Low Risk of Pneumonia From *Pneumocystis jirovecii* Infection in Patients With Inflammatory Bowel Disease Receiving Immune Suppression

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e114. Learning Objective–Upon completion of this activity, successful learners will be able to assess the risk of *Pneumocystis jirovecii* pneumonia in patients with inflammatory bowel disease and utilize pharmacological prophylaxis if warranted.

BACKGROUND & AIMS: **Use of immunosuppressants and inflammatory bowel disease (IBD) may increase the risk of pneumonia caused by *Pneumocystis jirovecii* (PJP). We assessed the risk of PJP in a population-based cohort of patients with IBD treated with corticosteroids, immune-suppressive medications, and biologics.**

METHODS: **We performed a population-based cohort study of residents of Olmsted County, Minnesota, diagnosed with Crohn's disease (n = 427) or ulcerative colitis (n = 510) from 1970 through 2011. Records of patients were reviewed to identify all episodes of immunosuppressive therapies and concomitant PJP prophylaxis through February 2016. We reviewed charts to identify cases of PJP, cross-referenced with the Rochester Epidemiology Project database (using diagnostic codes for PJP) and the Mayo Clinic and Olmsted Medical Center databases. The primary outcome was risk of PJP associated with the use of corticosteroids, immune-suppressive medications, and biologics by patients with IBD.**

RESULTS: **Our analysis included 937 patients and 6066 patient-years of follow-up evaluation (median, 14.8 y per patient). Medications used included corticosteroids (520 patients; 55.5%; 555.4 patient-years of exposure), immunosuppressants (304 patients; 32.4%; 1555.7 patient-years of exposure), and biologics (193 patients; 20.5%; 670 patient-years of exposure). Double therapy (corticosteroids and either immunosuppressants and biologics) was used by 236 patients (25.2%), with 173 patient-years of exposure. Triple therapy (corticosteroids, immunosuppressants, and biologics) was used by 70 patients (7.5%) with 18.9 patient-years of exposure. There were 3 cases of PJP, conferring a risk of 0.2 (95% CI, 0.01–1.0) to corticosteroids, 0.1 (95% CI, 0.02–0.5) cases per 100 patient-years of exposure to immunosuppressants, 0.3 (95% CI, 0.04–1.1) cases per 100 patient-years of exposure to biologics, 0.6 (95% CI, 0.01–3.2) cases per 100 patient-years of exposure to double therapy, and 0 (95% CI, 0.0–19.5) cases per 100 patient-years of exposure to triple therapy. Primary prophylaxis for PJP was prescribed to 37 patients, for a total of 24.9 patient-years of exposure.**

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; CS, corticosteroid; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IS, immunosuppressant; PCR, polymerase chain reaction; PJP, *Pneumocystis jirovecii* pneumonia; REP, Rochester Epidemiology Project; TMP-SMZ, trimethoprim-sulfamethoxazole; UC, ulcerative colitis.

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CONCLUSIONS: **In a population-based cohort of patients with IBD treated with corticosteroids, immunosuppressants, and biologics, there were only 3 cases of PJP, despite the uncommon use of PJP prophylaxis. Routine administration of PJP prophylaxis in these patients may not be warranted, although it should be considered for high-risk groups, such as patients receiving triple therapy.**

Keywords: Treatment; Calcineurin Inhibitors; Infliximab; Immunocompromised.

Pneumocystis jirovecii (formerly known as *Pneumocystis carinii*) is a ubiquitous fungus that causes pneumonia in immunosuppressed patients.[1] The incidence of *Pneumocystis jirovecii* pneumonia (PJP) is increasing in immunocompromised non–human immunodeficiency virus (HIV)-infected patients.[2,3] Risk factors include systemic corticosteroid (CS) use,[4] particularly at or above a daily dose of 16 mg of prednisone for at least 8 weeks,[5] other immunosuppressant (IS) use, lymphocyte count less than 600/mm^3, more specifically a CD4 cell count less than 300/mm,[3,6,7] and comorbidities such as cancer, solid organ or bone marrow transplantation, collagen vascular disease, preexisting lung disease, and inflammatory bowel disease (IBD).[8–12] IBD is associated with conditions that may predispose to opportunistic infections, such as malnutrition, surgery, and the use of immunosuppressive medications. As a result of the increasing use of immunosuppressive and biologic drugs, the occurrence of opportunistic infections has become a key safety issue for patients with IBD.[13,14]

There is a growing body of evidence suggesting an increased risk of PJP in IBD patients. Although the incidence has not been defined clearly, multiple cases of PJP in patients with IBD have been reported, associated with the use of IS alone and in combination, including cyclosporine,[15,16] azathioprine,[17,18] high-dose CS[19] (a systemically delivered corticosteroid in a dose equivalent to prednisone >20 mg/d), 6-mercaptopurine,[20] and infliximab.[21–25] In an analysis of the Federal Drug Administration database for the Adverse Event Reporting System, 84 cases of PJP were reported between 1998 and 2003 in patients receiving infliximab with or without concomitant IS.[26] Of these, 14 were receiving infliximab for Crohn's disease (CD) and 2 for ulcerative colitis (UC).[26] A recent study estimated the crude incidence of PJP in patients with IBD at 10.6 per 100,000 person-years,[27] increasing to 32 per 100,000 person-years in patients on IS, substantially higher than the crude incidence of PJP in patients without IBD at 3 per 100,000 person-years.[27] Of note, this study included enteral budesonide as IS although it has been shown not to increase pulmonary infection risk, possibly resulting in underestimation of risk.[28]

Despite its excess mortality and the efficacy of chemoprophylaxis,[29] there is no consensus on the need for primary PJP prophylaxis in IBD patients on immunosuppression.[30] Some experts have advocated for routine use of PJP prophylaxis in patients with IBD treated with a tumor necrosis factor-α inhibitor with or without combination IS, although the cases of PJP in patients treated with these medications represent a small fraction of all IBD patients so treated.[26,30–32] In 2014, the European Crohn's and Colitis Organisation published their second evidence-based consensus on the prevention, diagnosis, and management of opportunistic infections in IBD recommending primary PJP prophylaxis in patients on 3 immunosuppressants, if 1 agent is a calcineurin inhibitor or anti–tumor necrosis factor agent, and consideration of primary PJP prophylaxis in patients on double-immunosuppressive therapy if 1 is a calcineurin inhibitor.[33] No consensus was reached regarding primary PJP prophylaxis with single- or dual-agent combination therapy without a calcineurin inhibitor, leaving the decision for prophylaxis to a discussion between providers and patients with IBD who are taking these medications.[33] In a recent survey of gastroenterology providers in the United States, only 9% of respondents reported using PJP prophylaxis in patients treated with triple therapy.[34] Providers who prescribed PJP prophylaxis were more likely to have previous personal experience with PJP and practice in an academic medical center.[34] Moreover, a recent study, using a Markov microsimulation model to simulate the natural history of CD in 1 million virtual patients, concluded that at the current PJP incidence, no PJP prophylaxis was the preferred strategy from a population perspective.[35]

The existing literature on the risk of PJP in patients with IBD is subject to referral bias, and the true risk of PJP in a population-based cohort with IBD is unknown. Furthermore, the additive risk of combination therapy with CS and other IS and/or biologic therapy has not been well studied. Therefore, we aimed to estimate the risk of PJP infection in a well-defined population-based cohort of patients receiving CS, IS, and/or biologic therapy for IBD in an attempt to better define the subgroups who may benefit most from PJP prophylaxis.

Methods

Study Population

By using the data resources of the Rochester Epidemiology Project (REP) (discussed later), adult and pediatric residents of Olmsted County, Minnesota, diagnosed with CD or UC between 1970 and 2011 (inclusive), were identified. These cases have been validated previously.[36,37] Exclusion criteria included HIV infection, any solid organ or bone marrow transplant, current malignancy or chemotherapy during the study period,

hereditary immunocompromising conditions, or history of splenectomy.

Defining Immunosuppressive Therapy

The records of patients were reviewed to identify all episodes of immunosuppressive therapy including CS, IS and biologics, and concomitant PJP prophylaxis, through February 2016. For the purpose of this study, budesonide was not considered immunosuppressive therapy. A meta-analysis of 5 randomized controlled trials found no difference between oral budesonide and placebo with regard to respiratory infections,[28] justifying this decision. In this study, immunosuppressive therapy was divided into 3 groups: CS (prednisone and methylprednisolone), IS (azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, and tacrolimus), and biologic therapy (infliximab, adalimumab, certolizumab pegol, natalizumab, golimumab, and vedolizumab).

Identification of P jirovecii *Cases*

A manual chart review was performed on all IBD patients for cases of PJP, cross-referenced with the REP patient database (using PJP diagnostic codes) and 2 microbiology databases (Mayo Clinic and Olmsted Medical Center). The diagnosis of PJP was made by the identification of *Pneumocystis* from sputum, bronchoalveolar fluid, tracheal secretions, or lung tissue by special stains or a non-nested polymerase chain reaction (PCR), specifically designed to diagnose pneumonia rather than colonization.[38]

This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Study Setting

Olmsted County, in southeastern Minnesota, had a population of 144,248 during the 2010 census,[39] estimated to have increased to 151,436 in 2015.[40] Eighty-three percent of the current population is non-Hispanic white, and a substantial portion is of North European ancestry. The majority of people reside in Rochester, which is the urban center of an otherwise rural county. Although residents of Olmsted County are similar socioeconomically to the general US population, there are some differences, including ethnic diversity (86% of the county population is Caucasian compared with 72% of the US population) and education (39% have completed a bachelor's degree or higher compared with 28% of the US population).[41] Moreover, 25% of Olmsted County residents are employed in health care vs 8% nationwide.[42] The REP is a unique medical records linkage system that exploits the fact that virtually all of the health care for the residents of Olmsted County is provided by 2 organizations: Mayo Clinic and Olmsted Medical Center.[43] Information generated from all medical contacts for all Olmsted County residents seen since 1908 is available through a central diagnostic index. In any 3-year period, more than 90% of county residents are examined at either 1 of the 2 health care systems, with REP population estimates being consistently higher than those reported by the US Census.[44] Thus, it is possible to identify all diagnosed cases of a given disease for which patients sought medical attention.

Statistical Analysis

The risk of PJP and associated 95% confidence intervals (CIs) were estimated using a Poisson regression model. For CS, IS, or biologics, this risk was assumed to exist from the start of the single agent until the stop date for the same single agent, irrespective of additional concomitant immunosuppressant therapy. For double therapy (CS + either IS or biologic) and triple therapy (CS + IS + biologic) the risk was assumed to exist from the start to the end of the specific combination exclusively. Demographic and clinical data were summarized using frequency (percentage) for discrete variables, and mean ± SD or median (range) for continuous variables. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

Results

There was a total of 937 patients with IBD (510 with UC and 427 with CD). The total number of patient-years of follow-up evaluation from IBD diagnosis to last follow-up evaluation was 16,066.2 years (median, 14.8 years per patient). The demographic characteristics of the total cohort and of the cohort exposed to immunosuppressive therapy are outlined in Table 1. In 364 patients (39%), CS, IS, and a biologic were not used, and no cases of PJP were diagnosed in this group.

Corticosteroids were used in 520 patients (55.5%), with 555.4 patient-years of exposure. A total of 406 patients (43.3%) used CS for longer that 8 weeks. IS agents were used in 304 patients (32.4%), with 1555.7 patient-years of exposure, and biologic agents were used in 193 patients (20.5%), with 670 patient-years of exposure. Double therapy with systemic CS together with either IS or biologic agents were used in 236 patients (25.2%), with 173 patient-years of exposure. Triple therapy with CS, IS, and biologic therapy was used in 70 patients (7.5%), with 18.9 patient-years of exposure.

There were 4 cases of PJP in this cohort. One case occurred in 1997 in a patient with UC who had undergone colectomy in the 1970s, and was on no specific UC therapy. He developed PJP in the setting of chemoradiation therapy for a brain tumor, and thus was omitted from the formal analysis of PJP risk. The demographic and clinical features of the 3 remaining cases of PJP are shown in Table 2. None of the 3 cases had been receiving prophylaxis at the time of PJP onset.

Table 1. Demographics of Olmsted County Inflammatory Bowel Disease Cohort (1970–2011) and Subset Exposed to Immunosuppression

	Entire cohort (N = 937)			Cohort on immunosuppressive therapy (N = 573)		
	CD (N = 427)	UC (N = 510)	Combined	CD (N = 307)	UC (N = 266)	Combined
Female, n (%)	221 (52.8)	220 (43.1)	441 (47.1)	160 (52.1)	115 (43.2)	275 (48.0)
Median age, *y* (IQR)	29.5 (21.2–46.6)	35 (24.8–48)	32.8 (23.7–47.4)	27.9 (20.5–42.1)	34.2 (24.2–48.3)	30.8 (22.3–46.0)
White race, n (%)	412 (96.5)	487 (95.5)	899 (95.9)	296 (96.4)	259 (97.4)	555 (96.9)
Median follow-up period, y (IQR)	14.3 (7.9–24.1)	15.3 (7.8–25.8)	14.8 (7.9–25)	14.6 (8.2–24.7)	14.4 (8.3–23.2)	14.5 (8.3–23.9)

IQR, interquartile range.

The mean total lymphocyte count of these 3 cases was 970 ± 520 mm^3, compared with 1430 ± 780 mm^3 in a random sample of 30 patients without PJP older than age 60 years.

The risk of PJP was 0.6 cases or fewer per 100 patient-years of exposure in all study groups (Table 3). Additional subgroup analysis was performed in patients treated with CS + calcineurin inhibitors (61 days of exposure) and CS + methotrexate/thiopurines (145.4 years of exposure), showing no cases of PJP (95% CI, 0.0–21.7 and 0.0–2.5 per 100 patient-years of exposure, respectively).

Only 37 patients were prescribed primary PJP prophylaxis concomitantly with CS, or IS, or biologic therapy, for a total of 24.9 years during follow-up evaluation (3.5 years on CS, 9 years on biologics, 10 years on double therapy, and 2.4 years on triple therapy). Trimethoprim-sulfamethoxazole (TMP-SMX) was used for 23.3 years, dapsone for 1.3 years, and atovaquone for 0.3 years.

Discussion

In this population-based IBD inception cohort, in which most patients were treated with CS, IS, and/or biologics, there were only 3 cases of PJP despite very infrequent use of PJP prophylaxis. The risk of PJP was 0.3 cases or fewer per 100 patient-year of exposure in patients receiving either CS, IS, or biologics. The risk increased to 0.6 per 100 patient-years of exposure on double therapy. There were no cases while on triple therapy, although caution is advised in interpreting this result considering there were fewer than 19 patient-years of exposure studied. Our 3 cases of PJP were all older than age 60, 2 of the cases had a pulmonary comorbidity, and their mean total lymphocyte count was lower than a random comparable sample group that did not develop PJP.

These results are consistent with a recent retrospective cohort study of more than 100,000 IBD patients in the United States, which showed an increased risk of PJP in IBD patients as compared with the general population, with an overall hazard risk of 2.96, and 4.01 for CD patients.[27] However, the absolute risk was low, with 38 individuals (0.03%) with IBD developing PJP; of these, 20 (53%) were on CS alone or in combination with other immunosuppression.[27] The investigators calculated that the number needed to treat with prophylaxis was 3750 to prevent 1 case of PJP in the IBD cohort on immunosuppression.[27]

TMP-SMX is the treatment of choice for PJP prophylaxis in non–HIV-infected patients because it is effective and well tolerated,[45,46] with a meta-analysis of 12 randomized trials involving patients after transplant and with hematologic cancers showing a 91% relative risk reduction in PJP in patients on prophylaxis, leading to the conclusion that prophylaxis is warranted when the risk of PJP is higher than 3.5% in adults.[29] Mortality related

Table 2. Demographics and Clinical Features of the Patients Diagnosed With *Pneumocystis jiroveci* Pneumonia in the Olmsted Country Inflammatory Bowel Disease Cohort (1970–2011), With Follow-Up Evaluation Through February 2016

	Case 1	Case 2	Case 3
Age, *y*	63	74	78
Sex	Male	Male	Male
IBD subtype	CD	UC	UC
Duration of IBD at time of PJP diagnosis, *y*	9.2	6.2	5.2
Relevant comorbidities	COPD	None	Bronchiectasis
Immunosuppression	4.2 years of infliximab and methotrexate	1 month of infliximab and prednisone	3.7 years of azathioprine
PJP prophylaxis	No	No	No
Treatment	TMP-SMX	TMP-SMX, prednisone	TMP-SMX
Responded to treatment	Yes	Yes	Yes

COPD, chronic obstructive pulmonary disease.

Table 3. Risk of *Pneumocystis jiroveci* Pneumonia in the Olmsted Country Inflammatory Bowel Disease Cohort (1970–2011) in Patients Exposed to Immunosuppression, With Follow-Up Evaluation Through February 2016

	Patient-years of exposure	PJP cases per 100 patient-years of exposure (95% CI)	Patient-years of exposure per 1 PJP case
Corticosteroids	555.4	0.2 (0.01–1.0)	555
Immunosuppressants	1555.7	0.1 (0.02–0.5)	778
Biologic	670	0.3 (0.04–1.1)	335
CS + either IS or biologic	173	0.6 (0.01–3.2)	173
CS + IS + biologic	18.9	0.0 (0.0–19.5)	N/A

N/A, not applicable.

to PJP also was reduced significantly by prophylaxis (relative risk, 0.17; 95% CI, 0.03–0.94). Given this studied population, it is difficult to make direct inferences about the threshold of when to treat IBD patients on immunosuppression, but it does confirm that TMP-SMX is effective and well tolerated should it be decided to treat with PJP primary prophylaxis.

Sulfasalazine may have activity against PJP by reducing *Pneumocystis*-induced inflammation and enhancing macrophage-mediated *Pneumocystis* clearance during PJP.[47] Sulfasalazine was used in more than 40% of our cohort, none of whom developed PJP. However, patients with IBD treated with sulfasalazine typically are not receiving CS, IS, or biologics, and generally do not have severe IBD. Therefore, they often are not considered high risk for PJP. Nevertheless, the possible protective effects of sulfasalazine against PJP merits further study.

Strengths of this study include the large number of patients with prolonged follow-up evaluation, as well as detailed information regarding the use of CS, IS, and biologics, including periods of combination therapy. In addition, the study of a population-based cohort avoids issues with referral bias, with results potentially generalizable to a Western population of IBD patients with similar characteristics to our cohort. Limitations include the retrospective study design. It would have been helpful if specific CS dosage exposures were examined; however, because IBD patients typically are managed with a home tapering schedule, it was not possible for us to know reliably what dose they were on for a specified duration. The 1 case of PJP that occurred on CS therapy occurred after 4 weeks of exposure to prednisone on a tapering schedule, and the patient was on 10 mg/d at the time of diagnosis. Although it is plausible that PJP may have occurred in patients who then were treated at another facility, thus leading to failure to capture these events, such an occurrence is unlikely given the nature of health care in our region and the fact that more than 90% of Olmsted County residents are examined at either 1 of the 2 health care systems in any 3-year period.[43] It also is possible that a PJP diagnosis may have been missed, especially earlier in the study period. Our microbiology laboratory began using a sensitive PCR test on March 1, 2005.[38] Before this time, we used *Pneumocystis* stains, which are somewhat less sensitive than PCR.[38,48]

In summary, this was a population-based cohort study investigating the risk of PJP in IBD patients on immunosuppression, with only 3 clinically relevant cases of PJP identified, despite little use of TMP-SMX prophylaxis. Our results suggest that routinely initiating chemoprophylaxis against PJP in IBD patients on immunosuppression may not be warranted, given the low PJP risk. Caution is advised, however, in drawing conclusions about the risk of PJP (and consequently the advisability of prophylaxis) in patients on triple therapy given the low number of patient-years of follow-up evaluation of patients receiving triple therapy. Moreover, the risk of CS in combination with calcineurin inhibitors may be increased relative to methotrexate/thiopurines. There was no difference in this risk in our cohort; however, calcineurin inhibitors rarely are used in our local practice, therefore the patient-years of exposure are not high enough to enable definitive conclusions to be made in this regard. Given the potentially high morbidity and mortality associated with PJP, we recommend that gastroenterology providers continue to assess the need for primary PJP prophylaxis on a case-by-case basis, particularly in older patients with pulmonary comorbidities, patients on multiple immunosuppressive agents, and patients with lymphopenia, balancing the risks and benefits for each individual patient. Monitoring CD4 T-cell counts in patients with a total lymphocyte count of less than 600/mm^3 also may help to identify patients at high risk of PJP.[7] Providers should monitor patients on immunosuppressive medications closely, educate them about early or subtle signs of infection, and have a high index of suspicion for PJP in patients with respiratory symptoms or febrile illness.[49] Additional studies are warranted to better define subgroups of IBD patients who are at increased risk of PJP, and who therefore would be the most appropriate candidates to receive primary prophylaxis.

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Conflicts of interest
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