MAJOR ARTICLE

Clarithromycin Versus Azithromycin in the Treatment of Mediterranean Spotted Fever in Children: A Randomized Controlled Trial

Antonio Cascio,[1,a] Claudia Colomba,[1] Spinello Antinori,[1] David L. Paterson,[2] and Lucina Titone[1]

[1]Istituto di Patologia Infettiva e Virologia, Ospedale "G. Di Cristina," Università di Palermo, and [2]Infectious Diseases Section, University of Pittsburgh Medical Center Overseas, Palermo, Italy

We conducted an open-label randomized controlled trial to compare the efficacy and safety of clarithromycin (15/mg/kg/day in 2 divided doses for 7 days) with those of azithromycin (10 mg/kg/day in 1 dose for 3 days) in the treatment of children with Mediterranean spotted fever. Until now, there has not been a gold-standard therapy for this rickettsial disease in children. Eighty-seven children were randomized to receive 1 of the 2 drugs. The mean time to defervescence (± standard deviation) was 46.2 ± 36.4 h in the clarithromycin group and 39.3 ± 31.3 h in the azithromycin group. These differences were not statistically significant and both drugs were equally well-tolerated. Clarithromycin and azithromycin could be acceptable therapeutic alternatives to chloramphenicol and tetracyclines for children aged ≤8 years with Mediterranean spotted fever. Azithromycin, because it has a long half-life, offers the advantages of administration in a single daily dose and a shorter duration of therapy, which could increase compliance in children.

Mediterranean spotted fever (MSF) is caused by *Rickettsia conorii,* which is transmitted by the dog tick *Rhipicephalus sanguineus.* It is an acute infectious disease typically characterized by fever, skin rash, and a black eschar (tache noire) at the site of tick bite . Every year, 300 cases are notified (mainly from June through September) on the Italian island of Sicily [1–3]. Interestingly, the number of cases in Italy and elsewhere appears to have increased during the past 20 years [4–7]. Sporadic cases have been diagnosed in travelers in other countries as well, and, in North America, MSF is the most frequently imported type of rickettsiosis [8–10].

In the Western Hemisphere, Rocky Mountain spotted fever (RMSF), which is caused by *Rickettsia rickettsii,* can be a severe disease, but MSF is generally milder [11]. Historical studies have shown that MSF can lead to 10-14 days of fever if not treated, but it is rarely fatal in children [11]. Tetracyclines or chloramphenicol is considered standard treatment for MSF [12]. However, both these drugs can cause significant adverse effects, especially in children. Tetracyclines can cause staining of the teeth and bone toxicity [13]. Nevertheless, doxycycline is the treatment of choice for children aged ≤8 years who have RMSF [14].

Chloramphenicol can have severe adverse effects, such as gray syndrome ("gray-baby syndrome"), aplastic anemia, and acute hemolytic anemia, in patients with the Mediterranean form of glucose-6-phosphate

Received 16 May 2001; revised 15 August 2001; electronically published 4 December 2001.

Presented in part: 11th European Congress of Clinical Microbiology and Infectious Diseases, Istanbul, Turkey, 1–4 April 2001 (abstract P962).

[a] Current affiliation: Istituto di Malattie Infettive, Università di Messina, Messina, Italy.

Reprints or correspondence: Dr. Antonio Cascio, Istituto di Malattie Infettive, Università di Messina, Via Consolare Valeria, 98125 Messina, Italy (acascio @unime.it) or Dr. Claudia Colomba, Istituto di Patologia Infettiva e Virologia, Ospedale "G. Di Cristina," Università di Palermo, Piazza Montalto n. 8, 90134 Palermo, Italy (claudia.colomba@libero.it).

Clinical Infectious Diseases 2002; 34:154–8

1058-4838/2002/3402-0003$03.00

dehydrogenase (G6PD) deficiency [15–17].

The macrolides—clarithromycin, azithromycin, roxithromycin, and josamycin—do not have such adverse effects and seem to be effective in vitro; for this reason, they have emerged as a potential alternative therapy [18–25]. Members of the genus *Rickettsia* are obligate intracellular bacteria, and the main feature of MSF is generalized vasculitis and localization of *R. conorii* in endothelial cells [3]. Effective intracellular concentrations of antimicrobials are therefore considered the sine qua non for a successful treatment for this disease.

The aim of this study was to compare the efficacy and safety of azithromycin with those of clarithromycin for the treatment of children with MSF. Azithromycin achieves higher intracellular concentrations than do the other macrolides (including clarithromycin), and this ability may contribute to its efficacy in the treatment of infections caused by intracellular organisms, such as rickettsial infections. Furthermore, the long half-life of azithromycin offers the advantage that the drug can be administered in a single daily dose, which could increase compliance in children.

PATIENTS AND METHODS

All patients who were admitted to the "G. Di Cristina" children's hospital in Palermo, Italy, from June 1999 through September 2000, and had clinically suspected MSF (i.e., findings of fever, nonconfluent maculopapular rash, and tache noire that occurred during June–September) were evaluated for possible inclusion in the study. At admission, a complete physical examination was performed, the typical signs of MSF were sought, and a peripheral venous blood sample was obtained for performance of a complete blood cell count and determination of the erythrocyte sedimentation rate, C-reactive protein level, and liver function. An indirect immunofluorescence assay for *R. conorii* was performed with use of a commercial kit (*Rickettsia conorii*-Spot; bioMérieux). Informed consent to participate in the study was sought from parents of the patients.

Exclusion criteria were as follows: age >14 years; lack of parental informed consent; a history of allergy to the drugs being studied; presence of severe disease, defined by neurological signs (stiff neck or seizures), hemorrhagic manifestations, or sepsis (any combination of hypotension, tachycardia, and tachypnea with values greater than or less than the mean ± 2 standard deviations for the age]); alanine aminotransferase concentration >250 U/L; creatinine concentration >1.5 mg/dL; and a history of treatment with antibiotics potentially active against *Rickettsia* species (e.g., macrolides, tetracyclines, chloramphenicol, or quinolones) in the 7 days before hospitalization.

After informed consent was obtained, children with clinically suspected MSF and without exclusion criteria were randomly assigned to receive either clarithromycin (15/mg/kg/day in 2 divided doses for 7 days) or azithromycin (10 mg/kg once daily for 3 days). Simple randomization was performed according to a list of computer-generated random numbers with use of Epi-Info software (Centers for Diseases Control and Prevention [CDC]). Odd numbers indicated one treatment, even numbers the other. The randomization list was covered with opaque adhesive paper. The final study population was the group of enrolled children who had a confirmed diagnosis of MSF. Confirmation was defined as an MFS diagnostic score of >25, according to the scoring system described in Raoult et al. [26] (table 1).

Clinical response to antibiotic treatment was evaluated on the basis of the pattern of body temperature data and the improvement in the clinical signs and symptoms of the disease. The time to defervescence was defined as the time from the beginning of antibiotic therapy to the first achievement of persistent defervescence (i.e., an axillary body temperature of ≤37°C for at least 3 consecutive days) [27]. Body temperature was measured every 6 h by nursing personnel who were not involved in the study. Nurses were instructed to administer acetaminophen (10 mg/kg) every time a patient's temperature was >38.5°C, although not for >4 times per day.

Table 1. Diagnostic scoring system for Mediterranean spotted fever, as described in Raoult et al. [26].

Diagnostic criteria	Points
Epidemiologic	
Residence or recent travel in area of endemicity	2
Onset during May–September	2
Contact with dog ticks	2
Clinical	
Temperature >39°C	5
Tache noire	5
Maculopapular or purpuric eruption	5
2 of 3 criteria	3
All 3 criteria	5
Nonspecific biological	
Platelet count of $<150 \times 10^9$ cells/L	1
Liver enzyme level (AST or ALT) of >50 IU/L	1
Bacteriological	
Detection of *Rickettsia conorii* in skin biopsy specimen by use of IFA	25
Isolation of *R. conorii* from blood	25
Serological (determined by use of IFA)	
1 Sample with total Ig ≥1:128	5
1 Sample with IgG ≥1:128 and IgM ≥1:64	10
2 Samples with 4-fold titer elevation within 2 weeks	20

NOTE. A total of >25 points is consistent with a presumptive diagnosis of Mediterranean spotted fever. ALT, alanine transaminase; AST, aspartate transaminase; IFA, immunofluorescence assay; tache noire, black eschar that appears at the site of a tick bite.

Treatment safety and tolerability were judged on the basis of the incidence and severity of the drug-related adverse effects observed in the 2 groups. Immediately after therapy ended (after 3 or 7 days), liver function tests were performed and complete blood cell count and erythrocyte sedimentation rate were determined; serological testing was done after 30 ± 3 days. Clinical examination was performed again after 15 ± 2 days and 30 ± 3 days, in order to exclude relapses.

The analysis of the data was done with Statistica (StatSoft) and Epi-Info (CDC) software. Contingency data were analyzed by use of the 2-tailed χ^2 test or Fisher's exact test, continuous data were analyzed by use of the Student's *t* test, and non-normally distributed data were analyzed by use of the Mann-Whitney U test. The Pearson correlation coefficient was computed to verify the existence of correlations between variables. A P value <.05 in a 2-sided test was considered significant for all analyses. The clinical protocol was approved by the ethical committee and review board of the G. Di Cristina hospital, and the guidelines of the G. Di Cristina hospital were followed in the conduct of the clinical research.

RESULTS

A total of 105 patients with suspected MSF were admitted to hospital during the study period. Eight patients who had received drugs potentially active against *Rickettsia* species in the 7 days before hospitalization were excluded from randomization. Ninety-seven patients were randomized to receive the study drugs. Eighty-seven of these 97 patients had a diagnostic score of >25 and were considered the final study population; 45 were assigned to the clarithromycin group and 42 to the azithromycin group. The baseline characteristics of these patients are summarized in table 2; the 2 treatment groups were similar with respect to major demographic variables and characteristics of MSF at the time of study enrollment. There were no statistically significant differences between the 2 groups with respect to hematological, chemical, and inflammatory parameters (table 2).

In all patients, fever disappeared in ⩽7 days after the start of therapy. In the clarithromycin group, defervescence was achieved after a mean (±SD) of 46.2 ± 36.4 h (median, 32 h; range, 6–168 h); in the azithromycin group, defervescence was achieved after a mean (±SD) of 39.3 ± 31.3 h (median, 28 h; range, 6–144 h). These differences were not statistically significant ($P = .34$). Fever that persisted for >5 days was observed in 2 patients (1 in each treatment arm); chloramphenicol (12.5 mg/kg q6h) was administered to these 2 patients, who became afebrile 48 h later. The patient in the azithromycin group had undergone splenectomy 2 years previously because of β-thalassemia major (Cooley's anemia). There were no significant differences between the 2 groups with respect to the use of acetaminophen (which all patients received).

Table 2. Baseline characteristics of 87 patients with confirmed Mediterranean spotted fever.

Characteristic	Treatment group: Azithromycin (n = 42)	Treatment group: Clarithromycin (n = 45)	P
Male sex, *n*/*N* (%)	28/42 (66.6)	26/45 (57.7%)	NS
Age, years	5 (1–14)	6 (0.5–13)	NS
Fever, *n*/*N* (%)	42/42 (100)	45/45 (100)	NS
Duration of fever before treatment, days	3 (0–8)	3 (0–8)	NS
Duration of exanthema before treatment, days	1 (0–7)	1 (0–6)	NS
Exanthema, *n*/*N* (%)	42/42 (100)	45/45 (100)	NS
Tache noire, *n*/*N* (%)	37/42 (88)	33/45 (73.3)	.08
Arthralgia, *n*/*N* (%)	15/42 (35.7)	18/45 (40)	NS
Erythrocyte sedimentation rate, mm/h	26 (12–57)	26 (9–101)	.17
AST level, IU/L	38.5 (20–137)	38 (20–98)	.19
ALT level, IU/L	28.5 (7–212)	24 (11–46)	.19
Platelet count, × 10^3 cells/μL	199 (68–387)	207.5 (84–353)	NS
WBC count, × 10^3 cells/μL	6.3 (2.4–35)	6.5 (2.7–22.8)	NS
CRP level, mg/dL	2.3 (0.4–18)	2.7 (0.4–6)	NS

NOTE. Data are median value (range) unless indicated otherwise. ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; NS, not significant. There were no significant differences between the 2 groups in presenting characteristics (as determined by Student's *t* test or Mann-Whitney U test and χ^2 test).

The median duration of exanthema after the beginning of therapy was 3 days (range, 1–5 days) in both groups. At admission, leukopenia (<5000 cells/μL) and thrombocytopenia (<100,000 cells/μL) were observed in 14 and 2 patients in the clarithromycin group, respectively, and in 8 and 3 patients in the azithromycin group, respectively. Both leukopenia and thrombocytopenia normalized (to >5000/μL and >100,000/μL, respectively) in the 2 groups after a mean (±SD) of 6 ± 1 days. No relapses were observed during follow-up. For all the patients, a 4-fold increase of antibody titer to *R. conorii* was observed at 30 ± 3 days after hospitalization.

Clarithromycin and azithromycin were equally well-tolerated, and no major side effects were observed. Two patients treated with clarithromycin developed vomiting, 1 developed diarrhea, and 1 developed abdominal pain; only 1 patient treated with azithromycin complained of abdominal pain. None of these minor side effects required discontinuation of the drug treatment. All analyses were also performed for the 10 patients that did not have a diagnostic score of >25. No statistically significant differences were observed (data not shown).

Table 3. Summary of the findings of 5 randomized clinical trials of macrolide treatment for Mediterranean spotted fever in children.

Reference	Drugs and regimens studied	No. of patients	Findings
[27]	Clarithromycin, 7 days (7.5 mg/kg b.i.d.) vs. chloramphenicol, 7 days (12.5 mg/kg q.i.d.)	46	More-rapid disappearance of fever in the group treated with clarithromycin
[29]	Erythromycin stearate, 10 days (12.5 mg/kg q.i.d) vs. tetracycline hydrochloride, 10 days (10 mg/kg q.i.d.)	81	More-rapid disappearance of fever and symptoms in the group treated with tetracycline
[30]	Azithromycin, 3 days (10 mg/kg once a day) vs. doxycycline, 5 days (5 mg/kg once a day)	30	No statistically significant differences in time to defervescence
[31]	Doxycycline, 1 day (2.5 mg/kg b.i.d.) vs. josamycin, 5 days (25 mg/kg b.i.d.)	32	No statistically significant differences in time to defervescence
Present report	Azithromycin, 3 days (10 mg/kg once a day) vs. clarithromycin, 7 days (7.5 mg/kg b.i.d.)	87	No statistically significant differences in time to defervescence

DISCUSSION

Mediterranean spotted fever is an acute tickborne disease that is caused by *R. conorii* and usually has a benign course in children. Nevertheless, clinical manifestations are typically severe; they include abrupt onset of high fever, intense headache and malaise, myalgia, and maculopapular skin rash. If left untreated, MSF has a duration of 10–15 days [11].

Because *R. conorii* causes an intracytoplasmic infection, it is necessary that the antibiotics administered achieve good membrane penetration and concentrate within the cytoplasm. These criteria are met by tetracyclines and chloramphenicol, but neither drug should be routinely used in children, and less-toxic alternatives are needed. In contrast, the macrolides achieve high intracellular concentrations. Intracellular half-life varies considerably from one macrolide to another, but it is particularly long for azithromycin. This property, together with the ability of azithromycin to achieve high intracellular concentrations, suggests that it may be possible to reduce doses, to prolong the interval between administration of doses, and to shorten the duration of administration, relative to other drug treatments. Therefore, it may be an ideal drug for the treatment of MSF in children [28].

We previously conducted a randomized trial in which we found that clarithromycin was significantly more effective than chloramphenicol in the treatment of MSF in children [27]. In the present study, we conducted a prospective open-label comparative randomized trial to compare the safety and efficacy of clarithromycin versus those of azithromycin in the treatment of MSF in children. We were not able to demonstrate significant differences between the 2 treatment groups with respect to the time to defervescence and to disappearance of other symptoms.

What are the weaknesses of our study? The study was not double blinded, so we could not ensure that no bias occurred in the observation of fever by nurses who knew which drug the patient had received. However, the nurses who recorded the body temperatures were not involved with the study in any way, and intentional misrepresentation of fever seems unlikely to have occurred. Although this was the largest randomized trial of therapy of MSF ever performed, the sample size may still have been insufficient to allow statistically significant differences to be observed. With respect to the patients who were not enrolled in the study because their clinical MSF diagnostic score was $\leqslant 25$, we could not exclude the possibility that they actually had MSF. In fact, milder forms of MSF have been described, especially in children [1]. In addition, the results of serological testing are often negative at the beginning of the disease, and, in our laboratory, we were not able to perform isolation of *R. conorii* from blood samples or detection of the organism in skin biopsy specimens. However, when we analyzed the data for both our study groups and included the data for the 10 patients who did not have a diagnostic score of >25, our findings were not altered.

Four randomized clinical trials have been performed to compare macrolides in the treatment of MSF in children [27, 29–31] (table 3), but none of the studies have compared new macrolides. In all these studies, the drugs were administered orally, and the clinical response to the different antibiotic treatments was evaluated on the basis of the pattern of body temperature and the improvement of the clinical signs and symptoms of the disease. Only 1 study [27] that compared the efficacy of clarithromycin versus chloramphenicol obtained better (statistically significant) results for the clarithromycin group. On the other hand, only 1 of the other studies [29] showed that tetracycline hydrochloride is superior to erythromycin stearate. However, erythromycin demonstrates in vitro activity against *R. conorii* that is not as potent as that of newer macrolides, such as clarithromycin [18–25].

Clarithromycin and azithromycin could be acceptable ther-

apeutic alternatives to chloramphenicol and to tetracyclines for children aged ≤8 years with MSF. Azithromycin, because it has a long half-life, offers the advantages of administration in a single daily dose and a shorter duration of therapy, which could increase compliance in children. Further evaluation of macrolides in patients with severe symptoms or serious illness should be undertaken. Because these drugs have not been tested as treatment for RMSF or other rickettsioses, their use for these diseases is not recommended.

References

1. Cascio A, Dones P, Romano A, Titone L. Clinical and laboratory findings of boutonneuse fever in Sicilian children. Eur J Pediatr **1998**; 157: 482–6.
2. Gilot B, Laforge ML, Pichot J, Raoult D. Relationships between the *Rhipicephalus sanguineus* complex ecology and Mediterranean spotted fever epidemiology in France. Eur J Epidemiol **1990**; 6:357–62.
3. Raoult D, Roux V. Rickettsioses as paradigms of new emerging infectious diseases. Clin Microbiol Rev **1997**; 10:694–719.
4. Gross Ellis M, Yagupsky P, Toroh V, et al. Resurgence of Mediterranean spotted fever. Lancet **1982**; 2:1107.
5. Mansueto S, Tringali G, Walker DH. Widespread simultaneous increase in the incidence of spotted fever group rickettsioses. J Infect Dis **1986**; 154:539–40.
6. Espejo Arenas E, Font Creus B, Bella Cueto F, Segura Porta F. Climatic factors in resurgence of Mediterranean spotted fever. Lancet **1986**; 1: 1333.
7. Walker DH, Fishbein DB. Epidemiology of rickettsial diseases. Eur J Epidemiol **1991**; 7:237–45.
8. Harris RL, Kaplan SL, Bradshaw W, et al. Boutonneuse fever in American travellers. J Infect Dis **1986**; 153:126–8.
9. McDonald JC, MacLean JD, McDade JE. Imported rickettsial disease: clinical and epidemiological features. Am J Med **1988**; 85:799–805.
10. Schlaeffer F, Lederer K, Mates SM. Mediterranean spotted fever in an American woman. Arch Intern Med **1985**; 145:1733–4.
11. Cascio G, Titone L. Rickettsiosi. In: Introzzi P, ed. Enciclopedia medica italiana. Florence: Utet Edizioni Scientifiche. **1987**:1364–90.
12. Feigin RD, Snider RL, Edwards MS. Rickettsioses. In: Feigin RD, Cherry JD, eds. Textbook of pediatric infectious diseases. 3d ed. Philadelphia: Saunders, **1992**:1853–5.
13. American Academy of Pediatrics Committee on Drugs. Requiem for tetracycline. Pediatrics **1975**; 55:142–3.
14. Walker DH, Raoult D. *Rickettsia rickettsii* and other spotted fever group rickettsiae (Rocky Mountain spotted fever and other spotted fevers). In: Mandell GL, Bennett JE, Dolin R, eds. Principles and practice of infectious diseases. 5th ed. Philadelphia: Churchill Livingston, **2000**: 2035–42.
15. Luzzatto L. G6PD deficiency and haemolytic anemia. In: Nathan G, Oski FA, eds. Hematology of infancy and childhood. 4th ed. Philadelphia: Saunders, **1993**:674–731.
16. Craft AW, Brocklebank JT, Hey EN, et al. The "gray toddler": chloramphenicol toxicity. Arch Dis Child **1974**; 49:235–7.
17. Wallerstein RO, Condit PK, Kasper CK, et al. Statewide study of chloramphenicol therapy and fatal aplastic anemia. JAMA **1969**; 208: 2045–50.
18. Ives TJ, Marston EL, Regnery RL, Butts JD, Majerus TC. In vitro susceptibilities of *Rickettsia* and *Bartonella* spp. to 14-hydroxy-clarithromycin as determined by immunofluorescent antibody analysis of infected Vero cell monolayers. J Antimicrob Chemother **2000**; 45: 305–10.
19. Ives TJ, Manzewitsch P, Regnery RL, Butts JD, Kebede M. In vitro susceptibilities of *Bartonella henselae, B. quintana, B. elizabethae, Rickettsia rickettsii, R. conorii, R. akari,* and *R. prowazekii* to macrolide antibiotics as determined by immunofluorescent-antibody analysis of infected Vero cell monolayers. Antimicrob Agents Chemother **1997**; 41:578–82.
20. Maurin M, Raoult D. In vitro susceptibilities of spotted fever group *Rickettsiae* and *Coxiella burnetii* to clarithromycin. Antimicrob Agents Chemother **1993**; 37:2633–7.
21. Drancourt M, Raoult D. In vitro susceptibilities of *Rickettsia rickettsii* and *Rickettsia conorii* to roxithromycin and pristinamycin. Antimicrob Agents Chemother **1989**; 33:2146–8.
22. Raoult D, Rousselier P, Tamalet J. In vitro evaluation of josamycin, spiramycin, and erythromycin against *Rickettsia rickettsi* and *R. conorii.* Antimicrob Agents Chemother **1988**; 32:255–6.
23. Keysary A, Itzhaki A, Rubinstein E, Orou C, Keren G. The invitro antirickettsial activity of macrolides. J Antimicrob Chemother **1996**; 38: 727–31.
24. Rolain JM, Maurin M, Vestris G, Raoult D. In vitro susceptibilities of 27 *Rickettsiae* to 13 antimicrobials. Antimicrob Agents Chemother **1998**; 42:1537–41.
25. Raoult D, Roussellier P, Vestris G, Tamalet J. In vitro antibiotic susceptibility of *Rickettsia rickettsii* and *Rickettsia conorii:* plaque assay and microplaque colorimetric assay. J Infect Dis **1987**; 155:1059–62.
26. Raoult D, Tissot-Dupont H, Caraco P, Brouqui P, Drancourt M, Charrel C. Mediterranean spotted fever in Marseille: descriptive epidemiology and the influence of climatic factors. Eur J Epidemiol **1992**; 8:192–7.
27. Cascio A, Colomba C, Di Rosa D, Salsa L, di Martino L, Titone L. Efficacy and safety of clarithromycin in the treatment of Mediterranean spotted fever in children: a randomized controlled trial. Clin Infect Dis **2001**; 33:409–11.
28. Wildfeur A, Laufen H, Zimmermann T. Uptake of azithromycin by various cells and its intracellular activity under in vivo conditions. Antimicrob Agents Chemother **1996**; 40:75–9.
29. Munoz-Espin T, Lopez-Pares P, Espejo-Arenas E, et al. Erythromycin versus tetracycline for treatment of Mediterranean spotted fever. Arch Dis Child **1986**; 61:1027–9.
30. Meloni G, Meloni T. Azithromycin vs doxycycline for Mediterranean spotted fever. Pediatr Infect Dis J **1996**; 15:1042–4.
31. Bella F, Font B, Uriz S, et al. Randomized trial of doxycycline versus josamycin for Mediterranean spotted fever. Antimicrob Agents Chemother **1990**; 34:937–8.