Randomized Trial of Weekly Sulfadoxine/Pyrimethamine vs. Daily Low-Dose Trimethoprim-Sulfamethoxazole for the Prophylaxis of *Pneumocystis carinii* Pneumonia After Liver Transplantation

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We conducted a prospective, randomized clinical trial among liver transplant patients to assess the efficacy and safety of weekly sulfadoxine/pyrimethamine compared with daily trimethoprim-sulfamethoxazole in the prevention of *Pneumocystis carinii* pneumonia. The studied drugs were given during 6 months after transplantation. One hundred twenty patients were included. None of the 60 patients receiving weekly sulfadoxine/pyrimethamine developed *Pneumocystis carinii* pneumonia, whereas two cases (3%) developed among the 60 patients who received trimethoprim-sulfamethoxazole. For both patients, the studied medication had been discontinued several weeks earlier because of adverse effects. No differences were observed in the incidence of adverse effects. We conclude that weekly sulfadoxine/pyrimethamine is as effective and safe as is daily trimethoprim-sulfamethoxazole in the prophylaxis of *Pneumocystis carinii* pneumonia after liver transplantation.

*Pneumocystis carinii* pneumonia (PCP) is a common opportunistic infection in the setting of liver transplantation. Its incidence in the absence of prophylaxis has been shown to be ~3%–11% in the first 6 months after transplantation and can be even higher in the small group of patients with chronic rejection or who are treated with additional immunosuppressive therapy [1–6]. PCP is clearly an infection to be prevented rather than treated. The prophylactic drug most commonly used is trimethoprim-sulfamethoxazole, and it has become a part of the standard care at many transplant centers [7–13].

Patients and Methods

Patient population. Patients were eligible for this trial if they were >18 years old and had received a liver allograft at our institution. Patients were excluded if they had taken sulfonamides, other inhibitors of folic acid metabolism, or clindamycin within 6 months of the study.

Study protocol. After the patients had given informed consent, block randomization was done for every 10 patients. One group received weekly prophylaxis with 500 mg of sulfadoxine/25 mg of pyrimethamine (Fansidar; Roche, Basel, Switzerland). The control group received daily prophylaxis with 480 mg of trimethoprim-sulfamethoxazole (Septrim; GlaxoWellcome, Madrid). The first dose was administered when the patient was able to take oral medication, and never after day 7 after transplantation. When oral medication was not possible, the drug was administered by nasogastric tube. We planned to give prophylaxis during the first 6 months after transplantation. To prevent bone marrow suppression, folic acid supplementation was used.

The patients’ tolerance of prophylactic therapy and the presence of symptoms and signs of PCP were monitored weekly during the first 4 weeks, at week 8, and at month 3. After month 3, the patient was evaluated only when clinically indicated. The evaluation included history, physical examination, laboratory tests (complete blood cell count and differential, platelet counts, measurement of electrolytes, aspartate and alanine aminotransferases, alkaline phosphatase, total bilirubin, and cyclosporine levels, and renal function and coagulation tests), and chest radiograph. Induced sputum was also obtained and *P. ca-
rinii was identified by means of a monoclonal antibody. Leukopenia was defined as \(<3 \times 10^9\) leukocytes/L and thrombocytopenia as \(<100 \times 10^9\) platelets/L.

Maintenance immunosuppression consisted of standard triple therapy with cyclosporine, steroids, and azathioprine. Rejection episodes were treated with three doses of 1 g of methylprednisolone and/or an increase in oral prednisone that was reduced to the baseline in 5–7 days. Rejection episodes resistant to steroids were treated with OKT3 monoclonal antibody (5 mg/d for 7–10 days).

All patients received prophylaxis with high-dose acyclovir to prevent cytomegalovirus infection and disease. Cytomegalovirus infection was defined as isolation of the virus either from blood or during a biopsy. Cytomegalovirus disease was defined as culture or histological evidence of cytomegalovirus infection accompanied by consistent symptoms. Viral syndrome was defined as persistent fever and leukopenia, with or without anemia and thrombocytopenia, that could not be attributed to other causes in a patient with evidence of infection by culture. Organ disease was defined as symptomatic dysfunction with histological evidence of infection (definitive diagnosis) or isolation of virus from culture of a biopsy specimen without histological evidence (probable diagnosis). When evidence of dysfunction of two or more noncontiguous organs was demonstrated, the infection was considered disseminated.

PCP was diagnosed if the Pneumocystis organism was found in fluid obtained by bronchoalveolar lavage or in induced sputum. If PCP developed, the patient was withdrawn from the trial.

**Statistical analysis.** All patients who were randomized were included in the analysis according to the intention to treat with either trimethoprim-sulfamethoxazole or sulfadoxine/pyrimethamine. Statistical analysis was performed with \(\chi^2\) test for qualitative data and Student’s \(t\) test for quantitative data. The difference in the survival was calculated with the log-rank test. All \(P\) values were two-sided.

**Results**

One hundred twenty-five patients were included in the trial, but five patients were lost because of early death or noncompliance. At the end of the study, a total of 120 patients (60 patients in each group) were analyzed (table 1). Results are reported for all patients enrolled in the study (intention-to-treat analysis). The trimethoprim-sulfamethoxazole and sulfadoxine/pyrimethamine groups were well matched with regard to the number of patients, age, sex, underlying liver disease, pretransplant WBC count, pretransplant creatinine level, and cytomegalovirus status. Groups were also well matched regarding posttransplant parameters including surgical time, the number of days in the intensive care unit, the number of days of intubation, and the number of days receiving nonprophylactic antibiotics. The incidence of acute rejection and the use of steroids or OKT3 did not differ between groups.

### Table 1. Characteristics of the study groups in a trial comparing trimethoprim-sulfamethoxazole and sulfadoxine/pyrimethamine for prophylaxis of Pneumocystis carinii pneumonia among liver transplant recipients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trimethoprim-sulfamethoxazole</th>
<th>Sulfadoxine/pyrimethamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Age, y</td>
<td>45 ± 12</td>
<td>47 ± 97</td>
</tr>
<tr>
<td>Sex, no. male</td>
<td>36 (60)</td>
<td>40 (67)</td>
</tr>
<tr>
<td>Hepatopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic</td>
<td>25 (42)</td>
<td>27 (45)</td>
</tr>
<tr>
<td>Viral</td>
<td>25 (42)</td>
<td>26 (43)</td>
</tr>
<tr>
<td>Others</td>
<td>10 (16)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Pretransplant WBC count ((\times 10^9/L))</td>
<td>5.2 ± 3</td>
<td>5.6 ± 2.5</td>
</tr>
<tr>
<td>Pretransplant creatinine level ((mg/L))</td>
<td>1.2 ± 0.8</td>
<td>1.0 ± 0.9</td>
</tr>
<tr>
<td>Donor/recipient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cytomegalovirus serostatus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+/+</td>
<td>55 (92)</td>
<td>58 (97)</td>
</tr>
<tr>
<td>−/+</td>
<td>2 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>+/−</td>
<td>3 (5)</td>
<td>-</td>
</tr>
<tr>
<td>Surgical time, h</td>
<td>7 ± 2.4</td>
<td>6.8 ± 2</td>
</tr>
<tr>
<td>Intensive care unit stay, d</td>
<td>13 ± 7.2</td>
<td>19 ± 24</td>
</tr>
<tr>
<td>Time of intubation, d</td>
<td>3.1 ± 5.2</td>
<td>5 ± 9.4</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>22 (37)</td>
<td>20 (33)</td>
</tr>
<tr>
<td>High-dose steroid treatment</td>
<td>18 (30)</td>
<td>15 (25)</td>
</tr>
<tr>
<td>OKT3 treatment</td>
<td>3 (5)</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) or mean ± SD. No differences were statistically significant \((P > .05)\).

**Clinical outcome of prophylaxis.** Overall, there was no difference in the global incidence of infection (table 2). No episode of PCP was observed in the sulfadoxine/pyrimethamine group. In contrast, two patients (3%) in the trimethoprim-sulfamethoxazole group developed PCP. The scarce number of patients prevented observation of significant differences. In both patients, the administration of trimethoprim-sulfamethoxazole had been discontinued 4 and 6 weeks earlier because of leukopenia. They had not received an alternative prophylactic regimen. All patients with PCP recovered after treatment with trimethoprim-sulfamethoxazole given iv. There was no difference in the incidence of cytomegalovirus infection and disease (table 2).

**Adverse events and abnormal laboratory values.** Eleven patients receiving trimethoprim-sulfamethoxazole (18%) and 10 patients receiving sulfadoxine/pyrimethamine (17%) had side effects (table 3). Three patients in the trimethoprim-sulfamethoxazole group (5%) and four patients in the sulfadoxine/pyrimethamine group (7%) developed a progressive increase in liver enzymes. The liver dysfunction improved when the study drug was discontinued for one patient of the trimethoprim-sulfamethoxazole group and for two patients of the sulfadoxine/pyrimethamine group.

Although a trend toward higher incidence of leukopenia \(<3 \times 10^9\) leukocytes/L was observed in the trimethoprim-sulfamethoxazole group, the difference was not significant
Patients with PCP 2 (3) —

Patients with infections

No. of patients 60 60

Discussion

virus reinfection (3).
died in the sulfadoxine/pyrimethamine group as follows: bac-
losis (2), and cerebral hemorrhage (1). Twelve patients (20%)
infection (6), hepatitis virus reinfection (4), invasive aspergil-
sulfamethoxazole group for the following reasons: bacterial
of follow-up. Thirteen patients (22%) died in the trimethoprim-
plant patients. Recently, the effectiveness of daily low-dose
strength tablet b.i.d. 3 days/week) is highly effective for trans-
prim-sulfamethoxazole (one double-strength tablet once or
even discontinue the drug. This permitted us to control four
episodes in the trimethoprim-sulfamethoxazole group and two
in the sulfadoxine/pyrimethamine group. In the remaining pa-
tients of both groups, the prophylactic drug was discontinued,
and in all patients, the episode of leukopenia was resolved.

Mild gastrointestinal intolerance was reported in two pa-
tients (3%) of both groups (table 3). Discontinuation of therapy
was not necessary.

Mortality. Mortality was similar in both groups after 1 year
of follow-up. Thirteen patients (22%) died in the trimethoprim-
sulfamethoxazole group for the following reasons: bacterial
infection (6), hepatitis virus reinfection (4), invasive aspergil-
lossis (2), and cerebral hemorrhage (1). Twelve patients (20%)
died in the sulfadoxine/pyrimethamine group as follows: bac-
terial infection (8), invasive aspergillosis (1), and hepatitis
virus reinfection (3).

Table 2. Incidence of infections among liver transplant recipients in a study of prophylaxis for *Pneumocystis carinii* pneumonia (PCP).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Trimethoprim-sulfamethoxazole</th>
<th>Sulfadoxine/pyrimethamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Patients with infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>during the first 6 months</td>
<td>35 (58)</td>
<td>39 (65)</td>
</tr>
<tr>
<td>Patients with Cytomegalovirus infection</td>
<td>31 (52)</td>
<td>33 (55)</td>
</tr>
<tr>
<td>Cytomegalovirus disease*</td>
<td>5 (8)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Patients with PCP</td>
<td>2 (3)</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%). No differences were statistically significant (*P* > .05).

* In the trimethoprim-sulfamethoxazole group: pneumonia (1), hepatitis (2), and viral syndrome (2); in the sulfadoxine-pyrimethamine group: viral syndrome (2), hepatitis (1), colitis (1).

(table 3). When an episode of leukopenia was observed, the
first step of our policy was to reduce the dose of azathioprine
or even discontinue the drug. This permitted us to control four
episodes in the trimethoprim-sulfamethoxazole group and two
in the sulfadoxine/pyrimethamine group. In the remaining pa-
tients of both groups, the prophylactic drug was discontinued,
and in all patients, the episode of leukopenia was resolved.

Mild gastrointestinal intolerance was reported in two pa-
tients (3%) of both groups (table 3). Discontinuation of therapy
was not necessary.

The experience accumulated with trimethoprim-sulfameth-
oxazole prophylaxis in transplantation contrasts with the scarce
data regarding alternative regimens. A number of other drugs
have been proposed as prophylactic agents, but clinical ex-
perience is limited [15]. Pyrimethamine/sulfadoxine is an inex-
pensive longer-acting antipaludic agent that can be easily ad-
mastered weekly. Concern about this agent is derived from
occasional episodes of severe hepatitis and Stevens-Johnson
syndrome among patients taking medication for malaria pro-
phylaxis [16]. Cutaneous reactions, including toxic epidemic
necrolysis, have been observed among patients infected with
HIV [17–22]. All of these observations contrast with the ex-
perience recently summarized by Jurado et al. [14]. In that
study, 73 HIV-infected patients with <200 CD4 cells/mm³,
who had received a minimum of a 3-month course of prophy-
axis with weekly pyrimethamine/sulfadoxine (25 mg/500 mg),
were studied. No patients in the primary prophylaxis group (56
patients) developed PCP. Of the 17 patients who had previ-
ously experienced PCP, only 2 patients relapsed. The treatment
was well tolerated, and hepatitis, severe skin reactions, or
leukopenia was not observed.

On the basis of the previous experience, we decided to compare
weekly pyrimethamine/sulfadoxine with our reference standard
(daily low-dose trimethoprim-sulfamethoxazole). Our results in-
dicate that weekly pyrimethamine/sulfadoxine is safe and effec-
tive in preventing PCP in liver transplant recipients. None of the
patients treated with weekly pyrimethamine/sulfadoxine de-
veloped pneumocystosis. The efficacy of trimethoprim-
sulfamethoxazole prophylaxis was also high, because the drug had
been discontinued weeks earlier for the two patients with PCP.
These two cases indicate that an alternative regimen is immedi-
ately needed when any prophylactic regimen is stopped. Inhaled
or iv pentamidine could be the alternative regimen.

The efficacy of a prophylactic drug can be limited by the side
effects. The data from our study do not suggest any difference
in tolerance between the regimens. The observed side effects
were similar in both groups: leukopenia, digestive intolerance,
and increases in liver function test indicators. The potential
hepatotoxicity of a drug always causes concern when it is used

Table 3. Incidence of intolerance and side effects among liver transplant recipients in a study of prophylaxis for *Pneumocystis carinii* pneumonia.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Trimethoprim-sulfamethoxazole</th>
<th>Sulfadoxine/pyrimethamine Mean ± SD or no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Side effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>3 (5)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3 (5)</td>
<td>—</td>
</tr>
<tr>
<td>Digestive intolerance</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>3 (5)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Total with side effects</td>
<td>11 (18)</td>
<td>10 (17)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%). No differences were statistically significant (*P* > .05). Definitions: leukopenia, <3 × 10⁹ leukocytes/L; thrombocytopenia, <100 × 10⁹ platelets/L; hepatitis, evidence of mononuclear cell infiltration of the parenchyma and portal tracts in a liver biopsy sample with or without variable degrees of other changes. All thrombocytopenic patients were leukopenic as well.
to treat a liver transplant patient, in particular when severe episodes of hepatitis have been described with the same drug but in another indication. The incidence of hepatotoxicity was similar in both groups. Although the prophylactic treatment could be the cause of the abnormalities observed in liver function tests, the patients were treated with other potential hepatotoxic drugs, such as fluconazole, at the same time. It is difficult to know the contribution of each drug to liver toxicity.

There was no difference in the incidence of leukopenia. The benefits of the prophylactic treatment were not limited by leukopenia. Mild digestive intolerance was observed for two patients of each group, but they responded to symptomatic medication. Nevertheless, vomiting can limit the absorption of the drug. It can be of particular importance for patients treated with weekly regimens, among whom PCP can develop when blood levels decrease under the therapeutic range.

In conclusion, weekly sulfadoxine/pyrimethamine was effective and well tolerated in preventing PCP among liver transplant recipients. From the data derived from the trimethoprim-sulfamethoxazole group, it can be inferred that the risk of PCP after the prophylactic drug is stopped is very high. In this case, a second-line agent should be introduced.

References


