inhibitors (infliximab and etanercept). In a 2004 study at a center in an endemic area, the cumulative incidence of coccidioidomycosis over a 3-year period was 1 % (11/985 patients) [13]. Infliximab treatment carried a greater risk of infection than etanercept treatment. Pneumonia was the most common manifestation and dissemination occurred in one quarter of cases. Most cases are attributed to new infections rather than reactivation of old disease. Continuing or restarting biologic therapy after resolution of cocci infection is feasible, depending on severity of the preceding infection [65].

Blastomycosis

Little is known about blastomycosis and TNF-alpha inhibitors. Only a handful of cases have been reported in association with biologics.

Conclusions

Biologic therapies are an important part of treatment of IMIDs and have greatly improved treatment outcomes for patients suffering with debilitating illness. However, the use of these agents is associated with a small but important risk of serious and invasive fungal infections.

Unlike the success of screening patients for tuberculosis, the utility of screening patients for evidence of prior fungal infections before starting biologic therapy is unclear. Unlike TB, many fungal diseases in this population tend to be de novo infections as opposed to reactivation disease. Therefore, screening for these infections before initiation may not be useful. Data on use and effectiveness of antifungal prophylactic therapy among patients on biologic agents is scant.

Counseling patients who are being treated with biologic therapies on avoidance of high-risk activities such as spelunking and participating in demolition activities, especially in areas where certain fungi (e.g., *Histoplasma*, *Coccidioides*) are highly endemic, is an important prevention measure. Patients should also be educated on signs and symptoms of fungal infections and advised to seek care promptly to facilitate early diagnosis and treatment. In addition, educating clinicians about the risk of fungal infections, the varied manifestations of fungal infections among patients treated with biologics, and the need for early recognition and prompt treatment initiation are necessary to prevent morbidity and mortality from fungal infections.

Compliance with Ethical Standards

Conflict of Interest SV and TC declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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