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EPIDEMIOLOGY OF FUNGAL INFECTIONS (T CHILLER AND J BADDLEY, SECTION EDITORS)

Small-Molecule Protein Kinases Inhibitors and the Risk of Fungal Infections

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Abstract

Purpose of Review This review discusses fungal infections associated with licenced small-molecule protein kinase inhibitors. For each major drug class, the mechanism of action and targeted pathways and the impact on host defence against fungi are described.

Recent Findings Protein kinase inhibitors are successfully used in the treatment of malignancies and immune-mediated diseases, targeting signalling pathways for a broad spectrum of cytokines and growth-stimuli. These agents predispose to fungal infections by the suppression of integral components of the adaptive and innate immune response.

Summary The greatest risk of fungal infections is seen with bruton tyrosine kinase inhibitors, e.g. ibrutinib. Infections are also reported with agents that target mTOR, Janus kinase and break point cluster (Bcr) gene–Abelson (Abl) tyrosine kinase (BCR-ABL). The type of fungal infection fits mechanistically with the specific pathway targeted. Infections are often disseminated and present soon after the initiation of therapy. The pharmacokinetic profile, possibility of off-target kinase inhibition, and underlying disease pathology contribute to infection risk.

Keywords Small-molecule protein kinases inhibitors · BTK inhibitor · mTOR inhibitor · JAK inhibitor · BCR-ABL inhibitor · Fungal infections

Introduction

Small molecules that inhibit protein kinases are efficacious in the treatment of cancer, targeting specific mutations that drive tumorigenesis. The pathways targeted by these inhibitors are also important in the signalling and interaction of immune cells. Success in oncology, alongside an improved understanding of the inflammatory signalling cascades, has driven their pursuit in the treatment of immune-mediated diseases. Protein kinases inhibitors block the signalling pathways for a broad spectrum of cytokines and growth stimuli. Their downstream interference in these cascades has the potential to cause significant and unanticipated immune disturbances.

Fungal infections are of interest to physicians prescribing immunosuppressive therapies. Very few fungi are pathogenic in an immunocompetent host, often limited to those that are dimorphic in nature and endemic to certain geographic locations. Opportunistic fungal infections are invasive and can cause considerable morbidity and mortality in the immunocompromised individual. Specific defects in the immune system may provide clues to the risk of an associated opportunistic fungal infection. For example, patients with HIV/AIDS develop infections with *pneumocystosis*, *cryptococcosis*, *histoplasmosis*, and *talaromycosis* (formerly known as *penicilliosis*) as CD4 immunity is essential for the long-term control and memory responses to these fungi [1]. Similarly, TNFα inhibitors are associated heightened risk of granulomatous fungi including *histoplasmosis* and *coccidioidomycosis* due to the critical role of TNF-α in granuloma formation [2]. Invasive aspergillosis is associated with suppression of innate immunity, for example, with chemotherapy or corticosteroid-induced neutropenia [3]. Both innate resistance and acquired immunity play some role in the host defence against *Candida*. Neutrophils are critical for protection against systemic

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infections such as candidaemia, whilst CD4 cells-mediated immunity and the production of interleukin-17 are important for the protection against mucosal infection [4]. Engagement of pattern recognition receptor on macrophages induces the production of multiple cytokines, which in turn activate T effector responses. The IL-17 pathway appears integral in candida immunity, with upregulation of proinflammatory cytokines and antimicrobial peptides [5]. The IL-12 family also has an established role, IL-12 is important during systemic infection, whilst IL-23 and Th17 responses protect against mucocutaneous involvement [6].

The spectrum of invasive fungal infections observed in patients prescribed small-molecule protein kinases inhibitors reflects their diverse impact on the immune system, driven by the suppression of integral signally pathways that influence a spectrum of adaptive and innate immune responses.

Small-Molecule Protein Kinases Inhibitors

Protein kinases control cell transcription, proliferation, differentiation, survival, metabolism, movement, and participate in the immune response [7]. These enzymes modify proteins by 80 chemically adding phosphate groups t o them 81 (phosphorylation) and are divided into two major classes: those that phosphorylate tyrosine and those that phosphorylate serine and threonine. Mutations, overexpression, or dysregulation of protein kinases play an essential role in the pathogenesis of many illnesses. Over the last 20 years, this family of enzymes has become one of the most important drug targets [8••,9].

The discovery of small-molecule protein kinases inhibitors marked a revolutionary milestone in cellular biology research. In 2001, Imatinib became the first FDA-approved mechanism-based small-molecule kinases inhibitor [7]. There are currently 48 approved agents (Fig. 1), 25 inhibit receptor protein-tyrosine kinases, 10 inhibit non-receptor protein-tyrosine kinases, and 13 are directed at protein-serine/threonine protein kinases. Forty-three inhibitors are directed toward malignancies; 37 against solid tumours including lymphomas and 8 against non-solid tumours, e.g. leukaemia's. Seven are directed toward non-malignancies, including transplantation rejections, inflammatory arthritis, ulcerative colitis, polycythemia vera, idiopathic pulmonary fibrosis and glaucoma [8••].

Small-molecule protein kinases inhibitors offer advantages over chemotherapeutics, RNAi agents and immune-targeted biologics. Their specificity results in fewer side effects than cytotoxic chemotherapy, where all cells may be vulnerable. They are small chemical compounds that are easy to synthesize and being nonproteinaceous are orally bioavailable. In inflammatory disorders, these inhibitors interfere with a wide spectrum of cytokines involved in existing and potential inflammatory pathway, overcoming challenges in therapeutic efficacy seen with single cytokine inhibition. However, their use may be accompanied by resistance, caused by overexpression of the target kinase, a receptor mutation or activation of other signalling pathways [10]. They demonstrate a dose-proportional pharmacokinetic profile,

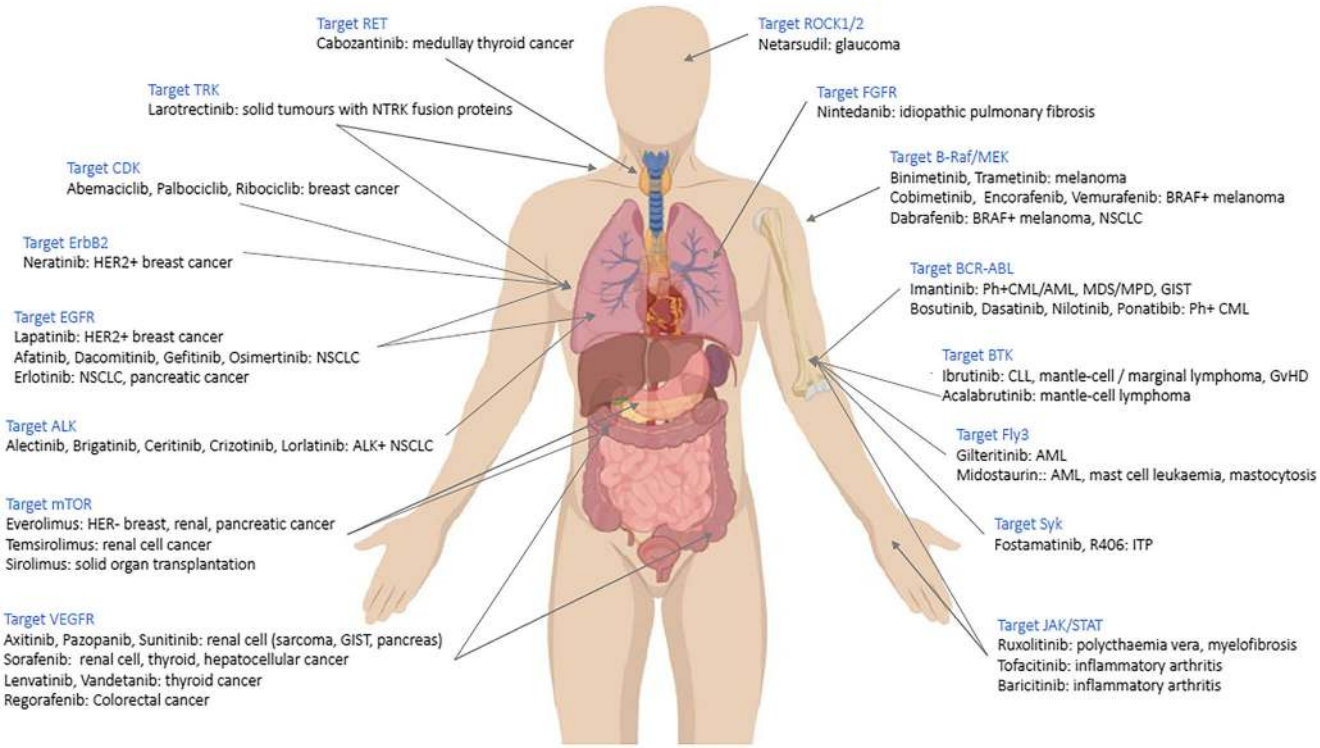

Fig. 1 Primary therapeutic targets of small-molecule protein kinases inhibitors (despite many being multikinase inhibitors) and licenced condition

with possible off-target kinase inhibition, and are subject to hepatic metabolism, renal clearance and drug interactions, alongside the generation of active metabolites which may exacerbate things further. There is increasing evidence that many of these inhibitors can have a substantial impact on immune function and a subsequent risk of opportunistic infections.

Fungal Infection by Protein Kinase Target

In this narrative review, we searched the literature using MEDLINE and EMBASE databases to identify publications on fungal infections with small-molecule protein kinases inhibitors. The search included all 48 approved agents as of March 2019. A total of 1101 articles were identified, of which 81 were eligible. A further 17 studies were excluded as they presented limited data on fungal infections, did not classify infections numbers by drug or only presented animal data on fungal infections. In total, 64 studies were eligible for inclusion in our analysis. Of the 48 small-molecule protein kinases inhibitors, only 18 had publications identified in the search.

Bruton tyrosine kinase inhibitor

Bruton tyrosine kinase (BTK) plays a crucial role in B cell development. Bruton's agammaglobulinemia is an X-linked primary immunodeficiency caused by mutations in BTK. Children with this condition suffer from opportunistic infections in early life. They have normal pre-B cell populations in their bone marrow, but these cells fail to mature and enter the circulation. Ibrutinib is a BTK inhibitor that results in decreased B cell survival (Table 1). Although the prominent effect is on B cells, other haemopoietic cells are affected, including T cells, natural killer cells and macrophages [11]. BTK has emerged as a key player in innate immunity. It is implicated in toll-like receptor (TLR) signalling pathways that regulate macrophage activation and the production of proinflammatory cytokines [12]. It also regulates a key innate inflammatory machinery, the NLRP3 inflammasome [13].

It is likely that fungal infection with BTK inhibitors results from a complex immunodeficiency affecting a broad range of immune cells in the adaptive and innate immune system. CD4 T cell–macrophage crosstalk plays an important role in the host's defence against fungal infections. Increased susceptibility may result from the inhibition of BTK signalling in monocytes and macrophages, impeding chemotaxis, adhesion, transmigration, reactive oxygen species production, cytokine response, and inflammasome activation [14••]. BTK gene knockout mice demonstrate increased mortality from fungal infections, particularly *aspergillus* and *cryptococcus* [15, 16]. Macrophage activation in the immune response against *Aspergillus* is driven by TLR9 signalling through BTK [17]. Furthermore, BTK inhibitors may have off-target effects on other kinases that affect CD4 T cell function, especially when the drug is given at higher doses.

The greatest number of publications on fungal infections with protein kinase inhibitors was identified with ibrutinib (Table 2). Aspergillosis was the most frequently reported fungal infection. These studies reported that most patients present within a few months of the initiation of ibrutinib therapy, with a high rate of CNS involvement and a low survival rate [11,18••]. Similar findings are noted with other fungal infections presenting soon after starting therapy [19]. One author noted that the early onset of disseminated cryptococcosis might suggest that patients had preceding pulmonary colonization [20]. In general, infections occurred at multiple sites, especially with *aspergillus* and *mucormycosis* [21]. There were a similar number of cases reported with ibrutinib monotherapy as combination therapy [19]. Steroid therapy, allogeneic stem cell transplantation, three or greater prior treatments, prolonged neutropenia, diabetes, and liver disease all represented additional risk factors for fungal infections [22–24]. Patients with *Pneumocystis jirovecii* pneumonia demonstrated normal CD4+ T cell counts and immunoglobulin levels, suggesting that a high level of clinical suspicion may be required to diagnose infections in these patients [25]. Acalabrutinib is a second-generation BTK inhibitor, designed to be more potent and selective than ibrutinib. The number of reported fungal infection is less than that seen with ibrutinib. A large safety analysis of 610 patients on acalabrutinib monotherapy described only 4 fungal infections [26] whilst just 1 case report was identified in the literature, of a patient with a disseminated cryptococcal infection [27].

Mechanistic target of rapamycin inhibitor

Mechanistic target of rapamycin inhibitor (mTOR) is a serine and threonine protein kinase, identified over 20 years ago as the target of the drug rapamycin (sirolimus), from which mTOR's name derives. It is now recognised that mTOR plays a crucial role in cell growth and proliferation [28]. mTOR inhibitors block signalling of growth factors and nutrients via the phosphoinositide 3-kinase (PI3K)/AKT/mTOR protein cascade (Table 1). Sporadic mutations or deregulation of PI3K and AKT, together with p53, are some of the most prevalent alterations in human cancer. mTOR inhibitors are used in the treatment of cancers and the prevention of renal allograft rejection. Signalling via mTOR is essential for IL-2 driven T cell proliferation and differentiation via nutrient availability and cytokine/growth factor signalling [29]. Interestingly, blocking mTOR signally leads to a differential development of T cell subpopulations, some of which inhibit an immune responses whilst others actually promote immunity [29]. Experimental studies suggest mTOR signalling also drives on B cell differentiation and activation of B cell differentiation and activation of B cell and the functioning of antigen-presenting cells, specifically their ability to stimulate T cell activation [30].

Table 1 Small-molecule protein kinases inhibitors, mechanism of action, target disease and drugs

Target	Mechanism of action	Diseases	Drugs
BTK inhibitor	Interferes with B cell signalling cascades via B cell receptor pathway - Binding to BTK, prevents key phosphorylation - Reduces B Cell differentiation, proliferation and migration - Decreasing B cell survival and anti-tumour activity Also interferes with TLR signalling, reducing macrophage activation [12] and regulates NLRP3 inflammasome [13]	Leukaemia (chronic lymphocytic leukaemia) Lymphoma (mantel cell marginal zone)	Imatinib Acalabrutinib
mTOR inhibitor	Interferes with signalling of growth factors and nutrients via the PI3K/AKT/mTOR protein cascade [64] Acts via mTOR complex 1 - Reduces protein synthesis, glycolysis, lipogenesis leading to autophagy - Reduces angiogenesis, proliferation and migration Acts via mTOR complex 2 - Blocks AKT activation, reducing proliferation & induces cell death (blocks G1/S cell cycle, cell)	Cancer (renal cell carcinoma, breast, pancreas) Renal transplant	Everolimus Temsirolimus Sirolimus
JAK inhibitor	Interferes with signalling via the JAK-STAT pathway - Signally requires 2 associated JAKs to phosphorylate, - JAK1 pairs with any of the 3 JAKs and signals IFNs, IL-10, IL-6 - JAK2 signals growth hormones (EPO, TPO, GM-CSF) - JAK3 signals γ-chain cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21) - TYK signals IFNα & β, IL-12 & IL-23 - Reduces activation of STATs (transcription factors) which would lead to gene transcription [65, 66]. - Decreasing cytokine driven activation and function of both innate and adaptive immune cells	Inflammatory arthritis Myelofibrosis, polycythemia vera	Tofacitinib Baricitinib Ruxolitinib
BCR-ABL inhibitor	Inhibit ABL tyrosine kinase activity, blocking autophosphorylation driven by the juxtaposition of BCR. Interferes with a number of survival pathways that are deregulated by BCR-ABL activation [46,47] - RAS/RAF/MEK/ERK pathway—reducing signalling of nuclear transcription factors which govern cell cycle control & thus decreases cell proliferation - JAK-STAT pathway—impairing transcriptional activity via cytokine & hormone signalling	Haematological malignancies (Philadelphia chromosome–positive chronic myeloid leukaemia, myelodysplastic syndromes, myeloproliferative disorder)	Imatinib Dasatinib Nilotinib Ponatinib Bosutinib

Table 1 (continued)

Target	Mechanism of action	Diseases	Drugs
	- PI3K/AKT/mTOR pathway—resulting in increased apoptosis		

mTOR inhibitors predominantly effect mTORC1. Ras-Raf-MEK-ERK pathway also known as the MAPK/ERK pathway

TLR Toll-like receptor; *PI3K* phosphoinositide 3-kinase; *AKT* protein kinase B; *MEK* mitogen-activated protein kinase/extracellular signal-regulated kinase; *IFN* interferon; *IL* interleukin; *EPO* erythropoietin; *TPO* thrombopoietin; *GM-CSF* ganulocyte-macrophage colony-stimulating factor

mTOR inhibitors have antifungal activity against *Cryptococcus neoformans, Candida* and possibly *Aspergillus*. This is mediated against the fungal homologue TOR kinases proteins, blocking its ability to promote fungal cell proliferation via nutrient-sensing pathways to promote fungal cell proliferation. Rapamycin was initially discovered as antifungal agent. However, the immunosuppressive effects of mTOR inhibitors dominate. The antifungal attributes may confer some protection which could manifest as a lower frequency of infections or a lower risk of dissemination [31].

Our results confirm relatively few cryptococcal or *candida* infections reported with rapamycin (Table 2). Cryptococcosis in transplant recipients likely resulted from reactivation of latent infection, and the incidence is low compared with other latent infections in transplant recipients [31]. In contrast, *P. jirovecii* pneumonia (PJP) was the most frequently reported fungal infection with mTOR, especially sirolimus. It is recognised that sirolimus-based regimens are a risk factor for PJP [32••]. A large retrospective cohort study of Medicare primary transplant recipients reported 41 events [32••]. There were no data on the proportion of patients treated with PJP prophylaxis. Other smaller studies have reported PJP infection with sirolimus in patients who have not received prophylaxis or occurring after the withdrawal of prophylaxis at 6 months [33]. Sirolimus-induced pneumonitis is a known side effect of sirolimus therapy and may be the underlying mechanism [32••]. There are fewer data regarding everolimus and temsirolimus. A large meta-analysis of randomised controlled trials data on 1601 patients reported 7 fungal infections, candida being the most commonly report fungi [34]. *Aspergillus* and *P. jirovecii* have also been reported. A retrospective review of 12 patients switched from tacrolimus to everolimus maintenance regimen for heart transplantation reported 6 cases of PJP infection, despite completing 6-month post-transplant PJP prophylaxis. These infections occurred on everolimus therapy, several months after withdrawal of prophylaxis. The authors suggested that the high frequency of PJP infection might be attributed to the high everolimus dose and high serum trough concentration [35].

Janus kinase/signal transducers and activators of transcription inhibitor

The Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway is regarded as a central communication node for the immune system [36]. It mediates the effect of many different cytokines, including interleukins, interferons and growth factors such as granulocytemacrophage colony-stimulating factors (GM-CSF) (Table 1). Signally via this pathway is critical for host defence and immunoregulation. Mutations in the JAK enzymes are associated with myeloproliferative haematological malignancies, autoimmunity and immunodeficiency syndromes. The effects of JAK inhibitors are influenced by their selectivity for a JAK enzymes subtypes; tofacitinib inhibits JAK1 and JAK3 [37], whilst baricitinib inhibits JAK1 and JAK2 and is considered JAK3 sparing [38]. Ruxolitinib targets JAK1 and JAK2, effecting the signally of growth factors erythropoietin, thrombopoietin and thrombopoietin and GM-CSF.

Cytokine balance plays a pivotal role in adaptive and innate immune defences against fungal infections. JAK inhibition downregulates cytokine signalling, decreasing the activation and infiltration of NK cells and macrophages into infected tissues and impacting subsequent phagocytic activity [39]. IFN-γ cytokine secretion generates a proinflammatory and microbicidal environment. In experimental models, resistance to *cryptococcosis* is associated with IFN-γ production, lymphocyte infiltration and macrophage activation [40]. Mice deficient in IFN-γ are significantly more susceptible to systemic *candida* [41], and recent findings have suggested that IFN-α and IFN-β may demonstrate an even more significant role than IFN-γ in host defence [39]. *G*M-CSF enhances the antifungal phagocytic activity of neutrophils, with deficient mice susceptible to a wide range of fungal pathogens [39].

There were few fungal infections reported in the literature with ruxolitinib (Table 2). Cryptococcal infection (pulmonary and extrapulmonary) were the most frequently reported fungus. [42]. Infections occurred at various intervals after the initiation of ruxolitinib, and whether the infection risk is dose-dependent remains controversial [43]. The number of reported fungal infections were slightly higher with tofacitinib. This might be due to extensive post-marketing surveillance with over 34,000 patient years of follow-up. In this large analysis, only 10 fungal infections were reported [44]. Overall, the commonest reported fungi were *Candida*, followed by *P. jirovecii* and *Cryptococcus*. In the RCTs and LTE studies, no cases of endemic mycotic infections (histoplasmosis, coccidioidomycosis and blastomycosis) were observed, but

Table 2 Small-molecule protein kinases inhibitors and published fungal infections

Therapeutic targets	Indication	Drugs	Year	Fungal infect.	Data source	Subtypes of fungal infection
BCR-ABL	Haematological malignancies	Imatinib (Gleevec)	2001	5	Case reports	Aspergillosis pulmonary ($n = 2$) [55,67],vCandida pneumonia (krusei and glabrata) ($n = 1$) [50] mucormycosis ($n = 2$) sinus [57] pulmonary [56]
		Dasatinib (Sprycell)	2006	13	Analysis Safety Data ($n = 165$)	PJP ($n = 2$), unspecified fungal ($n = 1$) [49••]
					Retrospective analysis* ($n = 69$)	*Candida krusei* ($n = 1$), unspecified fungal pneumonia ($n = 5$) [68],
					Retrospective analysis* (n = 16)	PJP ($n = 1$), unspecified fungal pneumonia ($n = 1$) [51]
					Case reports	PJP ($n = 2$) [58]
		Nilotinib (Tasigna)	2007	1	Retrospective analysis* ($n = 169$)	Unspecified fungal ($n = 1$) [69]
		Ponatinib (Iclusig)	2012	1	Retrospective analysis* ($n = 15$)	Unspecified fungal ($n = 1$) [70]
		Bosutinib (Bosulif)	2012	1	Case reports	Aspergillosis pulmonary ($n = 1$) [55]
BTK	Haematological malignancies	Ibrutinib (Imbruvica)	2013	269	Retrospective analysis database ($n =$ unknown)	Aspergillosis invasive ($n = 27$) cryptococcosis disseminated ($n = 4$), mucormycosis ($n = 1$), PJP ($n = 1$) [18,22].
					Retrospective multicentre ($n = 235$)	Unspecified fungal ($n = 11$) [71]
					Retrospective multicentre	Aspergillosis ($n = 18$), cryptococcosis (n = 7), PJP ($n = 1$), mucormycosis ($n = 3$), combined fungal ($n = 1$) [21]
					Retrospective database	Aspergillosis invasive ($n = 5$) [72]
					Retrospective analysis* ($n = 556$)	Aspergillosis ($n = 14$), blastomyces ($n = 1$), cryptococcosis ($n = 1$), histoplasmosis ($n = 1$) [23]•
					Retrospective analysis* ($n = 200$)	Aspergillosis invasive ($n = 5$), cryptococcal pneumonia ($n = 1$), unspecified fungal ($n = 1$) [73]
					Retrospective analysis* ($n = 68$)	Aspergillosis invasive ($n = 2$), cryptococcal disseminated ($n = 1$), mucormycosis ($n = 1$), PJP ($n = 1$) [74]
					Retrospective analysis* ($n = 37$)	*Candida albicans* ($n = 3$) *C. glabrata* ($n = 1$) *C. parapsilosis* ($n = 1$) C.

Table 2 (continued)

Therapeutic targets	Indication	Drugs	Year	Fungal infect.	Data source	Subtypes of fungal infection
						guilliermondii ($n = 1$) [75]
					Systematic review literature	Aspergillosis CNS, lung, cavernous sinus ($n = 18$), cryptococcosis CNS, lung, skin, blood ($n = 7$), histoplasmosis ($n = 1$), *Fusarium solani* (i = 1), mucormycosis ($n = 1$), PJP ($n = 7$), zygomycota ($n = 1$) [19]
					Systematic review literature	Aspergillosis ($n = 71$) [11]
					Systematic review literature	Aspergillosis ($n = 14$), cryptococcus ($n = 1$), histoplasmosis ($n = 1$), PJP ($n = 6$) [76],
					Case reports	Aspergillosis CNS ($n = 3$) [11,77,78], pulmonary ($n = 1$) [79], myocardial ($n = 1$) [80], cryptococcosis disseminated ($n = 2$) [81,82], CNS ($n = 4$) [20,83,84], pneumonia ($n = 1$) [83], empyema ($n = 2$) [19,85], Candida pneumonia ($n = 2$) [86,87], mucormycosis invasive ($n = 1$) [86], abdominal ($n = 1$) [84], sinus ($n = 1$) [88] skin ($n = 2$) [89,90], PJP ($n = 5$) [25]
		Acalabrutinib (Calquence)	2017	5	Analysis safety data ($n = 601$)	Aspergillosis ($n = 2$), cryptococcal pneumonia ($n = 1$), PJP ($n = 1$) [26]
					Case reports	Cryptococcal disseminated ($n = 1$) [27]
JAK/STAT	Polycythaemia vera inflammatory arthritis	Ruxolitinib (Jakafi)	2011	23••	Retrospective analysis database	Aspergillosis pulmonary ($n = 1$), cryptococcus pulmonary ($n = 1$), mucormycosis pulmonary ($n = 1$), PJP ($n = 1$) [91]
					Retrospective multicentre ($n = 446$)	Aspergillosis disseminated ($n = 1$), candida oesophageal ($n = 1$), intestinal ($n = 1$), onychomycosis ($n = 1$) [92]
					Retrospective analysis* ($n = 11$)	Unspecified fungal oesophagitis ($n = 1$) [93]

Table 2 (continued)

Therapeutic targets	Indication	Drugs	Year	Fungal infect.	Data source	Subtypes of fungal infection
					Systematic review literature	Cryptococcosis CNS, pulmonary, disseminated ($n = 3$), PJP (n = 2), mucormycosis ($n = 1$), talaromycosis disseminated ($n = 1$) [42]
					Case reports	Cryptococcosis CNS ($n = 2$) [94,95], pneumonia ($n = 2$) [96,97], disseminated + cardiac ($n = 1$) [98]. Combined cryptococcosis and histoplasmosis ($n = 1$) [43], talaromycosis pulmonary ($n = 1$) [99]
		Tofacitinib (Xeljanz)	2012	37	Safety data (34,223 patient-years)	Cryptococcosis pneumonia ($n = 3$), Candida oesophageal ($n = 2$), orpharyngeal ($n = 2$), histoplasmosis ($n = 2$), PJP ($n = 1$) [44]
					RCT and LTE studies ($n = 5671$)	Cryptococcosis pneumonia ($n = 2$), CNS ($n = 1$), candida oesophageal ($n = 9$), PJP ($n = 4$), toxoplasmosis ($n = 1$) [45]
					LTE studies ($n = 4967$)	Candida oesophagitis ($n = 5$), PJP ($n = 5$) [100]
					Retrospective analysis*	Histoplasmosis ($n = 1$) [101]
		Baricitinib (Olumiant)	2012	15	RCT and LTE studies ($n = 3492$)	Aspergillosis skin ($n = 1$), cryptococcal pneumonia ($n = 1$), candida oesophageal ($n = 6$), lung ($n = 1$), soft tissue ($n = 1$), histoplasmosis ($n = 1$) PJP ($n = 3$), PCM ($n = 1$) [45]
mTOR	Transplant Solid organ cancer (breast, pancreas, renal)	Sirolimus (Rapamycin)	1999	66	RCT ($n = 124$)	Cryptococcal CNS mortality ($n = 1$), unspecified fungal disseminated mortality ($n = 1$), PJP ($n = 7$, of which 3 died) [33]
					Retrospective database ($n = 4898$)	PJP ($n = 41$) [32••]
					Retrospective analysis* ($n = 79$)	Histoplasmosis ($n = 2$), cryptococcal meningitis ($n = 1$) [102]
					Retrospective analysis* ($n = 49$)	Unspecified fungal ($n = 9$) [103]
					Retrospective analysis* ($n = 33$)	Unspecified fungal ($n = 2$) [104]

Table 2 (continued)

Therapeutic targets	Indication	Drugs	Year	Fungal infect.	Data source	Subtypes of fungal infection
					Retrospective analysis* ($n = 20$)	PJP ($n = 2$) [105]
					Case reports	Fusarium ($n = 2$) [106]
		Temsirolimus (Torisel)	2007	11	Meta-analysis# ($n = 1601$)	Aspergillosis ($n = 2$), candida ($n = 6$), unspecified fungal ($n = 1$) [34]
					Case reports	Aspergillosis pulmonary ($n = 1$) [107], PJP ($n = 1$) [108]
		Everolimus (Afinitor)	2009	21	Meta-analysis# ($n = 1601$)	Aspergillosis ($n = 2$), candida ($n = 6$), unspecified fungal ($n = 1$) [34]
					Retrospective analysis* ($n = 12$)	PJP ($n = 6$) [35]
					Retrospective analysis* ($n = 7$)	Candida oesophageal ($n = 1$) [109]
					Case reports	Aspergillosis thyroiditis ($n = 1$) [110], PJP ($n = 4$) [111–113]
VEGFR	Solid organ cancer (hepatic, thyroid, renal, pancreatic, CRC)	Sorafenib (Nexavar)	2005	3	Case reports	Candida esophagitis ($n = 2$) [114], talaromycosis disseminated ($n = 1$) [99]
		Sunitinib (Sutent)	2006	2	Case reports	Aspergillosis pulmonary ($n = 2$) [115,116]
EGFR	Solid organ cancer (NSCLC, pancreas, breast)	Gefitinib (Iressa)	2003	1	Case reports	Aspergillosis invasive ($n = 1$) [117]
ALK	NSCLC	Crizotinib (Xalkori)	2011	1	Case reports	Aspergillosis invasive ($n = 1$) [118]

PJP Pneumocystis jirovecii pneumonia; *PCM* paracoccidioidomycosis

*Single centre retrospective analysis. #Meta-analysis of everolimus and temsirolimus randomised controlled trials

presumably few patients were enrolled from regions where these organisms are endemic [45]. The incidence of opportunistic infections including fungal were greater in patients receiving higher doses or steroid therapy. As seen with ruxolitinib, infections occurred at a variety of time points after starting therapy (range 6–179 weeks) [45]. Few fungal events were reported in the single included study for baricitinib, with the commonest fungi being *candida* [45].

Break point cluster (Bcr) gene–Abelson (Abl) tyrosine kinase (BCR-ABL) inhibitor

A translocation of genetic material between chromosome 9 and chromosome 22, results in a fusion gene called *BCR-ABL1*. This juxtaposition of BCR favours autophosphorylation of ABL tyrosine kinase, causing persistent activation [46,47]. This is turn stimulates a number of survival pathways which are deregulated in many cancers, including PI3K/AKT/mTOR, RAS/RAF/MEK/ERK, and JAK/STAT. BCR inhibitors block these pathways, reducing cell division and unchecked proliferation, and increasing cell apoptosis (Table 1). Imatinib, the first tyrosine kinase inhibitors targeting BCR-ABL profoundly changed the management of chronic myeloid leukaemia (CML). Second- and third-generation agents are more potent and used both frontline and in patients with disease refractory to imatinib.

By inhibiting haematopoiesis, BCR-ABL inhibitors may suppress the host's cellular immune response and predispose to fungal infections. The impact of altered cell numbers on immune function is not entirely understood. BCR-ABL inhibitors inhibit T cell proliferation halting at the G0/G1 phase of the cell cycle, in a dose-dependent manner [48–50]. This can occur through off target kinase inhibition [48,49••]. T cell activation is also reported to be compromised [51]. Although the number of NK cells is increased, most studies have found their cytotoxic potential to be decreased [52]. In vitro studies demonstrate suppression of dendritic cell function [53] and reduction in macrophage production of IL-6 and TNFα in response to TLR stimulation [54].

Despite widespread and long-term use of imatinib, there are few data supporting an association with fungal infections (Table 2). There were only 5 case reports; 2 patients were in haematologic remission and did not demonstrate neutropenia [50,55]. The risk of myelosuppression was higher with heavily pretreated patients leading to severe bone marrow aplasia and life-threatening infections [56,57]. Infections with dasatinib were predominantly of bacterial origin, and most often associated with neutropenia. There were few fungal infections in the literature. *P. jirovecii* pneumonia were reported in 5 patients. Two patients were in haematologic remission, receiving dasatinib for relatively long treatment periods. One of these patient received additional chemotherapy, whilst both were treated with steroids, intensifying the risk for infection [58].

Discussion

This review has demonstrated the frequency and spectrum of fungal infections with small-molecule protein kinases inhibitors. There has been an unprecedented expansion in the development of therapies that target immune-signalling pathways in malignant and autoimmune diseases. These drugs block essential pathways of antifungal innate and adaptive immunity.

The greatest number of publications on fungal infections with protein kinase inhibitors was identified with ibrutinib, the BTK inhibitor. Infections were often disseminated and presented soon after initiation of therapy. *Aspergillus* was the most frequently reported fungi. There were a moderate number of infections reported in the literature with the mTOR inhibitors, with *P. jirovecii* as the most frequently reported fungi. The number of infections seen with JAK inhibitors may be overestimated owing to the substantial patient exposure time from postmarketing surveillance analyses. There were fairly few fungal infections reported with agents targeting BCR-ABL, VEGFR, EGFR and ALK, and no publications with agents targeting RET, TRK, CDK, Erb2, ALK, ROCK1/2, FGFR, B-Raf, Fly3 and Syk.

The effects of small-molecule protein kinases inhibitors on the immune system and the associated risk for the development of fungal infections are difficult to predict. This probably relates to a constellation of predisposing factors, implicated in the pathogenesis of fungal infections [14••]. Certain malignancies like CLL induce a wide range of immune defects that worsen during progression of the underlying disease. The synergistic effects of other immunosuppressive medications including corticosteroids and chemotherapy increase the risk of fungal infections [14••]. The true incidence of infections is likely higher in clinical practice than reported in trials, which recruit patients with fewer comorbid conditions. At higher dose, kinase inhibitors demonstrate off-target effects. For example, tofacitinib selectively inhibits JAK 1 and 3 at the approved dose but becomes a 'pan-JAK' inhibitor at higher doses [59]. Host-related factors might influence drug serum concentrations as these medications undergo hepatic metabolism and renal clearance and are susceptible to drug-drug interactions [14••].

Despites the comparable immune dysfunction of a drug, not all patients are susceptible to fungal infections. This suggests that additional risk factors, specifically a genetic predisposition is important. Polymorphisms have been described in specific immune-related genes, including toll-like receptors (e.g. TLR4) and C-type lectin receptors (e.g. dectin-1) which recognize the fungal structures and initiate inflammatory and antimicrobial host defences. Genetic variants in cytokine

genes may also contribute to fungal infection vulnerability to fungal infection, including inborn errors in the IL-12/IFN-γ axis, promoter polymorphism of IL-10 and defective expression of the TNF receptor [60].

There are challenges in reviewing infectious events across a wide spectrum of therapies. With respect to clinical trials, there is a lack of standardisation across studies as well as variability in reporting practices. Very few of the larger studies reported an incidence rate. First generation medications, that have been licenced for several years will have been investigated across a greater number of trials compared to newer second or third generation agents. Medications that have initial safety signals will also have been examined in greater detail, including large safety data analyses. Similarly, therapies that have been used in clinic practice for several years will have more real-world data that newly licenced drugs. The discrepancy in publication numbers may overestimate the infection risk. A similar effect may be driven by publication bias. The inclusion of conference abstracts may also introduce bias as it is recognised that one fifth of toxicities published in peer-reviewed journals are not reported in the abstract form [61].

In our personal experience, these infections are rare, no matter the underlying exposure. In many cases, it is difficult to ascribe the infection to the kinase inhibitor, the underlying disease, concomitant therapies or whether it is a combination of all three. The profile of fungal infections with JAK inhibitors is similar to that seen with biologics, in particular, anti-TNF and anti-IL6 therapy. Although there are no direct comparisons, the spectrum and incidence of fungal infections is similar. Granulomatous infections (histoplasmosis and coccidioidomycosis), PJP and aspergillus are more common. Systemic candida is very rare, with the most invasive infection for the most part being oesophagitis. Considering this information, whilst rare, it is important that clinicians maintain vigilance for fungal disease in people taking small molecule kinase inhibitorsparticularly given the challenges surrounding fungal infection diagnosis.

There is a lack of evidence for antifungal prophylaxis in patients prescribed small-molecule protein kinases inhibitors. There is debate whether the degree of immunosuppression mandates the use of prophylaxis [43,62]. For some diseases, patients have received treatment with other agents which have long-lasting immunomodulatory effects contributing to the immunosuppressive state. Current guidelines recommend PJP prophylaxis for patients undergoing certain chemotherapy and antifungal prophylaxis with fluconazole in patients with anticipated neutropenia [63]. It would be prudent to identify high-risk patients through a proactive preemptive approach including routine screening. This approach is already taken for certain infections including tuberculosis and hepatitis. For fungi in which comparable latent states exist, similar screening paradigms could diminish risk of reactivation. Screening for prior exposure should also be proportionate to endemic risk. It is not appropriate to screen all patients; however, in endemic areas, for example Midwest USA, screening for *histoplasmosis* and *coccidioidomycosis* may be judicious.

Conclusion

Small-molecule protein kinases inhibitors predispose to opportunistic fungal infections; however, not all agents demonstrate the same risk. The greatest potential is seen with therapies that target bruton tyrosine kinase, such as ibrutinib. Infections are often disseminated and may present soon after initiation of therapy. The pattern of fungal infection with protein kinases inhibitors fits mechanistically with the specific pathway targeted. However, the drugs pharmacokinetic profile and possibility of off-target kinase inhibition, together with the underlying disease pathology, genetic predisposition for fungal infection and the synergistic effects of other immunosuppressive medications, complicate this picture.

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Compliance with Ethical Standards

Conflict of Interest James Galloway reports personal fees from the AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Pfizer, and Union Chimique Belge outside the submitted work. Kevin Winthrop reports personal fees from AbbVie, Gilead, Lilly, Pfizer, UCB, Roche, Galapagos, and GSK outside the submitted work. Katie Bechman declares no conflicts of interest relevant to this manuscript.

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.

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- • Of importance
- •• Of major importance

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