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Randomized Trial of Doxycycline versus Josamycin for Mediterranean Spotted Fever

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We undertook a randomized clinical trial comparing therapeutic efficacy of the 1-day doxycycline regimen with the 5-day josamycin regimen for Mediterranean spotted fever. All 59 patients recovered uneventfully, and results did not significantly differ between the two schedules. One-day doxycycline therapy is an effective, easy, and inexpensive treatment. Josamycin is a useful therapeutic alternative that may be particularly convenient for pregnant women and patients with a history of allergy to tetracyclines.

Mediterranean spotted fever is a tick-borne rickettsiosis caused by *Rickettsia conorii* (2). Tetracyclines are presently the drugs of choice for treatment of the disease, and among them doxycycline has shown advantages because of its antirickettsial activity (8) and pharmacokinetics. In a previous study of adult patients with Mediterranean spotted fever, two single doses of doxycycline have proven to be as effective as the classic 10-day tetracycline hydrochloride regimen (1). However, tetracyclines may cause untoward effects, particularly in children under the age of 8, pregnant women, and patients allergic to tetracyclines. The activity of chloramphenicol is similar to those of tetracyclines, but occurrences of aplastic anemia have led to restriction of the use of this drug. The potential usefulness of the new quinolone compounds has been recently reported (4, 6), although quinolones should not be prescribed for pregnant women or for children. Erythromycin has poor in vitro antimicrobial activity against *R. conorii* (8) and has been shown to be less effective than tetracyclines for treating boutonneuse fever (5). In vitro evaluation of josamycin against *Rickettsia rickettsii* and *R. conorii* has shown that this macrolide antibiotic may be of clinical use in treating spotted fever rickettsiosis (7).

In order to evaluate the clinical usefulness of josamycin, we studied all patients diagnosed as having Mediterranean spotted fever who were admitted during the summer of 1988 to the Departments of Internal Medicine and Pediatrics of the Hospital de Terrassa, Terrassa, and the Hospital de Sabadell, Sabadell, Barcelona, Spain. The protocol was approved by the Institutional Ethical Committees of both centers, and patients gave informed consent. Patients who were pregnant, had received antibiotics in the week preceding the study, or had a history of allergy to tetracyclines or macrolide antibiotics were excluded from the study.

Sixty-five patients fulfilled the eligibility criteria. The diagnosis was serologically confirmed in 59 patients by means of indirect immunofluorescence assay for *R. conorii* (seroconversion from negative to a titer of $\geq$1:80 in 42 cases and a fourfold rise in titer between the acute- and convalescent-phase sera in 17 cases). Six patients were dropped from the study because results of the indirect immunofluorescence assay for *R. conorii* were not diagnostic.

The patients were randomized at admission into two groups based on a set of computer-generated aleatory numbers. Patients in group 1 were given two oral doses of 200 mg of doxycycline separated by a 12-h interval (5 mg/kg of body weight in children). Patients in group 2 received oral doses of 1 g of josamycin every 8 h for 5 days (50 mg/kg of body weight at 12-h intervals in children). Temperature was taken at least every 6 h by nursing personnel not related to the study, and symptoms were evaluated daily until they disappeared. Upon admission of the patient and at the end of 3 weeks, hematologic, biochemical, and serologic determinations were carried out. Apyrexia was defined as temperature (taken in the armpit) of less than 37°C. The Student *t* test and the chi-square test were used to determine statistical significance.

Of the 59 patients who were finally evaluated, 30 were included in group 1 (1-day doxycycline course) and 29 were included in group 2 (5-day josamycin regimen). The following parameters were similar in both groups: age, presence of underlying disease, interval between the onset of symptoms and beginning of therapy, maximal registered temperature, and clinicobiological manifestations of severity (Table 1). All patients recovered uneventfully. Fever disappeared after 2.2 $\pm$ 1.0 days of therapy in group 1 and after 2.5 $\pm$ 1.1 days in group 2. The remaining clinical manifestations (headache, arthromyalgia) disappeared after 2.9 $\pm$ 1.0 days of treatment in group 1 and after 3.1 $\pm$ 1.2 days in group 2. The total duration of the fever period was 6.2 $\pm$ 2.3 days in group 1 and 6.3 $\pm$ 1.9 days in group 2 (Table 2). Differences between the two groups were not statistically significant. One patient in each group had side effects (gastrointestinal symptoms), but in none of them was suspension of the trial necessary. When only the 32 children (ages, 2 to 13 years) included in the study were considered, no significant differences between the groups were found.

The present study confirmed the usefulness of the 1-day doxycycline course for treating Mediterranean spotted fever in children, as has been previously established for adults (1). To our knowledge, this therapeutic regimen has not been used previously for children; however, the results we obtained with these shorter regimens are at least as good as those reported previously with a 10-day regimen (5). A 1-day doxycycline course offers additional advantages, such as greater convenience from less-frequent administration, decreased cost from smaller doses, and minimal risk of tooth staining and bone toxicity (provided that these effects are related mainly to the total dose administered during early

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TABLE 1. Clinical data for 59 patients with Mediterranean spotted fever receiving doxycycline or josamycin[a]

Parameter	Group 1[b] (n = 30)	Group 2[c] (n = 29)
Age (yr)	24.6 ± 23.4	23.3 ± 22.8
No. of children (<14 yr old)	16	16
Interval between onset of fever and therapy (days)	4.0 ± 2.0	3.8 ± 1.7
No. of patients with underlying disease	7	5
Chronic obstructive pulmonary disease	4	0
Diabetes	0	2
Hypertension	1	2
Alcoholism	2	0
Ischemic cardiopathy	0	1
Maximal temp (°C)	39.2 ± 0.7	39.4 ± 0.6
No. of patients with:		
Hypotension	2	1
Purpuric cutaneous rash	4	1
Creatinine of >130 μmol/liter	1	3
Anemia (hemoglobin, <11 g/dl)	3	2
Thrombocytopenia (<150,000/mm^3)	8	8
Hypoalbuminemia (<30 g/liter)	1	1
Na (<130 meq/liter)	1	1

[a] Results are expressed as either mean ± standard deviation or number of patients. Differences between the two groups were not statistically significant.
[b] Group 1 received doxycycline.
[c] Group 2 received josamycin.

childhood [3]). So, we consider 1-day doxycyline to be the regimen of choice for children.

Raoult et al. (7) evaluated the activity of josamycin against *R. conorii* and *R. rickettsii* in two tests: a dye uptake assay and a plaque assay. Both assays determined a josamycin MIC of 1 μg/ml for both strains. Before the onset of this trial, seven children with Mediterranean spotted fever received josamycin at conventional doses (25 mg/kg of body weight at 12-h intervals), and fever disappeared after 3.7 ± 1.7 days of treatment. One adult patient was also given josamycin (1 g every 12 h for 5 days), and fever disappeared after 7 days of therapy; the total duration of the fever was 12 days. These observations prompted us to use higher doses of josamycin (3 g/day in adults and 100 mg/kg of body weight per day in children). From the good results obtained and the excellent tolerance to such doses that was observed in the present study, it may be inferred that josamycin is a useful therapeutic alternative in cases of Mediterranean spotted fever. It may also prove to be particularly convenient in treating pregnant women and patients with a history of allergy to tetracycline compounds.

TABLE 2. Results of therapy with 1-day doxycycline course and 5-day josamycin regimen in patients with Mediterranean spotted fever[a]

Group[b]	Onset of apyrexia (days)[c] in:		Disappearance of symptoms (days)[c]	Duration of fever (days) in:	
	Whole group	Children only[d]		Whole group	Children only
1 (n = 30)	2.2 ± 1.0	2.0 ± 0.6	2.9 ± 1.0	6.2 ± 2.3	5.2 ± 1.8
2 (n = 29)	2.5 ± 1.1	2.5 ± 1.2	3.1 ± 1.2	6.3 ± 1.9	5.5 ± 1.5

[a] Results expressed as mean ± standard deviation. There were no relapses but there were two cases of side effects, one in each group. Differences between the two groups were not statistically significant.
[b] Group 1 received doxycycline, and group 2 received josamycin.
[c] After start of therapy.
[d] There were 16 children (patients under 14 years old) in each group.

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