Comparative, Double-Blind, Prospective, Multicenter Trial of Temafloxacin versus Trimethoprim-Sulfamethoxazole in Uncomplicated Urinary Tract Infections in Women

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In a double-blind, randomized, multicenter study, 400 women with symptoms of acute urinary tract infections were treated with either a 7-day course of temafloxacin hydrochloride (400 mg once a day; n = 204) or a 10-day course of trimethoprim (160 mg) and sulfamethoxazole (800 mg) (TMP-SMZ) twice daily (n = 196). The bacteriologic cure rates at 5 to 9 days posttherapy were 100% in the temafloxacin group and 97% in the TMP-SMZ group (P = 0.035). The clinical cure rates were 93% in the temafloxacin group and 95% in the TMP-SMZ group (P > 0.1). Adverse events, including nausea, vomiting, rash, headache, and dizziness, were experienced by 19.6% of the temafloxacin group and 23.5% of the TMP-SMZ group. Transient leukopenia occurred in 0.5 and 4.1% of the temafloxacin and TMP-SMZ groups, respectively. Temafloxacin, 400 mg once a day for 7 days, appears to be as safe and effective as a 10-day course of TMP-SMZ in the management of acute urinary tract infection in women.

Temafloxacin hydrochloride is a new fluoroquinolone with a broad spectrum of activity in vitro against both gram-negative and gram-positive uropathogens (12, 13, 24, 25). The in vitro activity of temafloxacin is comparable to those of ofloxacin and ciprofloxacin (13, 14). Pharmacokinetic studies indicate that temafloxacin has good gastrointestinal absorption, with complete dose linearity and a half-life in plasma of approximately 8 h (23). The volume of distribution of temafloxacin is high because of significant intracellular penetration and concentration. The major route of elimination is by urinary excretion, with approximately 60% of a dose being excreted in the urine in its active form (26). The high levels of drug in plasma, tissue, and urine are well above the MIC for most urinary pathogens (23, 26). Temafloxacin is well tolerated and is generally devoid of serious adverse effects (26-28). The favorable pharmacokinetic characteristics and antibacterial activity make temafloxacin a suitable antimicrobial agent for once-a-day use in the treatment of urinary tract infection (UTI).

In this double-blind, randomized, multicenter trial, the safety and efficacy of a 7-day course of temafloxacin (400 mg once daily) was compared with a 10-day course of trimethoprim-sulfamethoxazole (TMP-SMZ; 160/800 mg twice daily) in the treatment of UTI in women. TMP-SMZ was chosen as the control regimen because of its established safety and efficacy and its wide use in the treatment of UTI (1, 3-5, 8, 10, 14, 17).

MATERIALS AND METHODS

Patient selection. Four hundred women from 28 study sites nationwide (see Table 1) were enrolled in the study. All patients were age 18 or older and had symptoms of acute UTI. The criteria for inclusion were as follows: (i) symptoms of UTI, e.g., dysuria, frequency, and urgency; (ii) pyuria (>5 leukocytes per high-power field); and (iii) bacteriuria, with at least 10^5 CFU (per ml) of one or two pathogens not resistant to the study agents found on microscopic examination of urine sediment within 48 h prior to treatment. Patients had to meet all three criteria in order to be included in the efficacy analyses of the study. Pregnant or lactating women; patients who had more than one UTI within the previous year or other signs of a complicated UTI; and those with impaired renal or liver function, a history of folate deficiency, or a known hypersensitivity to quinolones, trimethoprim, or sulfonamides were excluded. Patients who had received antimicrobial therapy within the preceding week and those who were expected to consume antacids during the study period were also excluded.

Study sites. This multicenter trial was conducted by the following principal investigators: Kenny Anders (private practice, Monroe, La.), Gloria Bacon (private practice, Chicago, Ill.), Jacques Caldwell (private practice, Daytona Beach, Fla.), Richard Carson (Rehabilitation Clinic, Littleton, Colo.), John Carter (private practice, Tucson, Ariz.), Frank Cescio (University of Kentucky, Lexington, Ky.), David Florence (Family Clinic, Manchester, Tenn.), Randy Goodwin (H & M Medical Clinic, Concord, N.C.), Stephen Gregg (Solo Internal Medicine, Albuquerque, N.M.), Richard Griffin (Simon-Williamson Clinic, Birmingham, Ala.), Andrew Grubbs (Future Healthcare, Cincinnati, Ohio), Robert Guthrie (Ohio State University, Columbus, Ohio), Margaret Hessen (Medical College of Pennsylvania, Philadelphia, Pa.), Bruce Hetland (Mid Dakota Clinic, Bismarck, N.D.), Abdollah Iravani (University of Florida, Gainesville, Fla.), William Kerns (Front Royal Family Practice, Front Royal, Va.), Raza Khan (Urology, Waukegan, Ill.), Michael Kuglitsch (Madison Urologists, Madison, Wis.), Mark Kunkel (Danbury Hospital, Danbury, Conn.), Sivaprasad Madduri (Kneibert Clinic, Poplar Bluff, Mo.), Gholam Malek (Jackson Clinic, Madison, Wis.), Charles Maletz (Cassidy Medical Clinic, Vista, Calif.), James McCarty (Valley Medical Center, Fresno, Calif.), Herzl Melmed (Colorado Medical Research, Englewood, Colo.), Peter Misurec (private practice, Berwyn, Ill.), Michael Moore (private practice, Bensalem, Ala.), Thomas Nolen (private practice, Columbus, Ala.), C. Fredric Reid (private practice, Winston-Salem, N.C.), Howard Smith (Family Practice, Hous-
ton, Tex.), Norman Stevens III (Family Medical Center, Jackson, Ala.), William M. Stevens (private practice, Wichita, Kans.), Barrett Sugarman (Michigan State University, East Lansing, Mich.), Neil Tarzy (private practice, Escondido, Calif.), Jerome Weinbaum (Chico Medical Group, Chico, Calif.), Jeff Whitfield (private practice, Salt Lake City, Utah).

Study design. All patients enrolled in the study were assigned by 1:1 computer-generated randomization to receive either temafloxacin hydrochloride (400 mg; Abbott Laboratories, Abbott Park, Ill.) once a day for 7 days or a combination of TMP (160 mg) and SMZ (800 mg) (Becton Dickinson Microbiology Systems, Cockeysville, Md.) every 12 h for 10 days. To maintain the double blind, patients who received temafloxacin took a daily dose of two 200-mg capsules, followed 12 h later by two placebo capsules. This regimen continued for 7 days, and then the temafloxacin dose was replaced by two placebo capsules daily for the final 3 days of the study. Patients who received TMP-SMZ were given two capsules twice daily for 10 days.

Within 48 h before the start of treatment, each patient underwent a general physical examination. At least one clean-catch midstream urine specimen, in a few centers, a straight catheter urine specimen was obtained from each patient at this time, and a blood sample was obtained for hematologic and chemical analyses. Clinical evaluation and urine cultures were repeated 3 to 5 days and 8 to 10 days after the start of therapy and 5 to 9 days after the end of therapy; blood tests were repeated at the 8- to 10-day visit. All blood and urine samples were collected and handled in accordance with accepted laboratory procedures.

Bacteriologic techniques. Urine was cultured by standard laboratory practices (9, 30). If the culture could not be performed immediately after collection, the urine could be safely stored in a refrigerator for up to 4 h. The microscopic examination of urine was performed on a Gram-stained, centrifuged specimen.

Colonies counts and susceptibilities to temafloxacin and TMP-SMZ were determined for each pathogen isolated, using either the disk diffusion or the MIC method. The count had to be ≥10^8 CFU of a bacterium per ml of urine specimen for the patient to be eligible for inclusion in the efficacy analyses. Antibiotic susceptibility was tested by the disk diffusion method with 10-μg temafloxacin and 23.75/1.25-μg TMP-SMZ disks (2). Pathogens were considered resistant to temafloxacin and TMP-SMZ if they had zone diameters of ≤12 and ≤10 mm, respectively. Organisms for which the MIC was ≥8 mg/liter were considered to be resistant to both temafloxacin and TMP-SMZ. Patients whose urinary pathogens were resistant to either study drug were not included in the efficacy assessments.

Efficacy assessments. The complete disappearance of symptoms at 5 to 9 days after the end of treatment was considered a clinical cure, while persistence of symptoms was considered a clinical failure. If symptoms improved but did not completely resolve by days 5 to 9 posttreatment, the patient was considered clinically improved.

Bacteriologic eradication was defined as the absence of the original pathogen or a colony count of <10^4 CFU/ml by days 3 to 5 of treatment and up to 5 to 9 days after treatment. Persistence of the original pathogen at days 3 to 5 of treatment or at 5 to 9 days after treatment indicated bacteriologic eradication failure. The bacteriologic eradication cure rate was defined as the percentage of patients whose pretreatment pathogens were all eradicated.

Safety assessment. Adverse events were monitored and recorded. Changes in blood chemistry and complete blood cell counts were determined.

Consent. This clinical trial was approved by the institutional review boards of the participating institutions. A signed written consent form was obtained from each patient before she entered the study.

Statistical analyses. The sample size was preplanned to provide 80% power to detect at least a 15% difference between the treatment groups. All statistical tests were two tailed, and a P value of <0.05 was considered statistically significant. All analyses were performed by the SAS procedures (29).

The comparative susceptibilities of the urinary pathogens to the study drugs was analyzed by the McNemar test (11). To assess the comparability of treatment groups, quantitative variables such as age and weight were analyzed by a two-way analysis of variance. Categorical variables such as race were analyzed by the Mantel-Haenszel test (11). The investigator was the blocking or poststratification factor in these analyses.

All efficacy variables were analyzed by a Fisher exact test or chi-square test for the comparison between treatment groups (6). To assess the differences between treatment groups with respect to vital signs and laboratory data, a one-way analysis of variance on the change from the baseline to each evaluation time point was performed. Within each treatment group, shifts of laboratory values with respect to normal ranges were assessed by the Stuart-Maxwell or McNemar test (11).

RESULTS

Study population. Of the 400 patients enrolled in the study, 204 received temafloxacin hydrochloride and 196 received TMP-SMZ. The mean ages of the patients were 36 ± 19 years in the temafloxacin group and 38 ± 21 years in the TMP-SMZ group. Demographic characteristics and pretherapy clinical findings are given in Table 1. Each patient presented with various combinations of dysuria, frequency, and urgency. Some also showed upper UTI signs, such as costovertebral angle pain or tenderness. For 70% of the patients, this was the first UTI in at least 12 months. The history of two or three UTIs in the past year in six patients was not considered clinically significant, because all of them had simple cystitis. In the temafloxacin group, 60 and 6 patients had costovertebral angle tenderness and a fever of >38°C, respectively, whereas in the TMP-SMZ group, the corresponding clinical findings were found in 53 and 11 patients, respectively. These clinical findings are suggestive of upper urinary tract involvement in these patients.

The most common pathogens isolated in pretreatment urine specimens were Escherichia coli (76% of all bacterial isolates), Proteus mirabilis (6%), and Klebsiella pneumoniae (4%). There were a total of 168 pretherapy bacterial isolates in 151 patients in the temafloxacin group; 17 patients each had two bacterial isolates. The other 53 patients who received temafloxacin subsequently were found to have negative pretherapy urine cultures. There were 158 pretherapy bacterial isolates in 146 patients in the TMP-SMZ group; 12 patients each had two pathogens, and 50 had negative pretherapy urine cultures. All pathogens were susceptible to temafloxacin, but 16 were resistant to TMP-SMZ. Nine of the patients with resistant pathogens were assigned to the temafloxacin group, and the other seven patients were randomly allocated to receive a treatment to which the
TABLE 1. Patient demographics and pretherapy clinical findings

<table>
<thead>
<tr>
<th>Drug (no. of patients)</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Race (no.)</th>
<th>No. with:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>White 81  Black 20  Other 8</td>
<td>No UTI in past 12 mo 40  Fever &gt; 38°C 11  CVAT&lt;sup&gt;b&lt;/sup&gt; 11  Hematuria&lt;sup&gt;c&lt;/sup&gt; 3</td>
</tr>
<tr>
<td>Temafloxacin (204)</td>
<td>36 ± 19</td>
<td>140 ± 37</td>
<td>176 20 8</td>
<td>142 6 60 53 84</td>
</tr>
<tr>
<td>TMP-SMZ (196)</td>
<td>38 ± 21</td>
<td>148 ± 37</td>
<td>170 23 3</td>
<td>136 11 53 89</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are means ± standard deviations.
<sup>b</sup> CVAT, costovertebral angle tenderness.
<sup>c</sup> Hematuria was classified as >5 erythrocytes per high-power field.

pathogens showed resistance, that is, TMP-SMZ. The difference in the susceptibility of *E. coli* (n = 239) to temafloxacin (100%) and TMP-SMZ (90.4%) was statistically significant (*P = 0.002*).

**Clinical and bacteriologic efficacy.** Although all patients were included in the analysis of safety, 75 patients in the temafloxacin group were excluded from the bacteriologic efficacy analysis, and all but 3 of them were also excluded from the clinical efficacy analysis; 78 patients in the TMP-SMZ group were excluded from both the clinical and bacteriologic efficacy analyses. Thus, 132 patients in the temafloxacin group and 118 patients in the TMP-SMZ group were clinically evaluable, and all of them except 3 patients in the temafloxacin group were bacteriologically evaluable.

The main reason for exclusion was failure to isolate a pathogen in the pretreatment urine sample, which, as stated above, occurred in 53 patients in the temafloxacin group and 50 patients in the TMP-SMZ group. Missing examinations or cultures caused exclusion of 6 patients from the analysis of temafloxacin’s bacteriologic efficacy, 9 patients from the analysis of temafloxacin’s clinical efficacy, and 12 patients from both efficacy analyses in the TMP-SMZ group. Resistance to either study drug eliminated eight more patients assigned to the temafloxacin group and six patients assigned to the TMP-SMZ group. For five patients in each group, susceptibility tests were missing or inconclusive. Three patients in the temafloxacin group and five patients in the TMP-SMZ group were excluded from the efficacy analyses because of noncompliance or insufficient treatment duration.

The clinical and bacteriologic responses of evaluable patients on days 5 to 9 after treatment are summarized in Table 2. In the temafloxacin group, 123 patients (93%) achieved a clinical cure, and 7 (5%) were improved 5 to 9 days after therapy. The two clinical failures were in women over age 70 years. A clinical cure was achieved by 112 patients (95%) in the TMP-SMZ group, and the other 6 patients (5%) improved clinically. There were no clinical failures in the TMP-SMZ group.

**All 129 evaluable patients (100%) in the temafloxacin group and 114 patients (97%) in the TMP-SMZ group achieved a bacteriologic cure 5 to 9 days after therapy. The four patients in the TMP-SMZ group who were bacteriologic failures all had *E. coli* infections; three of the four were younger than age 40 years. The difference in bacteriologic response between the two treatment groups was statistically significant (*P = 0.035*).**

**Side effects.** A total of 40 of the 204 patients (19.6%) who received temafloxacin and 46 of the 196 patients (23.5%) who received TMP-SMZ experienced adverse events. Table 3 lists those adverse events that occurred in at least 1% of either treatment group. Therapy was discontinued because of adverse events in three patients in the temafloxacin group and eight patients in the TMP-SMZ group. The most common adverse events were nausea and vomiting, vaginitis, rash, and headache; all occurred more frequently in patients receiving TMP-SMZ. Whereas 65% of all adverse events in the temafloxacin group were reported during the first 48 h, the corresponding value for TMP-SMZ was 38%.

TABLE 2. Therapeutic responses at 5 to 9 days posttherapy

<table>
<thead>
<tr>
<th>Response</th>
<th>Temafloxacin</th>
<th>TMP-SMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically evaluable</td>
<td>132</td>
<td>118</td>
</tr>
<tr>
<td>Cure</td>
<td>123 (93)</td>
<td>112 (95)</td>
</tr>
<tr>
<td>Improvement</td>
<td>7 (5)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Failure</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Bacteriologically evaluable</td>
<td>129</td>
<td>118</td>
</tr>
<tr>
<td>Cure</td>
<td>129 (100)</td>
<td>114 (97)</td>
</tr>
<tr>
<td>Failure</td>
<td>0</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

<sup>a</sup> *P = 0.035.*

TABLE 3. Adverse events and laboratory abnormalities occurring in >1% of either treatment group

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Temafloxacin</th>
<th>TMP-SMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who experienced any adverse event</td>
<td>40 (19.6)</td>
<td>46 (23.5)</td>
</tr>
<tr>
<td>Patients who discontinued treatment because of adverse event</td>
<td>3 (1.5)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>Temafloxacin</td>
<td>TMP-SMZ</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>9 (4.4)</td>
<td>16 (8.2)</td>
</tr>
<tr>
<td><em>Candida</em> vaginitis</td>
<td>7 (3.4)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (1)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (2.5)</td>
<td>8 (4.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (2.5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Nervousness or depression</td>
<td>2 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (1.5)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3 (1.5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (1)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1 (0.5)</td>
<td>3 (1.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory abnormality</th>
<th>Temafloxacin</th>
<th>TMP-SMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>1 (0.5)</td>
<td>8 (4.1)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>4 (2)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Elevated lactose dehydrogenase</td>
<td>4 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Elevated SGPT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (1)</td>
<td>3 (1.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> SGPT, serum glutamic pyruvic transaminase.
Blood chemistry and hemograms. A total of 14 patients (6.9%) in the temafloxacin group and 15 patients (7.7%) in the TMP-SMZ group developed abnormal laboratory tests. No clinically significant trends were observed. Total bilirubin levels increased in two patients, and lactose dehydrogenase levels increased in four patients in the temafloxacin group. γ-Glutamyltranspeptidase levels increased in two patients in each group. Serum glutamic pyruvic transaminase levels rose in one patient in the temafloxacin group and in two patients in the TMP-SMZ group, whereas serum glutamic pyruvic transaminase levels were elevated in two patients who took temafloxacin and in three patients who took TMP-SMZ. All other blood chemistry values remained normal during therapy.

One patient in the temafloxacin group and eight patients in the TMP-SMZ group developed transient leukopenia. Eosinophilia occurred in four patients in the temafloxacin group and in three patients in the TMP-SMZ group (Table 3).

DISCUSSION

TMP-SMZ is used widely in the treatment of UTI in adults and children (1, 3, 4, 10, 17, 32). The results of the present study support its efficacy in the treatment of these infections. Our results are comparable to those achieved with other antimicrobial agents, including the new quinolones, in the treatment of UTI in women (1, 3, 7, 14, 16, 18–22, 31, 33). The favorable therapeutic results produced by temafloxacin (400 mg once daily) are consistent with the pharmacologic characteristics and broad-spectrum antimicrobial activity of this new quinolone (12, 13, 23–25).

The urinary pathogens in this study consisted of species of the family Enterobacteriaceae and gram-positive cocci, most of which were susceptible to both temafloxacin and TMP-SMZ. However, the difference between the in vitro activity against 239 isolates of E. coli—100% for temafloxacin and 90.4% for TMP-SMZ—was statistically significant (P = 0.002). These results are in agreement with previous reports of the in vitro activities of temafloxacin and TMP-SMZ against common uropathogens (4, 8, 12, 13, 24, 25, 34).

At 5 to 9 days following the completion of therapy, clinical success (cure or improvement) was achieved in 98% of patients in the temafloxacin group and 100% of patients in the TMP-SMZ group. The bacteriologic eradication rate was 100% in the temafloxacin group and 97% in the TMP-SMZ group. Bacteriologic eradication was achieved in the two clinical failures in the temafloxacin group, both of whom were elderly women. Patients with symptoms and signs of upper UTI were evenly distributed between the two treatment groups. Both drug regimens were similarly effective in those patients with a successful response.

Temafloxacin and TMP-SMZ were well tolerated by 80.4 and 76.5% of the patients, respectively. The adverse events were generally mild to moderate in severity and resolved without any specific treatment after the drug was discontinued. However, adverse events were severe enough to require discontinuation of therapy in three (1.5%) patients in the temafloxacin group and eight patients in the TMP-SMZ group.

In the treatment of over 4,000 patients, Hsu et al. (15) found that the incidence of discontinuation because of adverse events was comparable for temafloxacin, other quinolones, and nonquinolone reference drugs. According to Pernet et al. (28), the incidence of central nervous system-related adverse events with temafloxacin was comparable to the incidence with nonquinolone reference drugs, and gastrointestinal symptoms were less common with temafloxacin than they were with other quinolones. Parrish (27) reported that the incidence of adverse events (nausea, diarrhea, dizziness) was similar for temafloxacin and ciprofloxacin (27). In the study of Morrison et al. (26), the overall incidence of adverse drug events, as evaluated by subjects’ diaries and investigators’ global assessments, was significantly higher with placebo (75%) than it was with temafloxacin (44%) (26).

In the present study, the incidence of Candida vaginitis with temafloxacin (3.4%) and TMP-SMZ (5%) was lower than that in previous reports in comparable patient populations (16, 18, 19). Laboratory tests such as transaminase enzymes and complete cell counts remained normal in 93% of the temafloxacin group and 92% of the TMP-SMZ group. The laboratory abnormalities, including leukopenia and eosinophilia, were mild to moderate in severity and transient in both treatment groups.

In summary, a 7-day course of temafloxacin (400 mg once daily) was as well tolerated and as efficacious as a 10-day course of TMP-SMZ (160/800 mg twice daily) in the treatment of UTI in women.

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REFERENCES


