Randomized Trial of Clarithromycin for Mediterranean Spotted Fever

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The classic antibiotic treatment for Mediterranean spotted fever (MSF) is based on tetracyclines or chloramphenicol, but chloramphenicol’s bone marrow toxicity makes tetracyclines the treatment of choice. However, it is convenient to have alternatives available for patients who are allergic to tetracyclines, pregnant women, and children <8 years old. We conducted a randomized clinical trial to compare clarithromycin with doxycycline or josamycin in the treatment of MSF. Forty patients were evaluated (23 male; mean age, 39.87 years); 13 patients were aged <14 years. Seventeen patients received clarithromycin, and 23 received doxycycline or josamycin. The interval between the onset of symptoms and the start of treatment was 4.04 ± 1.70 days in the clarithromycin group versus 4.11 ± 1.60 days in the doxycycline/josamycin group (P = not significant [NS]). Time to the disappearance of fever after treatment was 2.67 ± 1.55 days in the clarithromycin group versus 2.22 ± 1.35 days in the doxycycline/josamycin (P = NS). The symptoms had disappeared at 4.70 ± 2.25 days in the clarithromycin group versus at 4.75 ± 3.08 days in the doxycycline/josamycin (P = NS). There were no adverse reactions to treatment or relapses in either group. In conclusion, clarithromycin is a good alternative to doxycycline or josamycin in the treatment of MSF.

Mediterranean spotted fever (MSF) is a spotted fever group rickettsiosis. Caused by Rickettsia conorii, MSF is endemic in the Mediterranean area. Clinically, MSF is characterized by fever, exanthema, and the inoculation eschar known as tache noire. MSF affects people of both sexes and all ages (1–3).

Antibiotic therapy helps prevent progression to severe disease and the associated mortality (4). Classic antibiotic therapy consists of tetracyclines or chloramphenicol, although the use of chloramphenicol in developed countries is limited by its bone marrow toxicity (5).

Both in vitro and in vivo studies have shown that doxycycline is highly efficacious in this group of rickettsiosis. Even short-course treatments with doxycycline are highly effective (6). Nevertheless, it would be useful to have alternative treatments for patients allergic to tetracyclines, pregnant women, and children <8 years old.

In vitro studies have shown that rifampin, the fluoroquinolones, and some macrolides have good activity against R. conorii (7, 8); however, of these, only josamycin has proven efficacy in vivo (9). Although josamycin has been commercially available for years in some countries (e.g., France, Switzerland, Austria, Italy, South Africa, and Spain), it is unavailable in many others. Thus, it would be useful to have another antibiotic that can be obtained in most countries to treat MSF.

Several studies showed that clarithromycin and its metabolite 14-hydroxyclarithromycin have excellent in vitro activity against R. conorii and Rickettsia rickettsii (10–12), and these results were confirmed in clinical studies, where clarithromycin was efficacious and safe in treating children with spotted fever group rickettsioses (13–15).

We conducted a randomized clinical trial to compare clarithromycin with doxycycline or josamycin in the treatment of MSF.

MATERIALS AND METHODS

Study design. We designed a randomized clinical equivalence trial to compare two treatment regimens in patients diagnosed with MSF. Patients were randomly assigned to receive one of the following treatment regimens: (i) for the clarithromycin regimen, in adults and children ≥14 years old, 500 mg/12 h PO for 5 days; in children <14 years old, 15 mg/kg/12 h PO for 5 days; (ii) for the doxycycline/josamycin regimen, in adults and children ≥14 years old, 200 mg doxycycline/12 h PO for 1 day, and in children <14 years old, 3 mg doxycycline/kg/12 h PO for 1 day or 50 mg josamycin/kg/12 h PO for 5 days (at the attending physician’s discretion).

The hospital’s ethics committee approved the study, and all patients or their legal representatives provided written informed consent.

Participants. We included all patients with clinical suspicion of MSF who were admitted to our center.

The clinical criteria for inclusion in the randomization were the presence of fever and exanthema. The diagnosis of MSF was confirmed by the presence of the tache noire and/or positive serum tests (4-fold increase in the initial titer or single significant titer ≥1/80 on indirect immunofluorescence). We excluded patients who did not fulfill the inclusion criteria; who were administered tetracyclines, quinolones, or macrolides since the onset of symptoms; in whom symptoms appeared ≥8 days before inclusion; and who had a known hypersensitivity to clarithromycin, doxycycline, or josamycin.

Procedure. After signing the informed consent form, patients received a consecutive study participation number and were randomly assigned to one of the two groups in equal proportions (1:1). The list of random numbers was generated by a computer program. Clinical observation consisted of an initial visit and a follow-up visit 4 weeks later. Both visits included (i) a complete physical examination, (ii) a laboratory workup (complete blood count, urea, creatinine, serum electrolytes, transaminases, gamma-glutamyl transpeptidase [GGT], alkaline phosphatase, creatine phosphokinase [CPK], lactate dehydrogenase [LDH], aldolases,
TABLE 1 Clinical and laboratory characteristics of patients randomized to receive clarithromycin versus doxycycline or josamycin for Mediterranean spotted fever

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clarithromycin group</th>
<th>Doxycycline/josamycin group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>17</td>
<td>23 (17 doxycycline, 6 josamycin)</td>
<td>NS</td>
</tr>
<tr>
<td>Male (n)</td>
<td>9</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age (range) (yr)</td>
<td>41.29 (1–79)</td>
<td>38.82 (1–86)</td>
<td>NS</td>
</tr>
<tr>
<td>Children aged &lt;14 years (n)</td>
<td>17</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Fever and exanthema (n)</td>
<td>17</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Tache noire (n)</td>
<td>13</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum axillary temperature (mean ± SD) (°C)</td>
<td>38.97 ± 0.94</td>
<td>39.28 ± 0.70</td>
<td>NS</td>
</tr>
<tr>
<td>Comorbidities (n)</td>
<td>2</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Indirect immunofluorescence positive for R. conorii (n)</td>
<td>15</td>
<td>22</td>
<td>NS</td>
</tr>
</tbody>
</table>

Laboratory findings (n)

<table>
<thead>
<tr>
<th>Laboratory finding</th>
<th>Clarithromycin group</th>
<th>Doxycycline/josamycin group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt;150,000/mm³</td>
<td>0/17</td>
<td>5/23</td>
<td>NS</td>
</tr>
<tr>
<td>AST &gt;32 IU/L</td>
<td>13/17</td>
<td>16/23</td>
<td>NS</td>
</tr>
<tr>
<td>ALT &gt;31 IU/L</td>
<td>10/17</td>
<td>17/23</td>
<td>NS</td>
</tr>
<tr>
<td>CPK &gt;200 IU/L</td>
<td>7/17</td>
<td>1/17</td>
<td>0.01</td>
</tr>
<tr>
<td>LDH &gt;1100 IU/L</td>
<td>2/13</td>
<td>1/17</td>
<td>NS</td>
</tr>
<tr>
<td>Aldolases &gt;7.6 IU/L</td>
<td>5/11</td>
<td>5/14</td>
<td>NS</td>
</tr>
</tbody>
</table>

a Breast cancer, liver disease.
b Rectal cancer, chronic bronchitis, diabetes mellitus (n = 2).
c AST, aspartate transaminase; ALT, alanine transaminase.

doxy^cyc^line and josamycin between the onset of symptoms and study inclusion (n = 17); and onset of symptoms ≥8 days before entering the study (n = 2).

Thus, 40 patients were evaluated (23 male; mean age, 39.87 years; age range, 1 to 86 years); 13 patients were <14 years old. All patients had a fever and exanthema. A tache noire was observed in 33 patients, and serum tests were positive for R. conorii in 37 patients.

A total of 17 patients (13 aged ≥14 years and 4 aged <14 years) received clarithromycin, and 23 patients (14 aged ≥14 years and 9 aged <14 years) received doxycycline or josamycin. Table 1 reports the clinical and laboratory characteristics of patients in each treatment group.

Table 2 shows the clinical responses to antibiotic treatment.

No relapse or significant adverse reactions to antibiotic treatment were seen in any patient.

DISCUSSION

To our knowledge, this is the first randomized clinical trial to compare clarithromycin with doxycycline and josamycin in patients with MSF. Moreover, 27 of the 40 patients in our study were adults, whereas previous studies focused exclusively on children. The clinical characteristics of the patients in our study did not differ between treatment groups and were similar to those in other series (16–22); all had fever and exanthema. None developed severe disease, and all had favorable outcomes.

We found no significant differences in the clinical response to

TABLE 2 Clinical response to antibiotic treatment for Mediterranean spotted fever

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>Clarithromycin group</th>
<th>Doxycycline/josamycin group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval between onset of symptoms and start of treatment (mean ± SD) (days)</td>
<td>4.04 ± 1.78</td>
<td>4.11 ± 1.64</td>
</tr>
<tr>
<td>Disappearance of fever after start of treatment (mean ± SD) (days)</td>
<td>2.67 ± 1.55</td>
<td>2.22 ± 1.35</td>
</tr>
<tr>
<td>Disappearance of symptoms after start of treatment (mean ± SD) (days)</td>
<td>4.70 ± 2.25</td>
<td>4.75 ± 3.08</td>
</tr>
</tbody>
</table>

a P = NS for all responses.
b Headache, arthromyalgia.
the two treatment regimens measured by the time to disappearance of fever and other symptoms of MSF. The time to defervescence and remission of other symptoms was short and similar to that reported in other studies (6, 9, 13, 14).

Doxycycline is the gold standard treatment for MSF, and it is the most commonly used treatment for this disease. Clinical studies have demonstrated that doxycycline shortens the course of MSF and induces a rapid remission of symptoms (4, 5). However, doxycycline is a tetracycline, and tetracyclines can have adverse effects, such as bone marrow toxicity and permanent staining of teeth, especially in children (23). Permanent discoloration of teeth has been reported after repeated treatment with tetracyclines in children <8 years old, so long treatment regimens with this class of antibiotics are not recommended for this age group (24). Permanent discoloration of teeth and other teratogenic effects can also occur in children exposed to these drugs during fetal development, so the tetracyclines are not recommended for pregnant women (23). However, in an earlier study comparing 1 day of treatment with doxycycline (200 mg/12 h) with 10 days of treatment with tetracyclines (6), our group showed that short treatment regimens are efficacious, well tolerated, and apparently safe even in children. Similarly, Cascio et al. (25) found no discoloration of teeth in children <8 years old treated with minocycline for 3 weeks.

Chloramphenicol was considered an alternative to the tetracyclines, but its bone marrow toxicity has limited its use (26, 27). Rifampin, the fluoroquinolones, and some macrolides have good in vitro activity against R. conorii (6, 7); however, the results in clinical studies are not so promising. One study found that rifampin was much less effective than doxycycline (28). Another study found that the fluoroquinolones were efficacious but not superior to doxycycline (29). A more recent retrospective study found that treatment with fluoroquinolones increased the severity of disease and was associated with longer hospital stays (30). Furthermore, the quinolones are not indicated for children or pregnant women.

Thus, it might be more logical to seek an alternative to doxycycline among the macrolides. Erythromycin is not active against R. conorii in vitro or in vivo (31). Roxithromycin is active in vitro and has pharmacokinetic advantages but failed in a clinical study (32). Josamycin is effective in vitro and in vivo. One study demonstrated the efficacy of josamycin to be similar to that of doxycycline (7), and clinical experience has confirmed its usefulness in children (2, 3). Azithromycin has also proved to be a good alternative in children (16–18).

However, clarithromycin has better in vitro activity than other macrolides against R. conorii (10, 12). Moreover, clarithromycin’s metabolite 14-hydroxyclarithromycin might lower MICs, resulting in greater in vivo postantibiotic effects than would be expected by in vitro studies measuring the effects of clarithromycin alone (11). Clinical studies have shown that clarithromycin is efficacious and well tolerated in the treatment of MSF in children. In the first clinical trial, clarithromycin (15 mg/kg daily in 2 divided doses for 7 days) resulted in faster defervescence than chloramphenicol (50 mg/kg daily in 4 divided doses for 7 days) (13). Another clinical trial compared clarithromycin (15 mg/kg daily in 2 divided doses for 7 days) versus azithromycin (10 mg/kg daily in a single dose for 3 days) and found similar results for the two antibiotics (14).

The most important limitation of the study was the number of patients in the cohort and the exclusion of all patients with clinical suspicion of MSF but an unconfirmed diagnosis.

In conclusion, a 5-day treatment with clarithromycin is a good alternative to treatment with doxycycline or josamycin for MSF. It is efficacious and well tolerated, even in children.

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REFERENCES


