

## 1-MINUTE CONSULT

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BRIEF ANSWERS  
TO SPECIFIC  
CLINICAL  
QUESTIONS

## Q: Do patients on biologic drugs for rheumatic disease need PCP prophylaxis?

**A:** *Pneumocystis jirovecii* (previously *carinii*) pneumonia (PCP) is rare in patients taking biologic response modifiers for rheumatic disease.<sup>1-10</sup> However, prophylaxis should be considered in patients who have granulomatosis with polyangiitis or underlying pulmonary disease, or who are concomitantly receiving glucocorticoids in high doses. There is some risk of adverse reactions to the prophylactic medicine.<sup>1,11-21</sup> Until clear guidelines are available, the decision to initiate PCP prophylaxis and the choice of agent should be individualized.

### ■ THE BURDEN OF PCP

PCP is a life-threatening opportunistic infection. Common causes of immunosuppression are advanced human immunodeficiency virus (HIV) infection, hematologic malignancy, anti-rejection drugs, chemotherapy, glucocorticoid therapy, and other immunosuppressive drugs. Here, we focus on the risk of PCP with immunomodulatory biologic drugs used for rheumatic disease that deplete B cells or inhibit T-cell activation, cytokine production, or cytokine function (Table 1).<sup>22</sup>

In a meta-analysis<sup>23</sup> of 867 patients who developed PCP and did not have HIV infection, 20.1% had autoimmune or chronic inflammatory disease and the rest were transplant recipients or had malignancies. The mortality rate was 30.6%.

### ■ PHARMACOLOGIC RISK FACTORS FOR PCP

#### Treatment with glucocorticoids

Treatment with glucocorticoids is an important risk factor for PCP, independent of biologic therapy.

Calero-Bernal et al<sup>11</sup> reported on 128 patients with non-HIV PCP, of whom 114 (89%) had received a glucocorticoid for more than 4 weeks, and 98 (76%) were currently receiving one. The mean daily dose was equivalent to 27.73 mg of prednisone per day in those on glucocorticoids only, and 21.34 mg in those receiving glucocorticoids in combination with other immunosuppressants.

Park et al,<sup>12</sup> in a retrospective study of Korean patients treated for rheumatic disease with high-dose glucocorticoids ( $\geq 30$  mg/day of prednisone or equivalent for more than 4 weeks), reported an incidence rate of PCP of 2.37 per 100 patient-years in those not on prophylaxis.

Other studies<sup>13,14</sup> have also found a prednisone dose greater than 15 to 20 mg per day for more than 4 weeks or concomitant use of 2 or more disease-modifying antirheumatic drugs to be a significant risk factor.<sup>13,14</sup>

#### Tumor necrosis factor alpha antagonists

A US Food and Drug Administration review<sup>1</sup> of voluntary reports of adverse drug events estimated the incidence of PCP to be 2.3 per 100,000 patient-years with infliximab and 1.6 per 100,000 patient-years with etanercept. In most cases, other immunosuppressants were used concomitantly.<sup>1</sup>

Postmarketing surveillance<sup>2</sup> of 5,000 patients with rheumatoid arthritis showed an incidence of suspected PCP of 0.4% within the first 6 months of starting infliximab therapy.

Komano et al,<sup>15</sup> in a case-control study of patients with rheumatoid arthritis treated with infliximab, reported that all 21 patients with PCP were also on methotrexate (median dosage 8 mg per week) and prednisolone (median dosage 7.5 mg per day).

PCP has also been reported after adalim-

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**TABLE 1**

**Biologic agents used for rheumatic disease**

**Anti-tumor necrosis factor alpha agents**

Adalimumab  
Certolizumab  
Etanercept  
Golimumab  
Infliximab

**Interleukin 1 receptor antagonists**

Anakinra  
Canakinumab  
Rilonacept

**Anti-interleukin 5 antibody**

Mepolizumab

**Interleukin 6 receptor antagonists**

Sarilumab  
Tocilizumab

**Interleukin 12/23 antagonist**

Ustekinumab

**Interleukin 17 antagonists**

Ixekizumab  
Secukinumab

**T-cell costimulation blocker**

Abatacept

**Anti-CD20 antibody**

Rituximab

**Anti-B-cell activating factor (B-lymphocyte stimulator) antibody**

Belimumab

umab use in combination with prednisone, azathioprine, and methotrexate, as well as with certolizumab, golimumab, tocilizumab, abatacept, and rituximab.<sup>3-6,24-26</sup>

**Rituximab**

**Calero-Bernal et al<sup>11</sup>** reported that 23% of patients with non-HIV PCP who were receiving immunosuppressant drugs were on rituximab.

**Alexandre et al<sup>16</sup>** performed a retrospective review of 11 cases of PCP complicating rituximab therapy for autoimmune disease, in which 10 (91%) of the patients were also on corticosteroids, with a median dosage of 30 mg of prednisone daily. A literature review of an additional 18 cases revealed similar findings.

**PATIENT RISK FACTORS FOR PCP**

Certain clinical, laboratory, and pharmacologic factors are associated with increased risk of PCP (Table 2).<sup>3-6,9,17-19,21,22,27</sup>

**Pulmonary disease, age, other factors**

**Komano et al<sup>15</sup>** in their study of patients with rheumatoid arthritis treated with infliximab, found that 10 (48%) of 21 patients with PCP had preexisting pulmonary disease, compared with 11 (10.8%) of 102 patients without PCP ( $P < .001$ ). Patients with PCP were older (mean age 64 vs 54,  $P < .001$ ), were on higher median doses of prednisolone per day (7.5 vs 5 mg,  $P = .001$ ), and had lower median serum immunoglobulin G (IgG) levels (944 vs 1,394 mg/dL,  $P < .001$ ).<sup>15</sup>

**Tadros et al<sup>13</sup>** performed a case-control study that also showed that patients with autoimmune disease who developed PCP had lower lymphocyte counts than controls on admission. Other risk factors included low CD4 counts and age older than 50.

**Li et al<sup>17</sup>** found that patients with autoimmune or inflammatory disease with PCP were more likely to have low CD3, CD4, and CD8 cell counts, as well as albumin levels less than 28 g/L. They therefore suggested that lymphocyte subtyping may be a useful tool to guide PCP prophylaxis.

**Granulomatosis with polyangiitis**

Patients with granulomatosis with polyangiitis have a significantly higher incidence of PCP than patients with other connective tissue diseases.

**Ward and Donald<sup>18</sup>** reviewed 223 cases of PCP in patients with connective tissue disease. The highest frequency (89 cases per 10,000 hospitalizations per year) was in patients with granulomatosis with polyangiitis, followed by 65 per 10,000 hospitalizations per year for patients with polyarteritis nodosa. The lowest frequency was in rheumatoid arthritis patients, at 2 per 10,000 hospitalizations per year. In decreasing order, diseases with significant associations with PCP were:

- Polyarteritis nodosa (odds ratio [OR] 10.20, 95% confidence interval [CI] 5.69–18.29)
- Granulomatosis with polyangiitis (OR 7.81, 95% CI 4.71–13.05)

**Treatment with glucocorticoids is an important risk factor for PCP, independent of biologic therapy**

- Inflammatory myopathy (OR 4.44, 95% CI 2.67–7.38)
- Systemic lupus erythematosus (OR 2.52, 95% CI 1.66–3.82).

Vallabhaneni and Chiller,<sup>26</sup> in a meta-analysis including rheumatoid arthritis patients on biologics, did not find an increased risk of PCP (OR 1.77, 95% CI 0.42–7.47).

Park et al<sup>12</sup> found that the highest incidences of PCP were in patients with granulomatosis with polyangiitis, microscopic polyangiitis, and systemic sclerosis. For systemic sclerosis, the main reason for giving high-dose glucocorticoids was interstitial lung disease.

Other studies<sup>19,20,28</sup> also found an association with coexisting pulmonary disease in patients with rheumatoid arthritis.

### ■ CURRENT GUIDELINES

There are guidelines for primary and secondary prophylaxis of PCP in HIV-positive patients with CD4 counts less than 200/mm<sup>3</sup> or a history of acquired immunodeficiency syndrome (AIDS)-defining illness.<sup>27</sup> Additionally, patients with a CD4 cell percentage less than 14% should be considered for prophylaxis.<sup>27</sup>

Unfortunately, there are no guidelines for prophylaxis in patients taking immunosuppressants for rheumatic disease.

The recommended regimen for PCP prophylaxis in HIV-infected patients is trimethoprim-sulfamethoxazole, 1 double-strength or 1 single-strength tablet daily. Alternative regimens include 1 double-strength tablet 3 times per week, dapsone, aerosolized pentamidine, and atovaquone.<sup>27</sup>

There are also guidelines for prophylaxis in kidney transplant recipients, as well as for patients with hematologic malignancies and solid-organ malignancies, particularly those on chemotherapeutic agents and the T-cell-depleting agent alemtuzumab.<sup>29–31</sup>

Italian clinical practice guidelines for the use of tumor necrosis factor antagonists in inflammatory bowel disease recommend consideration of PCP prophylaxis in patients who are also on other immunosuppressants, particularly high-dose glucocorticoids.<sup>32</sup>

Prophylaxis has been shown to increase life expectancy and quality-adjusted life-

TABLE 2

### Risk factors for *Pneumocystis jirovecii* pneumonia in patients on biologic therapy for rheumatic disease

#### Clinical risk factors

- Age > 65<sup>5,21,22</sup>
- Preexisting pulmonary disease<sup>9,21,22</sup>
- Granulomatosis with polyangiitis<sup>4,19</sup>
- Microscopic polyangiitis<sup>4</sup>
- Polyarteritis nodosa<sup>19</sup>
- Inflammatory myopathy<sup>19</sup>
- Systemic lupus erythematosus<sup>19</sup>

#### Laboratory testing indicators

- Lymphopenia (< 500 cells/mm<sup>3</sup>)<sup>5,18</sup>
- Low CD4 count (< 200 cells/mm<sup>3</sup>)<sup>5,18</sup>
- Low immunoglobulin G level<sup>9</sup>

#### Pharmacologic risk factors

- Concomitant chronic glucocorticoid therapy<sup>3–6,9,17,21,28</sup> (≥ 15 mg/day of prednisone for 4 weeks or longer)<sup>4,5</sup>
- Concomitant therapy with nonbiologic disease-modifying antirheumatic drug or cytotoxic agent<sup>5,7,9,22</sup>

years and to reduce cost for patients on immunosuppressive therapy for granulomatosis with polyangiitis.<sup>21</sup> The European Society of Clinical Microbiology and Infectious Diseases recently produced consensus statements recommending PCP prophylaxis for patients on rituximab with other concomitant immunosuppressants such as the equivalent of prednisone 20 mg daily for more than 4 weeks.<sup>33</sup> Prophylaxis was not recommended for other biologic therapies.<sup>34,35</sup>

### ■ THE RISKS OF PROPHYLAXIS

The risk of PCP should be weighed against the risk of prophylaxis in patients with rheumatic disease. Adverse reactions to sulfonamide antibiotics including disease flares have been reported in patients with systemic lupus erythematosus.<sup>36,37</sup> Other studies have found no increased risk of flares in patients taking trimethoprim-sulfamethoxazole for PCP prophylaxis.<sup>12,38</sup> A retrospective analysis of patients with vasculitis found no increased risk of combining methotrexate and trimethoprim-sulfamethoxazole.<sup>39</sup>

**Patient risk factors for PCP: older age, lung disease, granulomatosis with polyangiitis**

**KEY POINTS**

- PCP is an opportunistic infection with a high risk of death.
- PCP has been reported with biologics used as immunomodulators in rheumatic disease.

- PCP prophylaxis should be considered in patients at high risk of PCP, such as those who have granulomatosis with polyangiitis, underlying pulmonary disease or who are concomitantly taking glucocorticoids.

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