New Developments in the Treatment of Pneumocystis carinii Pneumonia*

Fred R. Sattler, M.D.;† and Judith Feinberg, M.D.‡

Pneumocystis carinii pneumonia and therapies to treat this infection are associated with frequent and severe morbidity in patients with acquired immunodeficiency syndrome (AIDS). Mortality rates remain in the 20 to 40 percent range for severe episodes. Thus, less toxic and more effective therapies are needed. For mild-to-moderately severe episodes (PaO₂>70 mm Hg or [A-a]DO₂<35 mm Hg), studies suggest that trimethoprim-dapsone, clindamycin-primaquine, and BW 566C80 may cause less toxicity than conventional therapy with trimethoprim-sulfamethoxazole or parenteral pentamidine. However, prospective, controlled trials are needed to establish whether the newer therapies are as effective as the existing licensed treatments. Aerosolized pentamidine is another new therapy that is better tolerated than trimethoprim-sulfamethoxazole but may not be as effective as parenteral treatment when there is extensive airspace consolidation. For severe episodes (PaO₂<70 mm Hg or [A-a]DO₂>35 mm Hg), recent studies have established that adjunctive therapy with corticosteroids reduces mortality approximately twofold. For patients who have failed conventional treatments and are unable to ingest oral medications, trimetrexate may be tried. Other compounds being tested may further expand the therapeutic armamentarium with safer and more effective drugs.

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**Pneumocystis carinii** pneumonia continues to cause severe morbidity and mortality in patients with acquired immunodeficiency syndrome (AIDS). Chest tightness, breathlessness, unremitting cough, high fever, drenching sweats, nosocomial bacterial infections, and treatment-associated adverse drug effects such as generalized rash, nausea, and vomiting result in considerable discomfort and anxiety for patients, their partners, and families. Drug-induced laboratory abnormalities such as neutropenia, thrombocytopenia, renal impairment, hepatitis, pancreatitis, and hypoglycemia are common with trimethoprim-sulfamethoxazole (TMP-SMX) or pentamidine and further complicate treatment of these patients. In addition, pneumothoraces that may occur spontaneously or after bronchoscopy often prolong hospitalization and contribute to morbidity. Finally, mortality rates remain in the range of 20 to 40 percent for patients with severe hypoxemia at the outset of therapy.1-5 Thus, safer less toxic and more effective therapies are needed for the treatment of pneumocystis pneumonia.

**Mild-to-Moderate Episodes**

Mild-to-moderate episodes may be defined by initial room air PaO₂ greater than 70 mm Hg or (A-a)DO₂<35 mm Hg, since the risk of a fatal outcome is only 10 to 20 percent.6 For these episodes less toxic, convenient, nonparenteral, and inexpensive therapies should be sought. In this context, reduced-dose TMP-SMX, trimethoprim-dapsone, dapsone alone, clindamycin-primaquine, and aerosolized pentamidine have been evaluated.

**Reduced-Dose TMP-SMX**

Bone marrow suppression caused by antifolate drugs is usually dosage dependent, whereas fever and rash are generally hypersensitivity reactions. In an attempt to reduce myelosuppression, the dosage of TMP-SMX was modified in one trial to keep trimethoprim concentrations in the 5- to 8-mg/L range. By design TMP-SMX therapy was continued even when fever and rash occurred.* The final dosage of TMP-SMX for the 36 patients treated in this manner was 12 mg/kg/day (TMP component). Drug-associated fever (78 percent), neutropenia (72 percent), rash (44 percent), and nausea or vomiting (25 percent) occurred but were not serious and were tolerated with symptomatic therapy (acetaminophen, antihistamines, antiemetics). Each patient was, therefore, able to complete a three-week course of therapy withTMP-SMX. In addition, 86 percent survived, which was remarkable since the median baseline room air (A-a)DO₂ was 44 mm Hg.

*Comment: Despite algorithms to treat through toxicities, the excellent bioavailability of oral TMP-SMX (>90 percent for TMP and SMX), and its low cost, adverse effects with TMP-SMX remain a frequent cause of morbidity and discomfort for patients. Thus, better tolerated agents are still needed.

**Trimethoprim-Dapsone**

In a double-blind trial, 60 patients with initial room...
Treatment-terminating air arm dapsone. Of definitive netic comparable effects concentrations progressed patients normal more often in patients treated with TMP-SMX. Intolerable rash and vomiting were similar in both groups. Methemoglobinemia was detected in all patients treated with dapsone but exceeded 20 percent in only one individual. Pneumocystis pneumonia progressed in 3 of 30 patients receiving TMP-SMX and 2 of 30 patients receiving trimethoprim-dapsone.

In a pharmacokinetic assessment of these patients and 18 additional subjects treated only with dapsone, concentrations of dapsone were 40 percent higher during concurrent therapy with trimethoprim than with dapsone alone. Similarly, concentrations of trimethoprim were 48 percent higher during concurrent therapy with dapsone than with SMX. Thus, drug concentrations of trimethoprim and dapsone are higher when the two agents are used together compared with their use alone or with other antifolate compounds.

Comment: The first study suggests that laboratory abnormalities occur less often with trimethoprim-dapsone than with TMP-SMX, although clinical side effects are similar with the two therapies. The trial did not establish whether trimethoprim-dapsone is of comparable efficacy to TMP-SMX because of the relatively small study population. The pharmacokinetic study suggests that treatment efficacy should be maintained with the lower doses of trimethoprim-dapsone since there is an interference in clearance of these drugs when they are used together. Thus, a definitive study is needed to evaluate larger numbers of patients treated with “low doses” of trimethoprim-dapsone.

Dapsone

In an uncontrolled trial, 18 patients with mild-to-moderate episodes were treated with 100 mg/day of dapsone alone. The 39 percent failure rate was unacceptably high. A second study evaluated 200 mg of dapsone daily for patients with initial room air PaO₂ >60 mm Hg. The study was terminated after seven patients had been enrolled because of two deaths and five failures. Treatment was terminated in four because of methemoglobinemia (9.5 to 17.4 percent) and respiratory distress, and none was able to successfully complete a full course of therapy with dapsone.

Comment: These data indicate that dapsone should not be prescribed alone for treatment of pneumocystis.

Clindamycin-Primaquine

Clindamycin and the antimalarial drug primaquine together have excellent activity against P. carinii in a limited culture system and in cortisone-treated rats, although neither agent is effective alone (although primaquine has some activity in vitro). In the first clinical investigation of this combination, 23 (92 percent) of 25 patients treated with 600 mg of clindamycin intravenously every 6 h and 15 mg of primaquine base once daily responded. However, 17 of the subjects had been treated previously with conventional therapies and the contribution of these therapies to the ultimate outcome could not be ascertained.

In another study, 22 previously untreated patients with (A-a)DO₂<30 mm Hg received 900 mg of clindamycin intravenously every 8 h for ten days and then 450 mg orally every 6 h for 11 days along with 30 mg of primaquine base orally once daily for three weeks. Twenty (91 percent) of these patients improved by day 7 of treatment and two failed and were switched to other therapies. Four patients were subsequently removed from study because of rash. Sixteen patients (73 percent) successfully completed the three-week course of therapy. Generalized rash was the most common toxic reaction and occurred in 15 patients but required treatment cessation in only three patients. Diarrhea occurred in one patient and was mild. The trial was extended to evaluate oral clindamycin (450 mg three times daily) and the same dose of primaquine in 46 patients who had baseline (A-a)DO₂ <40 mm Hg. Of the first 14 patients treated with all oral therapy, 13 (93 percent) responded, but generalized rash occurred in 7 (54 percent) but was not treatment limiting.

Comment: The combination of clindamycin and primaquine appears highly promising. A mild morbiliform rash has been the most common side effect. It is probably caused by clindamycin since almost three quarters of patients treated with clindamycin plus pyrimethamine for toxoplasmosis experience the same toxic reaction. Definitive studies are needed to establish the relative efficacy and safety of this combination compared with TMP-SMX and trimethoprim-dapsone.

Aerosolized Pentamidine

With aerosolized pentamidine, drug is delivered directly to alveoli, the putative site of P. carinii infection, with minimal systemic absorption. In a multicenter investigation, 364 patients with initial room air (A-a)DO₂<55 mm Hg were randomized to receive either 600 mg of aerosolized pentamidine once daily via a jet nebulizer (Respirgard II) or TMP-SMX at 15 mg/kg/day (TMP). There was no difference in survival after 21 days of treatment, but more deaths...
occurred in the TMP-SMX group by day 35 (two weeks after study therapy). By contrast, PaO₂ improved significantly faster with TMP-SMX. This disparity could not be explained. As expected, drug-related toxic reactions occurred significantly more often with TMP-SMX.

In two smaller studies, outcome with aerosolized pentamidine was not as effective as intravenous pentamidine. In the first trial, 45 patients with baseline room air PaO₂ > 55 mm Hg were randomized to aerosolized (600 mg once daily via the nebulizer [Respirgard II]) or intravenous pentamidine. Although initial failure rates were similar (12 vs 19 percent), recrudescence of symptoms (35 vs 0 percent) and relapse (24 vs 0 percent) were significantly more common with aerosolized pentamidine (p < 0.05 for both). In the second study, only 6 of 11 patients randomized to receive inhaled pentamidine (8 mg/kg/day via nebulizer [Respirgard II]) responded, whereas all ten assigned to the parenteral formulation responded (p = 0.02). Nonresponders to inhaled pentamidine had lower mean baseline PaO₂ compared with responders (60 vs 81 mm Hg, p = 0.005).

Comment: Although aerosol pentamidine causes less systemic toxicity than TMP-SMX or parenteral pentamidine, the treatment is expensive and requires both supervised administration and compressed oxygen. In addition, the treatment may not be effective in areas of the lung with extensive airspace consolidation, which could predispose to early relapse. Moreover, in sicker patients with higher minute ventilation or those with shallow, rapid respirations, peripheral alveolar deposition may be suboptimal, thereby predisposing these individuals to failure. Thus, aerosolized pentamidine is best suited for patients with mild pneumocystis who cannot tolerate other therapies.

SEVERE EPISODES

Conventional Therapies

In a prospective study in which 70 patients were randomized to receive only TMP-SMX or parenteral pentamidine for a three-week course of therapy, survival was 86 percent for TMP-SMX recipients and 61 percent for pentamidine (p = 0.03). Although the dosage of pentamidine (initially 4 mg/kg/day) was reduced by 30-50 percent for patients experiencing nephrotoxicity, only one of the eight patients receiving pentamidine who died had his dosage reduced. Thus, it is unlikely that the lower dosage contributed to the decreased survival with pentamidine.

Comment: TMP-SMX should remain the gold standard for comparison since to date no agent has been shown to be superior. Although parenteral pentamidine is an acceptable alternative, we believe the standard dosage should remain at 4 mg/kg/day for severe episodes, since studies evaluating lower initial dosages (3 mg/kg/day) have involved primarily patients with mild-to-moderately severe episodes of pneumocystis.

Trimetrexate

Trimetrexate is an antifolate drug that is concentrated in protozoan cells and binds to the dihydrofolate reductase of P carinii nearly 1,500 times more avidly than does trimethoprim. Concurrent therapy with leucovorin (folinic acid) attenuates trimetrexate-induced hematologic toxicity. In the first trial of trimetrexate, 16 patients with intolerance or failure to respond to TMP-SMX were treated with 30 mg/m² of trimetrexate intravenously once daily and 88 percent survived. In a dosage evaluation study, 36 patients with a median baseline (A-a)Do₂ > 30 mm Hg received 45 or 60 mg/m² of trimetrexate daily. Thirty-four (94 percent) survived and all completed a 21-day course of therapy, since hypersensitivity reactions were tolerable and hematologic toxic reactions were reversed within several days by modifying dosages of trimetrexate and leucovorin.

Expectations were, therefore, high for a multicenter trial initiated by the AIDS Clinical Trials Group (protocol 029/031) to compare trimetrexate (45 mg/m²/day) with TMP-SMX (20 mg/kg/day of TMP). Results (unpublished) were unblinded after 302 patients had been enrolled. The Kaplan-Meier survival curves were divergent and by week 7 (four weeks after study therapy), there was a significant benefit in favor of TMP-SMX. Additional patients were not enrolled since the chance of establishing that trimetrexate was 15 percent superior (original study hypothesis) was remote. However, the fact that 69 percent of these severely ill patients who were treated with trimetrexate survived establishes the efficacy of trimetrexate, although TMP-SMX appeared superior with an 81 percent survival rate.

Salvage Therapy: Trimetrexate has been available on a compassionate basis (800-537-9987) for patients intolerant of or failing standard treatment for ten days or more. Of 159 patients intolerant of both TMP-SMX and pentamidine and of 160 patients who had failed at least one conventional treatment, 84 (53 percent) and 48 (30 percent) patients, respectively, were treated for at least 14 days with trimetrexate and were alive after one month of follow-up. Of 111 patients receiving mechanical ventilation at study entry, 18 (16 percent) were extubated and alive at one month of follow-up. These results are similar to those obtained when patients overtly failing therapy with TMP-SMX or parenteral pentamidine and are crossed-over to the opposite therapy.

Comment: Based on in vitro activity, it is disappointing that trimetrexate was inferior to TMP-SMX in the controlled trial. In addition, therapy requires
frequent hematologic monitoring and leucovorin is expensive. Trimetrexate, therefore, should be reserved for patients requiring parenteral therapy because they are intolerant of or have failed TMP-SMX and pentamidine.

Eflornithine

Eflornithine (DFMO, Ornidyl) is an irreversible ornithine decarboxylase inhibitor with efficacy against murine pneumocystis. When administered compassionately at a dosage of 100 mg/kg intravenously or 75 mg/kg orally every 6 h to 345 patients who had failed or were intolerant to standard therapies, 66 percent of nonventilated patients survived. However, only 10 percent of respirator-dependent patients survived. For nonventilated patients, survival was greater (78 percent) for those who received >14 days of treatment compared with those who received <14 days (29 percent). For mechanically ventilated patients, the respective survival rates were 23 percent and 2 percent. However, eflornithine has not been tested adequately as initial therapy.

The most frequent and serious toxic reactions with eflornithine are thrombocytopenia (48 percent), diarrhea (20 percent), leukopenia (18 percent), and a clinically relevant hearing loss (10 percent). The hematologic toxic reactions are usually reversible when the dosage is reduced or treatment terminated.

Comment: Although eflornithine appeared to be useful for salvage therapy, the drug is not available even on a compassionate basis.

Adjunctive Corticosteroids

Three controlled studies indicated that the addition of corticosteroids within 72 h of beginning conventional therapy improves outcome and reduces mortality. In the first study involving 38 patients with baseline oxygen saturation of 85 to 90 percent or a >5 percent decline with exercise, only 6 percent of subjects randomized to receive 60 mg of prednisone daily for three weeks had a 10 percent or greater decline in oxygen saturation compared with 42 percent who received placebo. There was no survival benefit for the corticosteroid recipients. In the second study that evaluated 40 mg of prednisone twice daily for five days followed by tapering doses over the three weeks, there were major clinical benefits. Of 220 patients with proved and 31 with presumed pneumocystis pneumonia, “oxygenation failure” (PaO₂/FIO₂<75), need for mechanical ventilation, and death were each reduced approximately 50 percent in patients randomized to receive corticosteroids compared with patients not receiving corticosteroids. There was no survival benefit for patients with mild episodes (baseline PaO₂/ FIO₂>350). Although the study was not blinded, the nature of the end points makes it unlikely that bias could have affected the outcome significantly. The third study was a double-blind design. Patients with initial respiratory rates >30/min, (A-a)DO₂>30 mm Hg, or PaO₂<75 mm Hg with FIO₂>35 percent were randomized to 40 mg of methylprednisolone every 6 h for seven to ten days or placebo. The study was terminated after an interim analysis disclosed that only 2 of 11 patients receiving placebo had survived compared with 9 of 12 corticosteroid recipients. The only adverse consequence of steroids was an increased incidence of mucocutaneous herpes infections in the second trial.

By contrast, there is no evidence that adjunctive corticosteroids are beneficial for “salvage” therapy. In a trial in which 41 patients were randomized to receive 60 mg of methylprednisolone or placebo every 6 h at any time when their PaO₂ declined to <51 mm Hg, there was no advantage to corticosteroid treatment. However, most patients were randomized more than three days after initiation of specific antipneumocystis treatment. In this study, there were significantly more opportunistic complications in patients treated with corticosteroids.

Comment: These studies provide compelling evidence that adjunctive corticosteroid therapy improves outcome and reduces mortality approximately 50 percent when prescribed early in the course of treatment for patients with moderate-to-severe episodes of pneumocystis pneumonia (initial room air PaO₂<70 mm Hg or [A-a]DO₂>35 mm Hg). The current data do not indicate whether corticosteroids are beneficial for patients with milder episodes.

Efficacy for refractory episodes is less clear, since the sample size may have been too small to demonstrate a small but significant benefit for steroids in the only controlled salvage study. It is also possible that higher doses of corticosteroids or other anti-inflammatory therapies might improve outcome for patients failing standard therapies.

Adjunctive corticosteroids could have detrimental effects if prescribed empirically for other opportunistic infections (eg, tuberculosis or disseminated fungal infection) that may mimic pneumocystis pneumonia, if this treatment delays diagnosis and specific therapy. These infections might improve initially in response to corticosteroids providing the false impression that patients had pneumocystis pneumonia. In fact, consideration should be given to beginning antituberculosis therapy also in patients at risk for tuberculosis and in whom diagnostic tests for pneumocystis are not possible. Moreover, corticosteroids may aggravate and accelerate the progression of cutaneous and pulmonary Kaposi’s sarcoma. Thus, every effort should be made to establish a definitive diagnosis of pneumocystis in patients being treated with adjunctive corticosteroids.
EXPERIMENTAL THERAPIES

Several promising drugs are undergoing initial testing in humans and other compounds have been identified with good activity against *P carinii* in vitro or in animal models.

**Piritrexim**

Piritrexim is an oral antifolate drug that is similar to trimetrexate. In a pilot study of 15 patients with first episode of pneumocystis and baseline PaO₂ > 60 mm Hg, six patients were treated with 150 mg/kg of piritrexim twice daily and nine were treated with 250 mg/kg twice daily for three weeks along with 50 mg of leucovorin four times daily. All survived and four of six patients responded favorably at the lower dose and six of nine responded favorably at the higher dose. None developed neutrophil counts < 750/cu mm, but nine (60 percent) of the patients had relapsed within three months of completing therapy.

**Comment:** As with trimetrexate, the need for frequent hematologic monitoring and the expense of leucovorin may limit the usefulness of piritrexim. Studies are planned to determine if piritrexim plus pulsed doses of dapsone for the initial five to seven days of therapy will improve outcome and reduce the frequency of relapse.

**BW 566C80**

BW 566C80 is a hydroxynaphthoquinone originally developed in England as an antimalarial compound. It inhibits mitochondrial electron transport which is necessary for the biosynthesis of pyrimidines in protozoa. In the steroid-suppressed rat, which has been highly predictive of the effectiveness of anti-*P carinii* pneumonia (PCP) therapies in humans, BW 566 is not only curative at low doses but relapse does not occur after treatment is stopped. This suggests that unlike other agents BW566, may be "cidal" for *P carinii*. Several of its pharmacokinetic properties are unique, including a terminal serum half-life of approximately 50 h and bioavailability that increases several fold with food. In the first 100 patients treated with oral BW 566 for mild-moderate pneumocystis, the response rate has been good and toxic reactions have been minimal (W. Hughes, oral communication, January, 1991).

**Comment:** A large multinational double-blind study is ongoing to determine the relative efficacy and safety of this promising agent compared with oral TMP-SMX for mild-to-moderate episodes. Results may be available later in the year. The apparent lack of toxic reactions and long half-life would also make this an ideal agent to be used intermittently for prophylaxis of pneumocystis.

**Other Agents**

Analogues of pentamidine and the 8-aminoquino-...lines have been evaluated and used in third-world countries for treatment of other protozoan infections, namely malaria and leishmaniasis. Several compounds from these two classes of drugs are at least as potent as pentamidine and primaquine against *P carinii* in the laboratory and demonstrate good bioavailability in animals. WR-6026, an 8-aminoquinoquine, was developed by the military and used to treat leishmaniasis in Africa with a good safety profile. This will probably be the first of the agents to enter phase I testing in human immunodeficiency virus (HIV)-positive patients.

**DISCUSSION**

In the last four years, several new therapies (Table 1) have undergone initial testing and appear promising for treatment of pneumocystis pneumonia. Trimethoprim-dapsone, clindamycin-primaquine, and BW 566C80 appear to cause less hematologic and hepatic toxic reactions than TMP-SMX. However, controlled studies are needed to establish whether they are as effective as TMP-SMX for patients with mild-to-moderate severe episodes.

While aerosolized pentamidine appears less toxic than standard treatments, it is less attractive than systemic therapies. Regional alveolar deposition may be suboptimal in severe episodes, extrapulmonary pneumocystosis may occur, and the drug is expensive. Thus, aerosolized pentamidine is best suited for mild-moderate episodes in patients unable to tolerate oral drug therapy.

For severe episodes in patients who have failed both TMP-SMX and pentamidine and for whom oral therapies are not indicated, trimetrexate may be tried, since results from uncontrolled trials demonstrate that the drug has reasonable efficacy in this setting. However, trimetrexate was not as effective as TMP-SMX for initial therapy and should therefore be reserved for salvage.

**Table 1—New Therapies for Pneumocystis Pneumonia**

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<th>Therapy</th>
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<td><strong>Mild-moderate episodes</strong></td>
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<td>Low-dose oral TMP-SMX*</td>
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<td>Trimethoprim + dapsone</td>
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<td>Dapsone alone</td>
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<td>Primaquine + clindamycin</td>
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<td>Aerosolized pentamidine</td>
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<td><strong>Moderate-severe episodes</strong></td>
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<td>Trimetrexate (salvage)</td>
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<td>Eflornithine (salvage)</td>
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*Trimethoprim-sulfamethoxazole.
The major advance in new therapies has been the unequivocal documentation that adjunctive therapy with corticosteroids improves outcome and reduces mortality by nearly 50 percent when administered within the first 72 h for severe episodes (baseline PaO₂ <70 mm Hg or (A-a)DO₂ >35 mm Hg). However, it is uncertain whether this therapy is beneficial for either milder or refractory episodes. In addition, steroid therapy may worsen Kaposi’s sarcoma or obscure diagnosis and delay treatment of disseminated fungal or mycobacterial infections mimicking pneumocystis pneumonia. We therefore advise that steroid therapy be limited to severe episodes and every effort made to confirm that they do indeed have pneumocystis pneumonia and not another opportunistic infection or malignant neoplasm that could be made worse with steroids.

Other promising agents in laboratory development and early clinical testing will likely expand further the useful armamentarium of pneumocystis therapies. Thus, the new decade has been ushered in with good news that less toxic or more effective therapies are now available and more are on the horizon.

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