Prospective Cohort Study of Single-Day Doxycycline Therapy for Mediterranean Spotted Fever

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ABSTRACT The objective of this study is to evaluate the results of single-day doxycycline therapy for Mediterranean spotted fever (MSF). This is a prospective cohort study of cases with confirmed MSF treated with the single-day doxycycline regimen in a teaching hospital from 1990 to 2015. Patients received two oral doses of 200 mg of doxycycline for 1 day. The outcomes evaluated were the time interval between the start of treatment and apyrexia, the time interval between the start of treatment and disappearance of other symptoms, and the adverse reactions to treatment and death. The study included 158 subjects, 18 of whom (11.4%) had a severe form of MSF and 31 (19.6%) were >65 years. The interval between onset of symptoms and start of treatment was 4.31 ± 1.54 days. All patients recovered uneventfully. Fever disappeared 2.55 ± 1.14 days after the start of treatment. The remaining symptoms (headache, arthromyalgia) disappeared 3.63 ± 1.35 days after the start of treatment. Only one patient had a delay in reaching apyrexia (8 days). The fever disappeared somewhat later in severe cases (median, 3 days; interquartile range [IQR], 2 to 4 days) than in nonsevere cases (median, 2 days; IQR, 2 to 3 days). Likewise, the remaining symptoms disappeared later in severe cases (median, 5 days; IQR, 4 to 6 days) than in nonsevere cases (median, 3 days; IQR, 3 to 4 days). The outcome was similar in both elderly and nonelderly patients. Eight patients had mild adverse effects possibly related to treatment. The results of the study confirm that single-day doxycycline therapy is an effective and well-tolerated treatment for MSF, including elderly patients and severe cases.

KEYWORDS Mediterranean spotted fever, *Rickettsia conorii*, doxycycline, tick-borne diseases

Mediterranean spotted fever (MSF) is a tick-borne infection caused by *Rickettsia conorii* (1, 2). In Catalonia, as in other countries of the Mediterranean basin, the incidence of MSF increased in the 1970s and 1980s (3–5). In contrast, in the last 20 years, an important decrease in the incidence of the disease was observed in Catalonia, accompanied by a decrease in the seroprevalence in the human population (6). While in most cases the disease follows a benign course, some cases present with a severe form of MSF that can lead to death (7, 8).

Doxycycline is the preferred treatment for MSF (1, 9). Regarding the duration of treatment, several randomized clinical trials showed the efficacy of administering two single doses of doxycycline, with an interval of 12 h, both in adults and in children (10–12), and this short-course regimen has been included as a therapeutic option in various expert recommendations on the treatment of MSF (1, 9, 13). From 1990, single-day doxycycline therapy (two oral doses of 200 mg) is the treatment of choice at our institution for patients with MSF. However, no studies have been published that

Received 10 May 2018 **Returned for modification** 14 June 2018 **Accepted** 17 August 2018

Accepted manuscript posted online 27 August 2018

Citation Espejo E, Andrés M, Garcia M-C, Fajardo A, Pérez J, Bella F. 2018. Prospective cohort study of single-day doxycycline therapy for Mediterranean spotted fever. *Antimicrob Agents Chemother* 62:e00978-18. <https://doi.org/10.1128/AAC.00978-18>.

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TABLE 1 Main epidemiological and clinical characteristics of 158 patients with MSF

Characteristic	<i>n</i>	%
Men	97	61.4
Cases between June and September	145	91.8
Contact with dogs	144	91.1
Comorbidities ^a	65	41.1
Fever	158	100
<i>Tache noire</i>	124	78.5
Rash ^b	156	98.7
Headache	136	86.1
Myalgia	134	84.8
Arthralgia	121	76.6
Enlarged liver	49	31.0
Gastrointestinal symptoms ^c	45	28.5
Conjunctivitis	28	17.7
Cough	18	11.4
Systolic arterial hypotension	11	6.9
Impaired consciousness	10	6.3
Vertigo	9	5.7
Edema	7	4.4
Enlarged spleen	6	3.8
Hearing loss	4	2.5
Hypoxemia	3	1.9
Arthritis	2	1.3
Other ^d	6	3.8

^aChronic bronchitis (*n* = 20), hypertension (*n* = 12), alcoholism (*n* = 10), diabetes (*n* = 8), hepatic cirrhosis (*n* = 5), ischemic heart disease (*n* = 5), and other (*n* = 11).

^bMaculopapular (*n* = 136) or petechial (*n* = 20) exanthema.

^cNausea, vomiting, diarrhea, or abdominal discomfort.

^dHeart failure, myocarditis, pericarditis, lymphangitis, acute pancreatitis, or oculoglandular syndrome (one case of each).

analyze the effectiveness of this regimen in many patients. The objective of the present study is to evaluate the results of this therapeutic regimen in an extensive cohort of patients with MSF.

RESULTS

During the study period, 182 adult patients with MSF received single-day doxycycline therapy. Twenty-four patients were excluded. The reasons for exclusion were previous administration of antibiotics (*n* = 8) and onset of symptoms ≥ 8 days before the first dose of doxycycline (*n* = 16). Thus, 158 patients were finally included in the study. The mean age was 52.5 ± 16.3 years (range, 18 to 95 years). The epidemiological and clinical characteristics are summarized in Table 1. Eighteen patients (11.4%) presented with a severe form of MSF, and 8 cases (5.1%) fulfilled the definition of multiple organ dysfunction syndrome. The main laboratory alterations are shown in Table 2.

The median interval between onset of symptoms and the start of treatment was

TABLE 2 Main laboratory abnormalities in 158 patients with MSF

Laboratory finding	<i>n</i> ^a	%
Hemoglobin < 12 g/dl	14/158	8.9
Leukocyte count > 10,000/ μ l	20/158	12.7
Leukocyte count < 5,000/ μ l	35/158	22.2
Platelets < 150,000/ μ l	76/158	48.1
Aspartate transaminase > 40 IU/liter	112/158	70.9
Alanine transaminase > 40 IU/liter	93/153	60.8
Alkaline phosphatase > 130 IU/liter	48/150	32.0
Creatinine > 130 μ mol/liter	9/150	6.0
Lactate dehydrogenase > 480 IU/liter	38/133	28.6
Creatine phosphokinase > 200 IU/liter	24/142	16.9
Na < 130 mEq/liter	18/155	11.6
Albumin < 30 g/liter	14/145	9.7

^aThe denominator for each finding is variable since some data could be missing.

TABLE 3 Basal characteristics and outcome of severe and nonsevere cases of MSF treated with single-day doxycycline therapy

Characteristic	Severe (n = 18)	Nonsevere (n = 140)	P
Median age in yrs (IQR)	62 (47–75)	52 (43–62)	0.032
No. (%) male	11 (61.1)	86 (61.4)	0.979
No. (%) of cases with comorbidities	11 (61.1)	54 (38.6)	0.067
No. (%) of cases with chronic alcoholism	4 (22.2)	6 (4.3)	0.016
Median interval (days) between onset of symptoms and start of treatment (IQR)	4 (3–5)	4 (4–5)	0.515
Median time (days) to disappearance of fever after start of treatment (IQR)	3 (2–4)	2 (2–3)	0.161
Median time (days) to disappearance of symptoms ^a after start of treatment (IQR)	5 (4–6)	3 (3–4)	0.0025

^aHeadache, arthromyalgia.

4.31 ± 1.54 days. Two patients were treated with intravenous doxycycline because of the presence of vomiting that prevents oral treatment. All patients recovered uneventfully. There were no relapses. Fever disappeared 2.55 ± 1.14 days after the start of treatment. The remaining clinical manifestations (headache, arthromyalgia) disappeared 3.63 ± 1.35 days after the start of treatment.

Only one patient had a delay in reaching apyrexia. She was a 37-year-old woman, with no relevant medical history, who was admitted with a severe form of MSF, characterized by fever, headache, arthromyalgia, maculopapular rash, *tache noire*, hypotension, edema, a platelet count of 84,000/mm³, and hepatic involvement with serum aspartate transaminase at 165 IU/liter, alanine transaminase at 130 IU/liter, and alkaline phosphatase at 876 IU/liter. The treatment was administered on day 4 after the onset of symptoms. The headache and arthromyalgia disappeared on day 6, and the fever disappeared on the eighth day after the start of treatment. A transient positive titer (1:80) of anti-smooth muscle antibodies was observed. The patient recovered uneventfully.

Table 3 shows the basal characteristics and outcome of patients with severe and nonsevere forms of MSF. Figure 1 shows the time to the disappearance of fever and other symptoms (headache, arthromyalgia) after the onset of treatment in severe and nonsevere cases. Thirty-one patients (19.6%) were older than 65 years; eight of these subjects had a severe form of MSF. Table 4 compares the results obtained in patients >65 years old with those obtained in patients ≤65 years old. Eight patients (5.1%) had mild adverse effects possibly related to the treatment (nausea in two cases, vomiting in four cases, diarrhea in

FIG 1 Kaplan-Meier curves showing time to disappearance of fever (A) and the remaining symptoms (B) in severe and nonsevere cases of MSF treated with single-day doxycycline therapy.

TABLE 4 Clinical response in patients >65 years and ≤65 years with MSF treated with single-day doxycycline therapy

Clinical response	>65 yrs (n = 31)	≤65 yrs (n = 127)	P
No. (%) of subjects with severe MSF	8 (25.8)	10 (7.9)	0.0096
Median interval (days) between onset of symptoms and start of treatment (IQR)	4 (3–5)	4 (4–5)	0.193
Median time (days) to disappearance of fever after start of treatment (IQR)	2 (2–3)	2 (2–3)	0.764
Median time (days) to disappearance of symptoms ^a after start of treatment (IQR)	3 (3–4)	3 (3–5)	0.865

^aHeadache, arthromyalgia.

one case, and gastric discomfort in one case); however, it cannot be ruled out that these symptoms were due to MSF.

DISCUSSION

This is the largest study of patients with MSF treated with single-day doxycycline therapy, and it is the first study to evaluate the efficacy of this treatment in patients with severe MSF and in the elderly. All of the cases met the diagnostic criteria for MSF (14) and were confirmed serologically. The clinical and epidemiologic characteristics of the patients included in this study were similar to those in other studies (2, 15–17), and the rate of severe forms of MSF was within the previously reported range (16, 18, 19). The association of severe forms with advanced age and chronic alcoholism has also been previously described (1, 20).

Antibiotic therapy for MSF, administered in the first days of the disease, shortens the duration of symptoms and helps prevent progression to severe disease and the associated mortality (13). *In vitro* studies show that doxycycline is the most active antibiotic against *R. conorii* (21), and this antibiotic constitutes the gold-standard treatment for MSF (13). Although some macrolides, such as josamycin, and clarithromycin have been shown to be effective in treating MSF, none of these antibiotics provide superior results compared with doxycycline (11, 22). Rifampin and fluoroquinolones have good *in vitro* activity against *R. conorii* (21). However, randomized clinical trials have shown that both rifampin and ciprofloxacin provide inferior results compared with doxycycline (12, 23), which remains the treatment of choice. In addition, a retrospective study suggests that treatment with fluoroquinolones carries an increased risk of severe forms of MSF (16).

Regarding the duration of antibiotic treatment for MSF, the recommendations of the experts vary between 1 and 10 days of treatment (9, 13). As early as 1987, a randomized clinical trial showed that two doses of 200 mg of doxycycline during a single day were as effective as the 10-day treatment with tetracycline (10). This regimen allows blood levels of doxycycline greater than the MIC for *R. conorii* to be maintained for 48 h (24, 25), a period sufficient to eliminate the presence of rickettsiae in tissue specimens in experimental Rocky Mountain spotted fever (26). Treatment with doxycycline during a single day has been used as a comparator in several controlled clinical trials (11, 12, 22), and good results have been reported in descriptive studies (15, 17, 27), although only one of them describes separately the results obtained with the single-day doxycycline regimen (27). In that study the durations of fever (2.9 ± 1.1 days) and arthromyalgia (3.7 ± 1.4 days) were very similar to those observed in our study.

In the present study, the outcome was favorable in all patients, although in cases with severe forms, apyrexia and the disappearance of the remaining of symptoms were reached somewhat later than in nonsevere cases. It is noteworthy that the time to reach apyrexia and the disappearance of symptoms were similar in the elderly and in the younger patients, despite the fact that the percentage of severe forms was significantly higher in the elderly.

Only one patient had a delay in reaching apyrexia, remaining feverish until the eighth day after treatment. In this case, a transient positive titer of anti-smooth muscle

antibodies, coupled with a significant alteration of the liver biology, suggests a possible mechanism of autoimmunity triggered by MSF, similar to what has been described in some cases of Q fever (28).

Adverse effects possibly related to the treatment were infrequent, consisting of mild gastrointestinal alterations, and it cannot be ruled out that in some cases these symptoms were due to MSF, taking into account that gastrointestinal manifestations are relatively frequent in the natural course of the disease.

The main limitation of this study is that it has been carried out in a single center. Therefore, it has not been possible to evaluate possible geographical differences in the virulence of *R. conorii* that could condition different responses to treatment (1, 19). Another limitation of the study is that some factors that could influence the response to treatment, such as the comorbidity index of Charlson or the previous functional state, were not taken into account.

In conclusion, the results of the present study confirm that single-day doxycycline therapy is an effective treatment for MSF, including elderly patients and severe cases. This short-course regimen presents the advantages of being well tolerated and cost-effective. However, in patients with very serious forms of the disease who require admission to an intensive care unit, it may be advisable to continue the treatment with doxycycline until clinical improvement is achieved.

MATERIALS AND METHODS

This is a prospective observational study at a teaching hospital serving a population of about 200,000. All consecutive adult patients with MSF treated with 1-day doxycycline therapy from January 1990 to December 2015 were included in the study.

The diagnostic criteria for MSF were the presence of clinical manifestations compatible with MSF plus serological confirmation by means of indirect immunofluorescence assay for *R. conorii* (seroconversion from negative to a titer of $\geq 1/80$ or a 4-fold rise in titer between the acute and convalescent phases). All of the cases met the diagnostic criteria for MSF (score > 25) established by the ESCAR (ESCMID Study Group on *Coxiella*, *Anaplasma*, *Rickettsia*, and *Bartonella*) (14). Patients who were administered antimicrobial agents active against *R. conorii* (macrolides, fluoroquinolones, or tetracycline hydrochloride) since the onset of symptoms and patients who started the treatment > 7 days after the onset of symptoms were excluded.

All cases were directly evaluated by one of the authors. Axillary temperature was taken every 6 h, and symptoms were evaluated daily until they disappeared. Apyrexia was defined as a temperature of $< 37^{\circ}\text{C}$ taken in the armpit, according to the criterion used in other studies (10–12). Disease in all patients was controlled 30 days after the onset in order to repeat the serological tests and evaluate the final outcome. Information on baseline and epidemiologic characteristics, clinical features, laboratory values, side effects possibly related to antibiotic treatment and outcome were prospectively collected in an anonymized database.

A case was considered to be severe if it met any of the following criteria: admission to an intensive care unit, the presence of severe organ failure (heart, respiratory, central nervous system, renal or hepatic failure), or the combination of three or more of the following: purpuric rash, hypotension, lung infiltrate, serum creatinine level of $> 141 \mu\text{mol/liter}$, a platelet count of $< 100,000/\mu\text{l}$, rhabdomyolysis, a serum albumin level of $< 30 \text{ g/liter}$, serum sodium level of $< 130 \text{ mEq/liter}$ or proteinuria at $> 1 \text{ g/liter}$, as previously described (15). In addition, following Botelho-Nevers et al. (16), we identified cases that fulfilled multiple organ dysfunction syndrome criteria, defined as dysfunction of two or more organ systems, including dysfunction of the respiratory, renal, cardiovascular, neurological, hepatic or hematological systems, according to the ODIN model (29). In order to correlate age with the occurrence of severe MSF, patients were classified into two age categories: elderly (> 65 years) and nonelderly (≤ 65 years).

Patients received two oral doses of 200 mg of doxycycline for 1 day. Patients unable to take oral medication received intravenous doxycycline at the same doses and duration.

The outcomes evaluated were the time interval between the start of treatment and apyrexia, the time interval between the start of treatment and disappearance of other symptoms (headache, arthromyalgia), and adverse effects of treatment and death, measured from the start of treatment to 30 days after the start of treatment.

Descriptive statistical analysis was performed using counts and percentages for categorical variables, and means with standard deviations or medians with interquartile ranges (IQR) for continuous variables, depending on whether the data were skewed. Continuous variables were compared using the Mann-Whitney U test. Categorical and stratified continuous variables were compared using the chi-square test or Fisher exact test as appropriate. Kaplan-Meier curves were plotted to describe time to disappearance of fever and other symptoms in severe and nonsevere cases. The curves were compared using the log-rank test. All analyses were performed using the SPSS software package v.15 (SPSS, Inc., Chicago, IL).

The study was approved by the Institutional Review Board. Written informed consent was waived

because the patients included in the study received the standard therapeutic regimen at our institution, and no identifying patient information was included.

ACKNOWLEDGMENTS

We thank Enric Garcia Restoy (Consorti Sanitari de Terrassa) and Angeles Jaen (Fundació Docència i Recerca Mútua Terrassa) for their assistance in the statistical analysis.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

E.E. and F.B. were involved in the study design. E.E., M.A., M.-C.G., J.P., and A.F. were involved in data acquisition. E.E. and F.B. were involved in data analysis and interpretation. E.E. and F.B. drafted the manuscript. M.A., M.-C.G., J.P., and A.F. revised the manuscript critically. All authors approved the final version to be submitted.

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