ORIGINAL ARTICLE

Fluoroquinolones versus doxycycline in the treatment of rickettsial infection: A Tunisian multicenter prospective study

Fluoroquinolones comparées à la doxycycline dans la prise en charge des rickettsioses: Une étude multicentrique prospective menée en Tunisie

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Abstract

Introduction: Doxycycline is considered as the standard treatment of rickettsiosis. Fluoroquinolones used as an alternative therapy, until recent studies have shown that Fluoroquinolones are associated with a deleterious outcome.
Objectives: To compare therapeutic efficacy and safety of fluoroquinolones and doxycycline in the treatment of Rickettsiosis
Methods: we conducted an open-label randomized controlled multicenter study. This study aim to compare the efficacy and safety of oral ciprofloxacin (1000 mg/day) or ofloxacin (400mp/day) in 2 doses with those of oral doxycycline (200mg/day) once daily for 3 to 10 days, according to the severity of illness, in the treatment of Rickettsioses, We included patients more than 15 year-old who presented the characteristic clinical triad (eschar + rash + fever) and/or microbiological confirmation (positive serology and/or positive qPCR).
Results: Among 112 enrolled patients, 82 retained. Thirty-four patients received fluoroquinolones and 48 received doxycycline. Patients in both groups were comparable with respect to age. Two severe cases were noted with fluoroquinolones (meningitis = one, encephalitis= 1) and three with doxycycline (myocarditis=one, severe sepsis = l and encephalitis =1) .|The defervescence period was 2.6 + 1.04 days in the doxycycline group and2.31.09 days in the fluoroquinolones group (p20.05). All patients recovered. One patient treated by doxycycline had a digital necrosis, generating amputation.
Conclusions: Both fluoroquinolones and doxycycline were effective for treating patients with rickettsia infections. Even that doxycycline remains the standard of treatment, with the advantage of a single daily dose; fluoroquinolones are an interesting alternative with no deleterious outcome.

Keywords: Rickettsial infections, fluoroquinolones, doxycycline

Résumé

Introduction : La doxycycline est considérée comme le traitement de référence des rickettsioses. Les fluoroquinolones ont été utilisées un traitement alternatif, jusqu'à ce que des études récentes montrent qu'elles pourraient être associées à une évolution défavorable.
Objectifs : Comparer l'efficacité thérapeutique et la tolérance des fluoroquinolones à celles de la doxycycline dans le traitement des rickettsioses.
Méthodes : Nous avons mené une étude contrôlée randomisée, multicentrique, comparant l'efficacité et la tolérance de la ciprofloxacine per os (1000 mg/j) ou de l'ofloxacine (400 mg/j) en deux prises, à celles de la doxycycline per os (200 mg/j en une prise quotidienne), pendant 3 à 10 jours selon la sévérité du tableau clinique. On a inclu les patients âgés de plus de 15 ans présentant la triade clinique caractéristique (escarre d'inoculation + éruption cutanée + fièvre) et/ou une confirmation microbiologique (sérologie positive et/ou qPCR positive).
Résultats : Parmi les 112 patients inclus, 82 ont été retenus pour l'analyse. Trente-quatre patients ont reçu des fluoroquinolones et 48 ont reçu de la doxycycline. Les deux groupes étaient comparables en termes d'âge. Deux cas sévères ont été rapportés dans le groupe fluoroquinolones (méningite = 1, encéphalite = 1) et trois dans le groupe doxycycline (myocardite = 1, sepsis sévère = 1, encéphalite = 1). Le délai de défervescence était de 2,6 ± 1,04 jour dans le groupe doxycycline et de 2,3 ± 1,09 jour dans le groupe fluoroquinolones (p > 0,05). Tous les patients ont évolué favorablement. Un cas de nécrose digitale ayant nécessité une amputation a été observée chez un patient traité par doxycycline.
Conclusion : Les fluoroquinolones et la doxycycline se sont révélées efficaces dans le traitement des rickettsioses. Bien que la doxycycline reste le traitement de référence, avec l'avantage d'une prise quotidienne unique, les fluoroquinolones représentent une alternative intéressante, sans effet délétère noté dans cette étude.

Mots-clés: Rickettsioses, fluoroquinolones, doxycycline

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Introduction

Obligate intracellular bacteria, of the genus Rickettsia, cause Rickettsiosis. Primarily transmitted through arthropod vectors. In Tunisia, both the spotted fever group (SFG) and typhus group (TG) of rickettsial infections was documented since the early 20th century (1–4). Mediterranean spotted fever (MSF), caused by Rickettsia conorii and transmitted by the dog tick (Rhipicephalussanguineus), is the most commonly reported form (1,3,4). In contrast, typhus group rickettsioses, caused by R. typhi and R. prowazekii, have become less frequently reported compared to the 1970s.The standard treatment for rickettsial infections has remained unchanged for decades, with doxycycline considered the antibiotic of choice (2,5). Chloramphenicol is a recognized alternative, although its use is limited due to the risk of aplastic anemia. Fluoroquinolones, such as ciprofloxacin, have been used as substitutes; however, recent studies have suggested they may be associated with worse clinical outcomes. This study aimed to evaluate and compare the efficacy and safety of fluoroquinolones and doxycycline in the treatment of rickettsial infections in a Tunisian population.

Methods

We conducted a prospective, open-label, randomized controlled trial in six infectious disease departments across Tunisia between January 2012 and December 2014.

Inclusion Criteria

Patients aged 15 years and older, hospitalized for acute febrile illness (defined as fever lasting fewer than 15 days), were eligible for inclusion. Patients are enrolled if they presented with either:

- The classical clinical triad of fever, rash, and eschar or a Raoult diagnostic score ≥17 or laboratory confirmation of rickettsial infection.

Rickettsial infections were classified as:

- **Confirmed**: presence of the clinical triad plus at least one positive confirmatory test (e.g., qPCR from blood or eschar biopsy; or paired serology).
- **Probable**: presence of compatible clinical features and a single positive serologic result.

Serologic testing performed using micro immunofluorescence (MIF), the reference method for rickettsial diagnosis, with antigens from R. conorii and R. typhi. Diagnostic cut-offs defined as ≥1:120 for IgG and ≥1:32 for IgM.

Exclusion Criteria

Patients were excluded if they were pregnant, had received antibiotics prior to admission, or were unable to take oral medications due to vomiting.

Randomization and Treatment Protocol

Eligible patients were randomized at admission into two groups. We performed a simple random draw from the list of eligible patients to assign them to either the doxycycline or fluoroquinolone group, with a 1:1 allocation ratio.

- **Group 1**: Oral doxycycline, 200 mg once daily
- **Group 2**: Oral fluoroquinolones — either ciprofloxacin 500 mg or ofloxacin 200 mg, twice daily

Treatment duration was 3 days for uncomplicated cases and 5 days for severe cases, defined by the presence of one or more organ dysfunctions (hepatic, renal, respiratory, cardiac, or neurologic).

Outcomes and Statistical Analysis

The primary outcome was time to defervescence. Secondary outcomes included incidence of severe complications and adverse events.

Data were analysed using SPSS version 17. Descriptive statistics were expressed as means ± standard deviation or frequencies as appropriate. Comparisons between groups were made using chi-square tests for categorical variables and Student's t-tests for continuous variables. A p-value <0.05 was considered statistically significant.

Ethical considerations

The study protocol was approved by the Ethics Committee (Comité de protection des personnes) and registered as a clinical trial with the Directorate of Pharmacy and Medicine.

Results

A total of 112 patients were enrolled; 82 met inclusion criteria and were analysed. Forty-eight patients received doxycycline (Group 1), and 34 received fluoroquinolones (Group 2). Baseline characteristics, including age, sex, and symptoms duration before treatment, and clinical presentation, were similar between the two groups (Table 1).Severe forms of illness were observed in both groups. In the fluoroquinolone group, there were two cases: one of meningitis and one of encephalitis. In the doxycycline group, four severe cases were recorded: myocarditis (1), encephalitis (1), meningoencephalitis (1), and severe sepsis (1).All patients recovered. However, one patient in the doxycycline group developed digital necrosis requiring amputation. The mean duration of fever resolution was 2.3 ± 1.09 days in the fluoroquinolone group and 2.6 ± 1.04 days in the doxycycline group ($p > 0.05$), indicating no statistically significant difference (Table 2).Both treatment regimens were well tolerated, with no drug-related adverse effects reported.

Table 1. characteristics of 82 rickettsial infections treated with fluoroquinolones or doxycyclines

Parameter	Treatment group	
	fluoroquinolones	**doxycycline**
Number of patients	34	48
Age (mean years ± SD)	42,41 ± 12,9	41,96±16,5
Male (number)	17	32
Days of fever before treatment		
≤ 5 days	11	18
≥ 5 days	23	30
Clinical findings		
Fever	34/34	47/48
Eruption	31/34	47/48
Eschar(s)	14/34	22/48
Respiratory signs	6/34	4/48
Neurologic signs	1/34	0/48
Severe cases (number)		
Myocarditis	0	1
Encephalitis	1	1
Meningitis	1	0
Meningoencephalitis	0	1
Severe sepsis	0	1
Renal insufficiency	0	0
Laboratory findings		
Leucocytes(number/total) (mean±SD)	33/34 (7633±3688)	47/48(7347±2897)
Platelets (number/total) (mean±SD)	32/34 (141562±54839,9)	47/48 (131510±63694,1)
ALT(number/total) (mean±SD)	29/34 (60±30)	42/48 (66±37,3)
AST (number/total) (mean±SD)	29/34 (79±46,7)	42/48 (72±49,5)
Creatinine (number/total) (mean±SD)	27/34 (76±17,9)	42/48 (81±16,6)

Table 2. Results of therapy with fluoroquinolones or doxycyclines in 82 patients with rickettsial infection

Symptom	Treatment group		P value
	Fluoroquinolones	**Doxycycline**	
Age (mean year ±SD)	42,41 ± 12,9	41,96 ±16,5	0,89
Gender			
Male	17	32	0,129
Female	17	16	
Total duration of fever			
≤ 5 days (number)			
≥ 5 days (number)	11	18	0,405
	23	30	
Duration of treatment	3,29 ± 0,71	3,52 ± 2,36	0,59
Apyrexia after starting therapy (days ; mean ± SD)	2,35 ± 1,09	2,78 ± 1,04	0,16

Discussion

Rickettsial diseases are a group of infections caused by Gram-negative bacteria of the genus Rickettsia. Most species are zoonotic and are responsible for typhus and spotted fever syndromes. Rickettsial spotted fevers are transmitted to humans primarily by ticks, while the vectors of typhus vary depending on the Rickettsia species involved (6–8). These infections are commonly observed in Mediterranean countries. Although often benign, severe cases can occur. Tetracycline and chloramphenicol have both proven effective in treating rickettsial infections (3,9,10). However, tetracycline has been more widely used due to the hematologic side effects associated with chloramphenicol. More recently, fluoroquinolones have also been reported as effective treatment options for rickettsial infections (11,12).We conducted a multicentre prospective study involving 82 confirmed or probable cases. In this open-label study, both fluoroquinolones and doxycycline were effective in treating rickettsial infections. Although the defervescence period was shorter in patients treated with fluoroquinolones, the difference was not statistically significant. In a non-blinded comparative study of ciprofloxacin (750 mg every 12 hours) versus doxycycline in non-severe Mediterranean spotted fever (MSF), Ruiz Beltrán et al. found no significant difference between the two treatment regimens (13). Subsequently, Gudiol et al.(14) conducted a double-blind randomized study comparing a two-day course of oral ciprofloxacin (500 mg twice daily) with oral doxycycline (100 mg twice daily) in 43 patients with non-severe MSF. They observed that fever and major symptoms lasted significantly longer in the ciprofloxacin group.In our study; severe cases were more frequently observed among patients treated with doxycycline, although this difference was not statistically significant. The presence of organ dysfunction in this group may explain the longer time to defervescence. Hospital stays were slightly longer in the doxycycline group (3.52 ± 2.36 days vs. 3.29 ± 0.71 days, p = 0.59) was observed in patients treated with doxycycline compared with the group treated with
fluoroquinolones. In one patient treated with doxycycline, an unfavourable outcome was observed—specifically, digital necrosis that led to amputation. This required prolongation of the treatment duration. This complication does not appear to be directly related to the use of doxycycline itself but may rather be explained by a delayed diagnosis of rickettsial infection, which led to a postponed initiation of antimicrobial therapy.

A recent plaque assay was conducted to evaluate the effect of ciprofloxacin on cells infected with R. conorii. The control groups included mock-treated infected cells and infected cells treated with doxycycline. Didier Raoult and colleagues employed real-time quantitative RT-PCR to quantify vapC and vapB transcripts in R. conorii-infected cells treated with either ciprofloxacin or mock treatment. Fluoroquinolones were found to be effective against R. conorii infection but also showed a deleterious effect on host cells. This effect was linked to the induction of the toxin–antitoxin (TA) module of R. conorii (14–16).

In an analysis of risk factors for malignant Mediterranean spotted fever, doxycycline—considered the gold standard treatment for both spotted (17,18) and typhus group rickettsioses (19) was associated with decreased disease severity and earlier defervescence compared to other treatment regimens (20). However, in the present study, the rate of disease severity among patients treated with doxycycline was higher than in previously reported studies from the same center.

Conclusion

This study showed the effectiveness of fluoroquinolone therapy for rickettsial infections and suggests that this class of antibiotics may serve as a valuable alternative to doxycycline for the treatment of adult patients. Further evaluation is warranted, particularly in patients with severe forms of the disease.

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