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Incidence of Invasive Fungal Infections in Patients Initiating Ibrutinib and Other Small Molecule Kinase Inhibitors—United States, July 2016–June 2019

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Abstract

We analyzed administrative data to determine the 1-year incidence of invasive fungal infections (IFIs) in patients beginning small molecule kinase inhibitor (SMKI) therapy. The incidence of IFIs by small molecule kinase inhibitor ranged from 0.0% to 10.6%, with patients taking midostaurin having the highest incidence. An IFI developed in 38 of 1286 patients taking ibrutinib (3.0%).

Keywords

small molecule kinase inhibitors; ibrutinib; invasive fungal infections; cancer; opportunistic infections

Small molecule kinase inhibitors (SMKIs) are increasingly used to treat cancers and inflammatory conditions [1]. Because they target the immune signaling pathways implicated in disease-specific pathologies, SMKIs are often better tolerated and more effective than conventional chemotherapeutic agents [2]. Ibrutinib is a particularly effective and widely prescribed SMKI used to treat patients with chronic lymphocytic leukemia or small cell lymphoma, previously treated mantle cell lymphoma, Waldenström macroglobulinemia, and other conditions [2].

As the use of ibrutinib and other SMKIs has increased, so have reports of invasive fungal infections (IFIs) in patients receiving these drugs [3, 4]. IFIs can be life-threatening and may necessitate discontinuation of SMKI therapy [5]. Patients receiving SMKIs may have

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Disclaimer. This activity was reviewed by the Centers for Disease Control and Prevention (CDC) and was conducted consistently with applicable federal law and CDC policy (eg, 45 CFR part 46, 21 CFR part 56, 42 USC §241[d], 5 USC §552a, and 44 USC §3501 et seq). The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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an elevated IFI risk for several reasons. First, certain SMKIs are designed to target molecular pathways that can affect antifungal innate immunity. Second, SMKIs may have off-target drug effects causing broad immunosuppression. Finally, the risk of IFIs may be elevated by the underlying condition being treated, concurrent immunosuppressive therapies, and other patient or environmental factors [2].

Most data on SMKI-associated IFI risk come from clinical trials, single-center studies, and case series [2–4, 6, 7], which may not represent the broader patient populations taking SMKIs. Prospective data on SMKI-associated IFIs are lacking and might inform clinical practice regarding IFI screening and prophylaxis. We analyzed a large US administrative data set to determine the incidence of IFIs in patients starting treatment with SMKIs and identified IFI risk factors in those starting ibrutinib treatment.

METHODS

We analyzed data from the IBM MarketScan Research Databases (https://www.ibm.com/products/marketscan-research-databases). These deidentified data sets include outpatient visits, outpatient prescriptions, and hospitalizations for commercially insured employees, dependents, and retirees throughout the United States. We accessed the data through MarketScan Treatment Pathways (https://www.ibm.com/us-en/marketplace/marketscan-treatment-pathways), a web-based platform that included data from >40 million patients with health insurance plans that contributed prescription drug data to MarketScan during the analytic period.

We identified 38 SMKIs approved by the US Food and Drug Administration during 2001–2017 and selected patients who received an initial outpatient SMKI prescription from 1 July 2016 to 30 June 2019. We restricted the analysis to patients with continuous insurance coverage during the 180 days before to 365 days after initial SMKI prescription, which excluded approximately 50% of patients. To attempt to identify incident IFI diagnoses, we excluded an additional 1% of patients who received IFI diagnoses during the 180 days before the SMKI initiation date. We followed up the cohorts of patients receiving each SMKI until 1 year after initial prescription to ascertain IFI diagnoses and diagnosis setting (ie, inpatient vs outpatient). We excluded SMKIs (n = 9) with <100 patients meeting inclusion criteria.

For ibrutinib, we compared patients in whom an IFI developed with patients in whom an IFI did not develop stratifying by demographic features; ibrutinib indication; underlying conditions that might increase IFI risk (ie, diabetes, neutropenia, stem cell or solid organ transplant, and human immunodeficiency virus); cytotoxic chemotherapy within 180 days before starting ibrutinib; and certain outpatient drug prescriptions received during 90 days before starting ibrutinib, including long-term corticosteroid use (defined as a ≥3-week outpatient supply of oral prednisone or prednisolone), other immunosuppressive therapy (eg, mycophenolate or tacrolimus), and antifungal prophylaxis. Drug indications were not available in the data, but we defined antifungal prophylaxis as a ≥3-week outpatient supply of atovaquone, fluconazole, isavuconazole, posaconazole, trimethoprim-sulfamethoxazole, or voriconazole.

We used *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes to identify IFIs and underlying conditions (Supplementary Table 1). We compared categorical variables using χ^2 or Fisher exact tests for proportions ($\alpha = .05$).

RESULTS

For the 29 cohorts of patients beginning outpatient SMKI treatment, the IFI incidence ranged from 0.0% (in patients receiving axitinib, regorafenib, and ribociclib) to 10.6% (11 of 104 patients receiving midostaurin) (Table 1). Overall, the time to IFI development varied by SMKI, but most IFI diagnoses occurred >90 days after drug initiation, and 42.7% of initial IFI diagnoses (93 of 218) occurred in the inpatient setting. Among 7 SMKI cohorts in which an IFI occurred in ≥10 patients, 4 cohorts involved a predominant IFI type affecting more than one-third of patients; the predominant IFI type was candidiasis in patients receiving palbociclib (9 of 14 [64%]) or tofacitinib (15 of 24 [63%]), *Pneumocystis* pneumonia in those receiving dasatinib (8 of 20 [40%]), and aspergillosis in those receiving ibrutinib (14 of 38 [37%]).

For the 1286 patients starting treatment with ibrutinib, the most common indications were chronic lymphocytic leukemia or small cell lymphoma (73.9%), Waldenström macroglobulinemia (7.5%), and mantle cell lymphoma (6.2%) (Supplementary Table 2). Within 1 year, 38 of 1286 patients (3.0%) had an IFI diagnosis. The median time to IFI diagnosis was 169 days (interquartile range, 91–272 days). The IFI incidence did not differ significantly by age, sex, US census region, or ibrutinib indication, although relapsed chronic lymphocytic leukemia was more common in patients with than in those without IFIs (13.2% vs 6.2%; $P = .09$).

Patients in whom an IFI developed after initiation of ibrutinib were more likely to have a history of neutropenia (18.4% vs 8.1% in those without IFIs; $P = .02$), stem cell transplant (21.1% vs 6.8%; $P < .001$), or receipt of chemotherapy (28.9% vs 15.9%; $P = .03$) and more likely to be receiving long-term corticosteroids (18.4% vs 8.3%; $P = .03$), tacrolimus (7.9% vs 2.0%; $P = .047$), or antifungal prophylaxis (n = 28.9% vs 9.1%; $P < .001$) before starting ibrutinib.

DISCUSSION

In our analysis of US insurance claims data, the 1-year incidence of IFIs in patients receiving SMKI therapy varied by drug, ranging from 0.0% to 10.6%. Patients experienced a wide array of IFIs, spanning mold, yeast, yeastlike, and dimorphic fungal infections, with differences in predominant infection type noted for certain SMKIs. A substantial proportion (42.7%) of IFI diagnoses occurred in the inpatient setting, likely reflecting severe illness. IFI timing (generally >90 days after SMKI initiation, including for >75% of ibrutinib-associated IFIs) was consistent with previous reports [2, 4]. However, clinicians should remain vigilant for IFIs throughout the entire course of SMKI treatment, because severe early-onset IFIs in SMKI-treated patients have been documented, specifically in patients receiving ibrutinib [3]. The wide range of IFI risk among different SMKI cohorts likely reflects the diverse mechanisms of action underpinning the different SMKIs and the heterogeneity of the patient

populations being treated [2]. Further studies are warranted to understand the degree to which SMKIs independently increase IFI risk, a question that our analysis was not designed to answer. Given the expanding population of patients receiving SMKIs for a variety of indications, our findings underscore the need for comprehensive clinical surveillance for IFIs in patients receiving these drugs.

IFI surveillance is particularly important for ibrutinib, given the drug's widespread use, which encompasses >200 000 patients worldwide [8]. Our observed 1-year incidence of IFIs (3.0%) and the predominance of *Aspergillus* infections in patients starting ibrutinib treatment were comparable to findings reported for single-center studies from New York City (4.2%) [4] and Japan (2.0%) [7] and a nationwide study from Israel (2.4%) [9]. We were unsurprised by the significant associations we observed between increased IFI risk and long-term steroid use, neutropenia, and stem cell transplant history, as these are known IFI risk factors [10]. We found that patients taking ibrutinib in whom IFIs developed were more likely to have a previous antifungal prophylaxis prescription, which probably reflects a higher baseline IFI risk in these patients, unrelated to ibrutinib. Although specific ibrutinib indications were not associated with higher IFI risk in our study, this might reflect an underpowered statistical analysis rather than a true lack of association. In-depth clinical studies of SMKI-associated IFIs are needed to delineate who is at greatest risk of IFIs and, consequently, which patients would benefit most from closer monitoring and antifungal prophylaxis.

The highest IFI incidence occurred in patients receiving midostaurin, a drug primarily used to treat acute myeloid leukemia (*FLT3*-TKD/ITD^{mut} type). Patients with this disease may have a high baseline IFI risk owing to disease-associated impaired neutrophil function and receipt of cytotoxic chemotherapy. Researchers have previously described the challenge of prescribing antifungal prophylaxis in patients receiving midostaurin, given drug-drug interactions with azole antifungals [11]. This concern extends to other SMKIs, including ibrutinib [5], and highlights the need for further studies to optimize antifungal prophylactic strategies in patients receiving SMKIs.

Our analysis has several notable limitations. Although MarketScan data are broadly representative of the commercially insured population, they do not represent patients with other insurance types or patients without insurance. The data also lack information on race/ethnicity, laboratory values that could help further stratify IFI risk (eg, white blood cell counts), and patient mortality rates. Because we excluded patients without continuous enrollment during the year after SMKI initiation, our analysis might underestimate IFI incidence if a substantial number of patients died of fungal infections soon after beginning therapy; however, results were similar after removal of the continuous enrollment requirement (data not shown). Finally, *ICD-10-CM* codes are subject to potential undercoding and disease misclassification. Nonetheless, using MarketScan data allowed for a prospective analysis of IFIs in a broad range of patients receiving SMKIs. Our findings reinforce the importance of clinician vigilance and prospective surveillance for SMKI-associated IFIs and the need for in-depth clinical studies to stratify IFI risk, clarify the contribution of SMKIs to IFI risk, and guide antifungal prophylaxis strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

One-Year Incidence of Invasive Fungal Infections in Patients Beginning Treatment With a Small Molecule Kinase Inhibitor—United States, July 2016–June 2019[a]

SMKI	IFI Incidence, No./Total (%)[b]	Time to 1st IFI Diagnosis, Median, (IQR), d	Patients Hospitalized at Time of 1st IFI Diagnosis, No. (%)	IFI Types Diagnosed Within 1 y (No. of Patients)
Abemaciclib	4/281 (1.4)	44 (9–147)	3 (75.0)	Candidiasis (2); PCP (1); not specified (1)
Afatinib	5/133 (3.8)	215 (208–257)	1 (20.0)	Candidiasis (2); PCP (2); not specified (1)
Alectinib	1/185 (0.5)	313 (313–313)	0 (0.0)	Aspergillosis (1)
Axitinib	0/108 (0.0)	…	…	…
Bosutinib	1/133 (0.8)	134 (134–134)	0 (0.0)	PCP (1)
Cabozantinib	5/331 (1.5)	215 (68–358)	2 (40.0)	Candidiasis (2); coccidioidomycosis (1); not specified (2)
Crizotinib	2/114 (1.8)	143 (140–146)	1 (50.0)	Aspergillosis (1); not specified (1)
Dabrafenib	4/226 (1.8)	265 (195–293)	1 (25.0)	Candidiasis (2); coccidioidomycosis (1); PCP (1)
Dasatinib	20/620 (3.2)	111 (59–210)	11 (55.0)	PCP (8); candidiasis (3); histoplasmosis (1); mucormycosis (1); not specified (7)
Erlotinib	2/211 (0.9)	16 (14–18)	2 (100.0)	Candidiasis (2)
Everolimus	22/1084 (2.0)	109 (68–229)	11 (50.0)	Aspergillosis (5); candidiasis (4); PCP (4); coccidioidomycosis (2); cryptococcosis (1); mucormycosis (1); not specified (6)
Ibrutinib	38/1286 (3.0)	169 (91–272)	17 (44.7)	Aspergillosis (14); PCP (7); candidiasis (6); coccidioidomycosis (2); mucormycosis (2); cryptococcosis (1); not specified (9)
Imatinib	5/902 (0.6)	155 (23–225)	1 (20.0)	Candidiasis (1); histoplasmosis (1); not specified (3)
Lapatinib	1/150 (0.7)	107 (107–107)	0 (0.0)	Candidiasis (1)
Lenvatinib	3/156 (1.9)	220 (193–279)	0 (0.0)	Candidiasis (1); not specified (2)
Midostaurin	11/104 (10.6)	131 (84–214)	6 (54.5)	Aspergillosis (3); PCP (3); candidiasis (1); not specified (5)
Neratinib	1/327 (0.3)	325 (325–325)	1 (100.0)	Candidiasis (1)
Nilotinib	2/277 (0.7)	56 (50–61)	2 (100.0)	PCP (1); not specified (1)
Nintedanib	6/422 (1.4)	257 (167–279)	2 (33.3)	Aspergillosis (2); candidiasis (1); histoplasmosis (1); coccidioidomycosis (1), cryptococcosis (1)
Osimertinib	3/444 (0.7)	234 (143–236)	0 (0.0)	Aspergillosis (1); candidiasis (1); PCP (1)
Palbociclib	14/2207 (0.6)	212 (137–324)	8 (57.1)	Candidiasis (9); aspergillosis (2); not specified (3)
Pazopanib	3/525 (0.6)	286 (185–303)	1 (33.3)	Aspergillosis (1); candidiasis (1); not specified (1)
Regorafenib	0/176 (0.0)	…	…	…
Ribociclib	0/144 (0.0)	…	…	…

SMKI	IFI Incidence, No./Total (%)[b]	Time to 1st IFI Diagnosis, Median, (IQR), d	Patients Hospitalized at Time of 1st IFI Diagnosis, No. (%)	IFI Types Diagnosed Within 1 y (No. of Patients)
Ruxolitinib	26/531 (4.9)	191 (78–224)	11 (42.3)	Candidiasis (6); aspergillosis (5); PCP (3); coccidioidomycosis (1); cryptococcosis (1); histoplasmosis (1); not specified (10)
Sorafenib	9/252 (3.6)	224 (146–328)	2 (22.2)	Aspergillosis (4); candidiasis (1); not specified (4)
Sunitinib	3/320 (0.9)	263 (142–266)	2 (66.7)	Candidiasis (2); PCP (1)
Tofacitinib	24/5923 (0.4)	193 (114–282)	6 (25.0)	Candidiasis (15); PCP (3); coccidioidomycosis (1); not specified (5)
Trametinib	3/255 (1.2)	292 (249–294)	2 (66.7)	PCP (1); aspergillosis (1); candidiasis (1)

Abbreviations: IFI, invasive fungal infection; PCP, *Pneumocystis* pneumonia; SMKI, small molecule kinase inhibitor.

[a]The analysis included SMKIs approved by the US Food and Drug Administration during 2001–2017, accessed at the official website (https://www.fda.gov/drugs/nda-and-bla-approvals/new-molecular-entity-nme-drug-and-new-biologic-approvals); the following SMKIs were excluded because <100 patients receiving the drug met study inclusion criteria: acalabrutinib, brigatinib, ceritinib, cobimetinib, gefitinib, ponatinib, temsirolimus, vandetanib, and vemurafenib.

[b]Incidence was calculated as the number of patients in whom an IFI developed per person-year. Patients could receive >1 IFI diagnosis.

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