CLARITHROMYCIN FOR MEDITERRANEAN SPOTTED FEVER: A RANDOMIZED TRIAL

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Running head: Clarithromycin in Mediterranean Spotted Fever

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ABSTRACT

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 other alternatives available for patients who are allergic to tetracyclines, pregnant women, and children under 8 years old. We conducted a randomized clinical trial to compare clarithromycin with doxycycline or josamycin in the treatment of MSF.

40 patients were evaluated (23 male; mean age, 39.87 years). 13 patients were aged <14 years. 17 patients received clarithromycin and 23 doxycycline or josamycin. The interval between the onset of the symptoms and the start of treatment was 4.04 ±1.7 days in the clarithromycin group vs. 4.11 ±1.6 days in the doxycycline/josamycin group (p=NS). The time to the disappearance of fever after treatment was 2.67 ± 1.55 days in the clarithromycin group vs. 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 vs. 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.

Introduction.

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 persons of both sexes and all ages (1-3).

Antibiotic therapy helps prevent progression to severe disease and associated mortality (4). Classical antibiotic therapy consists of tetracyclines or chloramphenicol, although in developed countries the use of chloramphenicol 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 rickettsioses. 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 less than 8 years old.

In vitro studies have shown that rifampicin, 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 have shown that clarithromycin and its metabolite 14-hydroxylclarithromycin have excellent in vitro activity against R. conorii and R. rickettsii (10-12), and these results have been 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:

- Clarithromycin: in adults and children ≥ 14 years old, 500 mg/12h PO for 5 days; in children < 14 years old, 15 mg/kg/12h PO for 5 days.
Doxycycline/Josamycin: in adults and children ≥ 14 years old, 200 mg doxycycline/12h PO for one day; in children < 14 years old, 5mg doxycycline/kg/12h PO for 1 day or 50 mg josamycin/kg/12h 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 (fourfold increase in the initial titer or single significant titer >1/80 on indirect immunofluorescence). We excluded patients who did not fulfill the inclusion criteria, those administered tetracyclines, quinolones, or macrolides since the onset of symptoms, those in whom symptoms appeared ≥ 8 days before inclusion, and those with 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 a) a complete physical examination, b) laboratory workup (complete blood count, urea, creatinine, serum electrolytes, transaminases, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), aldolases, prothrombin time, and shell-vial cell cultures and indirect immunofluorescence against *R. conorii*), and in some cases at the discretion of the attending physician c) a chest X-ray.

Outcome measures

The clinical efficacy of the treatment regimens was measured by the duration of fever and the other symptoms (headache, arthromyalgia) from the start of antibiotic treatment. The absence of fever was defined as an axillary body temperature < 37°C. Patients provided information about the time of disappearance of fever and other symptoms on a questionnaire.
Statistical analysis

To calculate the necessary sample size, we assumed a one-sided alpha error of 0.025 and a beta error of 0.10 for a statistical power of 1-\(\beta\)=90%. We assumed that the common standard deviation would be 0.93 and that none of the patients included would be lost to follow-up. Thus, we sought a sample of 38 patients.

To determine equivalence between groups we used chi-square tests or Fisher’s exact test for categorical variables and Student’s t-test or the Mann-Whitney U for quantitative variables, as appropriate. Statistical significance was set at p<0.05. We used SPSS for all analyses.

Results.

In the 9-year study period, a total of 59 patients with clinical suspicion of MSF were randomized to one of the treatment groups; 19 of these were excluded, 12 (6 children < 14 years old) from the clarithromycin group and 7 (5 children < 14 years old) from the doxycycline/josamycin group. The reasons for exclusion were: failure to fulfill the diagnostic criteria for MSF (n=15: absence of exanthema (n=5) or fever and exanthema without confirmation by tache noire or positive serum test (n=10)), receiving tetracyclines, quinolones, or macrolides between
the onset of symptoms and study inclusion (n=2), 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, 1-86); 13 patients were aged <14 years.

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.

A total of 17 patients (13 aged ≥14 years and 4 aged <14 years) received clarithromycin and 23 (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 response 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 the two treatment regimens measured by the time to the 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 the MSF and induces rapid remission of symptoms (4,5). However, doxycycline is a tetracycline, and tetracyclines can have adverse effects, especially in children, such as bone marrow toxicity and permanent staining of teeth (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 in this age group (24). Permanent discoloration of teeth and other teratogenic effects can also occur in children exposed during fetal development, so the tetracyclines are also not recommended in pregnant women (23). However, in an earlier study comparing one-day treatment with doxycycline (200 mg/12h) with 10-day treatment with tetracyclines (6), our group showed that even 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 have limited its use (26,27). Rifampicin, 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 rifampicin was much less effective than doxycycline (28). Another 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 in 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* either *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 both *in vitro* and *in vivo*. One study demonstrated efficacy similar to doxycycline (7), and clinical experience has confirmed its usefulness in children (2,3). Azithromycin has also proven a good alternative in children (16-18).

However, clarithromycin has better *in vitro* activity against *R. conorii* than other macrolides (10,12). Moreover, clarithromycin’s metabolite 14-hydroxyclarithromycin might lower minimum inhibitory concentrations, resulting in greater *in vivo* post-antibiotic 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/day in 2 divided doses for 7 days) resulted in faster defervescence than chloramphenicol (50 mg/kg/day in 4 divided doses for 7 days (13). Another clinical trial compared clarithromycin (15 mg/kg/day in 2 divided doses for 7 days) versus azithromycin (10 mg/kg/day in a single dose for 3 days) and found similar results for the two antibiotics (14).
The most important limitation of the study is the number of patients in the cohort and the exclusion of all patients with clinical suspicion of Mediterranean spotted fever but the diagnosis of them was not confirmed.

In conclusion, 5-day treatment with clarithromycin is a good alternative to doxycycline or josamycin in the treatment of MSF: it is efficacious and well tolerated, even in children.
References


Table 1: Clinical and laboratory characteristics of patients randomized to receive clarithromycin vs. doxycycline or josamycin for Mediterranean spotted fever

<table>
<thead>
<tr>
<th></th>
<th>Clarithromycin</th>
<th>Doxycycline or josamycin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>17</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mean age (range)</strong></td>
<td>41.29 years (1-79)</td>
<td>38.82 years (1-86)</td>
<td>NS</td>
</tr>
<tr>
<td>Children &lt;14 years</td>
<td>4</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Fever + Exanthema</td>
<td>17</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Tache noire</td>
<td>13</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Maximum axillary temperature (mean ± SD)</td>
<td>38.97±0.94</td>
<td>39.28±0.70</td>
<td>NS</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>2*</td>
<td>4#</td>
<td>NS</td>
</tr>
<tr>
<td>Indirect immunofluorescence</td>
<td>15</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Laboratory findings:</td>
<td></td>
<td></td>
<td></td>
</tr>
<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 UI/L</td>
<td>13/17</td>
<td>16/23</td>
<td>NS</td>
</tr>
<tr>
<td>ALT &gt; 31 UI/L</td>
<td>10/17</td>
<td>17/23</td>
<td>NS</td>
</tr>
<tr>
<td>CPK &gt; 200 UI/L</td>
<td>7/17</td>
<td>1/17</td>
<td>0.01</td>
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<td>LDH &gt;1100 UI/L</td>
<td>2/13</td>
<td>1/17</td>
<td>NS</td>
</tr>
<tr>
<td>Aldolases &gt;7.6 UI/L</td>
<td>5/11</td>
<td>5/14</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Breast cancer, liver disease

#Rectal cancer, chronic bronchitis, diabetes mellitus (n=2).
AST, aspartate transaminase; ALT, alanine transaminase
Table 2: Clinical response to antibiotic treatment for Mediterranean spotted fever

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

\# P=NS

* headache, arthromyalgia