COST-EFFECTIVENESS OF PROPHYLAXIS AGAINST PNEUMOCYSTIS CARINII PNEUMONIA IN PATIENTS WITH WEGENER’S GRANULOMATOSIS UNDERGOING IMMUNOSUPPRESSIVE THERAPY

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Objective. To assess the incremental cost-effectiveness of 3 Pneumocystis carinii pneumonia (PCP) prophylaxis strategies in patients with Wegener’s granulomatosis (WG) receiving immunosuppressive therapies: 1) no prophylaxis; 2) trimethoprim/sulfamethoxazole (TMP/SMX) 160 mg/800 mg 3 times a week, which is discontinued if patients experience an adverse drug reaction (ADR); and 3) TMP/SMX 160 mg/800 mg 3 times a week, which is replaced by monthly aerosolized pentamidine (300 mg) if patients experience an ADR.

Methods. A Markov state-transition model was developed to follow a hypothetical cohort of WG patients over their lifetimes starting from the time of initial exposure to the immunosuppressive therapy. The effect of PCP prophylaxis on life expectancy, quality-adjusted life expectancy, average discounted lifetime cost (ADLC), and incremental cost-effectiveness was estimated based on data obtained from a literature review. Direct medical costs were examined from a societal perspective, and costs and benefits were discounted at 3% annually.

Results. No prophylaxis resulted in a life expectancy of 13.36 quality-adjusted life years (QALY) at an ADLC of $4,538. In comparison, prophylaxis with TMP/SMX alone increased the QALY to 13.54 and was cost saving, with an ADLC of $3,304. The addition of pentamidine in patients who had an ADR to TMP/SMX resulted in 13.61 QALY, with an ADLC of $7,428. Compared with TMP/SMX alone, TMP/SMX followed by pentamidine increased the QALY by 0.07 at an incremental cost of $58,037 per QALY. Both TMP/SMX alone and TMP/SMX followed by pentamidine prophylaxis strategies dominated the no prophylaxis strategy until the incidence of PCP fell below 0.2% and 2.25%, respectively. Institution of pentamidine therapy for patients with a TMP/SMX ADR increased quality-adjusted life expectancy compared with that with TMP/SMX alone until the incidence of PCP rose above 7.5%.

Conclusion. Prophylaxis using TMP/SMX alone increased life expectancy and reduced cost for patients with WG receiving immunosuppressive therapy. Replacing TMP/SMX with monthly aerosolized pentamidine in cases of ADR further increased life expectancy, although at an increased cost.

Wegener’s granulomatosis (WG) is a systemic necrotizing vasculitis with significant morbidity (1) and mortality (2). Diagnostic and therapeutic advances, primarily the use of immunosuppressive therapy, have changed this once-fatal disorder into a suppressible chronic inflammatory disease (3). Opportunistic infection, an unfortunate and to some extent unavoidable consequence of immunosuppression, has emerged as a significant cause of mortality in WG patients.

Pneumocystis carinii pneumonia (PCP), a common infectious complication in immunocompromised patients, is associated with significant morbidity and mortality (4–6). Trimethoprim/sulfamethoxazole (TMP/SMX), pentamidine, or dapsone is widely used as prophylaxis against PCP in patients with a variety of immunocompromised conditions. Among these regimens, TMP/SMX 3 times a week is the most cost-effective prophylaxis regimen for those patients with acquired immunodeficiency syndrome (AIDS) who can tolerate it (7,8). Although this regimen has also been used since the 1970s in patients with hematologic malignancies and in those receiving immunosuppressive drugs.
for organ transplantation, scant attention has been paid to the use of PCP prophylaxis in immunosuppressed patients with systemic rheumatic or inflammatory conditions.

In this study, we assessed the cost-effectiveness of 3-day-a-week TMP/SMX prophylaxis in comparison with no prophylaxis in patients with WG who were receiving immunosuppressive therapy. We also examined the incremental cost-effectiveness of monthly aerosolized pentamidine if TMP/SMX is discontinued because of an adverse drug reaction (ADR).

PATIENTS AND METHODS

Analytic framework. We developed a computer-based simulation of the natural history of a cohort of patients with WG to examine the effect of PCP prophylaxis on life expectancy, quality-adjusted life years (QALY), and direct medical costs. The analysis included the probability of disease-related death, PCP, and ADR, and the cost related to treatment of PCP and ADR to prophylactic treatment. Health-related quality of life weights were assigned to each event. Direct medical costs were examined from a societal perspective (i.e., all direct costs and benefits regardless of whether they are incurred by the patient, employer, provider, or a third-party payor). Time effects of costs and survival were discounted at an annual rate of 3% (9). Sensitivity analyses were performed to explore the robustness of the results to reasonable variations in model variables. Model outcomes included survival rates, QALY estimates, costs, and incremental cost-effectiveness.

The model. A Markov state-transition model was constructed using DATA 3.0 (Williamstown, MA) to compare the
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cost-effectiveness of 3 PCP prophylaxis strategies: 1) no prophylaxis; 2) TMP/SMX (160 mg TMP/800 mg SMX) 3 times a week with no prophylaxis following an ADR; and 3) TMP/SMX (160 mg TMP/800 mg SMX) 3 times a week replaced by monthly aerosolized pentamidine in patients experiencing an ADR to TMP/SMX (Figure 1). A hypothetical cohort of WG patients was tracked over their lifetimes from the initiation of immunosuppressive therapy at the age of 35. Patients with prior allergic reactions to sulfa medications were not eligible for TMP/SMX prophylaxis and were excluded from the model. Patients were cycled through the model at 1-year intervals. In the first year, patients were assigned to 1 of the 3 strategies.

At the end of each model-year cycle, patients moved from one state of health to another depending on the probability of an intervening event during that year. Health states included 1) alive with WG, 2) ADR, 3) PCP, 4) death from PCP, or 5) death from all other causes (Figure 2). Patients who started out in the no prophylaxis group but who developed PCP were treated and then maintained on TMP/SMX prophylaxis. For the 2 strategies in which patients started with TMP/SMX prophylaxis, the ensuing steps differed if a patient experienced an ADR to TMP/SMX. In one strategy, prophylaxis was discontinued altogether, while in the other strategy, monthly aerosolized pentamidine was substituted for TMP/SMX. If a patient experienced an ADR to pentamidine, it was discontinued and no further prophylaxis was instituted. Table 1 summarizes the model parameters examined, the base-case estimates, and the range of values evaluated in the sensitivity analyses for each parameter.

Incidence of PCP in systemic rheumatic diseases. The annual incidence rate of PCP in WG (0.85%) was estimated from a retrospective study by Oñibene et al, in which 11 cases of PCP were identified among 180 WG patients receiving immunosuppressive therapy over a period of 7.2 years (13). Other studies that reported the occurrence of PCP in the course of immunosuppressive treatment for a variety of inflammatory diseases were used to establish a reasonable range for sensitivity analyses (3,13,20–25) (Table 2).

Incidence of ADR. The incidence of adverse reactions to TMP/SMX among WG patients was estimated from a prospective, randomized, placebo-controlled study of TMP/SMX given twice daily for 24 months to prevent relapses in patients with WG (16). Because a single dose given only 3 times a week is less likely to lead to adverse reactions, lower rates of drug reactions were examined in sensitivity analyses (Table 1). Adverse reactions to monthly inhaled pentamidine (300 mg) are more common, but primarily consist of mild bronchospasm, cough, fatigue, and nausea. In the study by Leong et al of PCP prophylaxis in AIDS patients, 20% of the patients on a 300 mg monthly pentamidine regimen experienced side effects requiring termination of the prophylaxis over an 18-month period (11).

Prophylaxis characteristics. TMP/SMX prophylaxis against PCP in non-AIDS patients is almost 100% efficacious (14,15). We estimated the effectiveness of TMP/SMX to be 90% compared with no prophylaxis, to account for an estimated 10% noncompliance rate (7). Similarly, aerosolized pentamidine was reported to be 87–90% effective in AIDS patients (11,31). We utilized the lower value for the base-case analysis.

Costs. For medication costs, we used the average wholesale price incurred by the hospital pharmacy. At $0.09 per 160 mg TMP/800 mg SMX tablet, the yearly cost of a 3-times-a-week regimen was estimated to be $14.04 (10). We assumed that those taking TMP/SMX did not incur any additional monitoring costs beyond what was routine for their underlying disease process. The monthly cost of aerosolized pentamidine was estimated to be $154 (annual cost $1,853), which included the medication, respiratory therapy, and bronchodilators (8,10). The mean cost of an episode of PCP in the non-AIDS population ($38,824) was estimated from a retrospective review by Nicolau et al of hospital charges in 32 human immunodeficiency virus (HIV)–negative patients (12).

Quality-of-life adjustments. Otherwise healthy patients in both the prophylaxis and no prophylaxis groups were assigned a quality adjustment factor of 1. The base case of those who became infected with PCP was assigned a quality adjustment of 0.3 for 1 year, and patients who experienced an ADR were assigned a quality adjustment factor of 0.9 for 1 year. In the absence of data in the literature, Freedberg’s estimates of quality adjustments in AIDS patients (7,9) were revised based on the available literature about the differences in PCP in patients with and without AIDS (17,18,33,34).

Mortality from PCP. The PCP mortality rate (40.8%) was estimated from an aggregate of all inflammatory conditions, because the published number of incident cases of PCP in each individual disease was small (Table 2). This mortality rate is in close agreement with that estimated by other investigators for mortality from PCP in the setting of inflammatory diseases (17,18).

Mortality from WG. Five-, 10-, and 15-year survival rates of 75%, 64%, and 55%, respectively, were derived from a multicenter cohort study of long-term survival of patients with WG (2).

Mortality from other causes. Population age-specific risk of death from all other causes for the cohort was obtained from the National Center for Health Statistics (19).

RESULTS

Total medical costs (Table 3). In a 35-year-old patient with WG, the average discounted lifetime cost was $4,538 for no prophylaxis, $3,304 for prophylaxis with TMP/SMX with therapy discontinued in response to a TMP/SMX ADR, and $7,428 for TMP/SMX prophylaxis with pentamidine therapy instituted in patients who experienced an ADR to TMP/SMX.

Life expectancy (Table 3). Without prophylaxis, the mean discounted life expectancy for a 35-year-old patient with WG undergoing immunosuppressive treat-
ment was 13.36 QALY. Prophylaxis with TMP/SMX alone 3 times per week increased life expectancy by 0.18 QALY, to 13.54 QALY. Switching to pentamidine in patients who experienced an ADR to TMP/SMX increased the QALY further to 13.61 QALY. The non–quality-adjusted life expectancies for the no prophylaxis, TMP/SMX alone, and TMP/SMX followed by pentamidine strategies were 13.41, 13.63, and 13.73, respectively.

**Incremental cost-effectiveness of prophylaxis (Table 3).** Both of the TMP/SMX–based prophylaxis regimens improved life expectancy compared with no prophylaxis. Although the prophylaxis using TMP/SMX alone also reduced costs, the TMP/SMX regimen combined with pentamidine resulted in higher costs compared with no prophylaxis using base-case estimates. On the other hand, adding aerosolized pentamidine after an adverse reaction to TMP/SMX gained 0.07 QALYs com-

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Incidence of PCP</th>
<th>Mortality from PCP</th>
<th>Corticosteroid dose</th>
<th>Other immunosuppressants</th>
<th>Time until PCP</th>
<th>Lymphocyte count at the time of PCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0/22 with α-GBMD; 1/19 with SLE; 0/18 with WG; 1/16 with systemic vasculitis</td>
<td>1/1 with SLE; 1/1 with systemic vasculitis</td>
<td>Prednisone 60 mg/day</td>
<td>CYC 3 mg/kg/day; AZA 1 mg/kg/day</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>26</td>
<td>NR</td>
<td>1/1 with systemic vasculitis; 1/1 with WG</td>
<td>Prednisone 30 mg/day; prednisone 60 mg/day</td>
<td>CYC 100 mg/day; CYC 175 mg/day</td>
<td>NR</td>
<td>&lt;800; &lt;200</td>
</tr>
<tr>
<td>21</td>
<td>5/86 with SLE and DPGN</td>
<td>NR</td>
<td>Prednisone started at 60–80 mg/day</td>
<td>CYC 2–3 mg/kg/day</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>22</td>
<td>1/41 with RA</td>
<td>1/1 with RA</td>
<td>Prednisone 1 mg/kg 3/6 prednisone mean dose 43.3 mg/day (range 30–60); 3/6 MP mean dose 38.67 mg/day (range 36–40)</td>
<td>MTX 10 mg/week CYC 2.5 mg/kg/day 3/6 CYC mean dose 250 mg/day (range 100–500); 3/6 AZA mean dose 100 mg/day (range 50–150)</td>
<td>8 months</td>
<td>Mean 5.83 weeks (range 2–17)</td>
</tr>
<tr>
<td>3</td>
<td>6/158 with WG</td>
<td>NR</td>
<td>4/6 with SLE</td>
<td>Mean 368.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>NR</td>
<td>6/23 with WG</td>
<td>Prednisone mean dose at onset of PCP 56.6 mg/day (range 40–80)</td>
<td>Mean 2.5 months (range 1.25–5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>12/100 with WG; 5/250 with DM/PM; 6/750 with SLE; 4/250 with PAN; 2/1,500 with RA</td>
<td>5/12 with WG; 3/5 with DM/PM; 2/6 with SLE; 0/4 with PAN; 0/2 with RA; 0/1 with adult Still’s disease; 1/2 with pemphigus; 0/1 with pemphigoid; 0/1 with sarcoid</td>
<td>32/34 prednisone mean dose 1.2 mg/kg/day</td>
<td>25/34 within the first 8 months of diagnosis of CTD</td>
<td>31/34 with &lt;1,500; 26/34 with &lt;800</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>NR</td>
<td>11/180 with WG</td>
<td>Prednisone 60 mg/day</td>
<td>Mean 1,052.7 (mean 1,841.6 in patients without PCP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1/11 with SLE</td>
<td>1/11 with WG</td>
<td>Prednisone 60 mg/day</td>
<td>6/11 CYC; 3/11 MTX; 1/11 AZA; 2/11 CSA</td>
<td>All within 1 year</td>
<td>61–658</td>
</tr>
<tr>
<td>25</td>
<td>1/59 with SLE; 3/6 with DM; 3/10 with PM; 1/3 with systemic vasculitis</td>
<td>NR</td>
<td>Prednisolone mean ± SD 42.46 ± 12.9 mg/day (all given 40 mg/day or higher)</td>
<td>Mean 1,052.7 (mean 1,841.6 in patients without PCP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>NR</td>
<td>3/4 with DM</td>
<td>Prednisone mean dose 67.5 mg/day (range 50–75)</td>
<td>Mean 465 (range 240–760)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>NR</td>
<td>2/3 with GCA</td>
<td>NR</td>
<td>NR</td>
<td></td>
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</tr>
</tbody>
</table>

*α-GBMD = α-glomerular basement membrane disease; SLE = systemic lupus erythematosus; WG = Wegener’s granulomatosis; CYC = cyclophosphamide; AZA = azathioprine; NR = not reported; DPGN = diffuse proliferative glomerulonephritis; RA = rheumatoid arthritis; MTX = methotrexate; MP = methylprednisolone; IV = intravenous; DM/PM = dermatomyositis/polymyositis; PAN = polyarteritis nodosa; CTD = connective tissue disease; CSA = cyclosporin A; GCA = giant cell arteritis.

Table 2. Published cases of *Pneumocystis carinii* pneumonia (PCP) in patients without acquired immunodeficiency syndrome and inflammatory diseases used in the analysis*
pared with using TMP/SMX alone. The incremental cost-effectiveness of adding aerosolized pentamidine to the TMP/SMX regimen was $58,037 per QALY gained compared with the TMP/SMX regimen without pentamidine.

Sensitivity analyses. In one-way sensitivity analyses of the parameters shown in Table 1, we found that TMP/SMX alone and TMP/SMX followed by pentamidine prophylaxis dominated the no prophylaxis strategy until the incidence of PCP fell below 0.2% and 2.25%, respectively. The TMP/SMX followed by pentamidine dominated the TMP/SMX alone strategy when the incidence of PCP rose above 7.5%. The incremental cost-effectiveness of each strategy for the incidence of PCP ranging from 0% to 3% is shown in Figure 3.

When the effect of the rate of ADR to TMP/SMX was subjected to sensitivity analysis, the no prophylaxis strategy was found to dominate the TMP/SMX alone strategy only when the incidence of ADR rose above 49%. Otherwise, both TMP/SMX-based strategies resulted in increased quality-adjusted life expectancy compared with the no prophylaxis strategy. The incremental cost-effectiveness of each strategy for the incidence of ADR ranging from 10% to 50% is shown in Figure 4. For all other parameters tested, the TMP/SMX-based prophylaxis regimens improved quality-adjusted life expectancy compared with no prophylaxis throughout the range of variable estimates examined.

We also modeled PCP prophylaxis for 2 years based on the National Institutes of Health experience described by Hoffman et al (3), in which patients were treated with cyclophosphamide for 1 year after they had achieved remission and corticosteroids were tapered off between 6 and 12 months after the start of treatment when possible. The period of the most intensive treatment, and therefore the highest risk for PCP, likely occurs during this early period. The 2 prophylaxis strategies became more cost-effective compared with the no prophylaxis strategy when we concentrated the risk of PCP in the first 2 years, rather than using the base-case estimate of uniform PCP risk. Running the model for 2 years with the redistributed PCP risk, we found that prophylaxis with TMP/SMX or TMP/SMX followed by pentamidine resulted in a gain of 0.0269 QALY and 0.0275 QALY, respectively, compared with no prophylaxis. Both TMP/SMX-based strategies also saved cost (by $1,606 for TMP/SMX alone and $1,543 for TMP/SMX followed by pentamidine), thus dominating the no prophylaxis strategy.

**DISCUSSION**

This cost-effectiveness analysis demonstrated that 3-times-a-week TMP/SMX prophylaxis increases life expectancy and QALY and reduces cost in WG patients receiving immunosuppressive therapy. This ad-

### Table 3. Comparisons of the costs, effectiveness, and incremental cost-effectiveness of various prophylaxis regimens using base-case estimates

<table>
<thead>
<tr>
<th>Prophylaxis strategy</th>
<th>Cost, $</th>
<th>Incremental cost, $</th>
<th>Effectiveness, QALY</th>
<th>Incremental effectiveness, QALY</th>
<th>Incremental cost-effectiveness, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP/SMX</td>
<td>3,304</td>
<td></td>
<td>13.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>4,538</td>
<td>1,234</td>
<td>13.36</td>
<td>-0.18</td>
<td>(Dominated)</td>
</tr>
<tr>
<td>TMP/SMX + pentamidine</td>
<td>7,428</td>
<td>4,124</td>
<td>13.61</td>
<td>0.25</td>
<td>58,037</td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>4,538</td>
<td></td>
<td>13.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMP/SMX + pentamidine</td>
<td>7,428</td>
<td>2,890</td>
<td>13.61</td>
<td>0.25</td>
<td>11,560</td>
</tr>
</tbody>
</table>

* See Table 1 for definitions.
vantage persists as long as the annual risk of PCP infection in WG patients is \(0.2\%\), a level well below even the most conservative published estimates (35). Adding aerosolized pentamidine after an adverse reaction to TMP/SMX further increased life expectancy, but at increased costs, with an incremental cost-effectiveness of \(\$58,037\) per QALY when the incidence of PCP was the base-case estimate of 0.85%. The incremental cost per additional QALY decreased as the incidence of PCP increased. However, the incremental cost-effectiveness of adding pentamidine rapidly increased as the annual incidence rate fell below 0.85% (Figure 3). Thus, the decision to add pentamidine in cases of adverse reactions to TMP/SMX depends on the estimated incidence of PCP. The conventional threshold of incremental cost-effectiveness of 50,000 per QALY is reached when the incidence of PCP exceeds 0.93%.

TMP/SMX given twice daily has been shown to reduce the rate of relapse in patients with WG (16). The mechanism for this is unknown, but may relate to the presence of *Staphylococcus aureus* in the nasal passages of patients with WG (36). Although the dose of TMP/SMX used in our analysis differs from that used to reduce recurrences, it suggests additional benefits of prophylaxis beyond prevention of PCP.

Virtually all patients with PCP have been exposed to immunosuppressive therapies that consist of corticosteroids alone or in combination with cytotoxic agents, and most cases have occurred in the setting of lymphopenia (33,37). However, there are scattered reports of PCP in the setting of no immunosuppressive therapy or low-dose treatment (38–41). Treatment with cyclophosphamide in WG is not conventionally intended to generate leukopenia, nor is it a reliable guide to susceptibility to PCP (42). However, oral cyclophosphamide appears to confer a greater susceptibility to PCP than intravenous pulse cyclophosphamide (43). In addition, alternative chemotherapy with methotrexate does not eliminate, and possibly does not reduce, the risk of PCP (42). Although it is difficult to recommend a threshold for initiating PCP prophylaxis, in general those who develop PCP have more severe lymphopenia (lymphocyte count <1,000) and receive higher doses of corticosteroids (1 mg/kg/day of prednisone with or without cytotoxic agents such as oral or intravenous pulse cyclophosphamide) (27).

Although AIDS accounts for the majority of PCP cases, there are numerous reports of PCP in patients with systemic rheumatic diseases (28,30,44–52). The incidence of PCP appears to be rising in general (18), which may be explained by several factors. More patients are becoming therapeutically and more profoundly immunosuppressed for an increasing number of indications. There is also strong evidence of nosocomial spreading in susceptible individuals (4,40,41,53–59). Lastly, reporting bias may occur more frequently as clinicians’ awareness of PCP increases.

Compared with AIDS patients, non-AIDS patients have a lower rate of adverse reactions to TMP/SMX, a higher mortality rate associated with PCP (6,7,17,18,33,34), and higher hospital costs associated with the diagnosis (12). Clearly, any vasculitis or inflammatory condition requiring prolonged corticosteroid therapy with or without cytotoxic agents predisposes patients to PCP and should prompt consideration of prophylaxis. In addition, TMP/SMX also may provide benefits beyond PCP prophylaxis, including prevention of other opportunistic infections, such as listeriosis and nocardiosis (60). Dapsone and atovaquone, which have been shown to be safe and effective alternatives to TMP/SMX in PCP prophylaxis for HIV patients, are reasonable alternative agents for prophylaxis in WG patient populations (61), but were not evaluated in our model.

PCP prophylaxis with TMP/SMX has dramatically improved the outlook for AIDS patients at risk for PCP (62,63). This analysis indicates that the same will be true in patients with WG and possibly in other groups of patients with systemic rheumatic or inflammatory dis-

**Figure 4.** Incremental cost-effectiveness of the 3 prophylaxis strategies in relation to the incidence of ADR to TMP-SMX. The no prophylaxis strategy dominated the TMP-SMX alone strategy when the incidence of ADR rose above 49%. Otherwise, both TMP-SMX-based strategies resulted in increased quality-adjusted life expectancy compared with the no prophylaxis strategy. See Figures 1 and 3 for definitions.
eases who are being treated with immunosuppressive regimens.

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