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Short Communication

Comparison of minocycline and azithromycin for the treatment of mild scrub typhus in northern China

Minxing Zhao [a], Ting Wang [a], Xiaoyu Yuan [a], Weiming Du [b], Miaoxin Lin [c], Yanbo Shen [a,*]

[a] Department of Emergency Medicine, Affiliated Hospital of Nantong University, 20 Xisi Road, Nantong, Jiangsu 226001, China
[b] BDM Consulting Inc., 100 Franklin Square Drive, Suite 102, Somerset, NJ 08873, USA
[c] Waksman Institute of Microbiology, Rutgers University, 190 Frelinghuysen Road, Piscataway, NJ 08854, USA

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ABSTRACT

Scrub typhus, caused by *Orientia tsutsugamushi*, has recently emerged in northern China where the disease had not been known to exist. Although doxycycline and azithromycin are the recommended agents for the treatment of scrub typhus, clinical responses depend both on the susceptibilities of various *O. tsutsugamushi* strains and the severity of the disease. A retrospective analysis was conducted on patients diagnosed with mild scrub typhus from August 2013 to January 2016 in the Affiliated Hospital of Nantong University, northern China. A total of 40 patients who received minocycline treatment and 34 patients who received azithromycin treatment were included in the analysis. All patients except one defervesced within 120 h after initiating antimicrobial therapy. Kaplan–Meier curves in association with log-rank test showed that the median time to defervescence was significantly shorter for the minocycline-treated group than the azithromycin-treated group ($P = 0.003$). There were no serious adverse events during treatment. No relapse occurred in either group during the 1-month follow-up period. In conclusion, both minocycline and azithromycin are effective and safe for the treatment of mild scrub typhus, but minocycline is more active than azithromycin against *O. tsutsugamushi* infection acquired in northern China.

1. Introduction

Scrub typhus, also known as tsutsugamushi disease, is an acute febrile illness among humans caused by infection with *Orientia tsutsugamushi* following the bite of an infected larval trombiculid mite. It is endemic to a 13,000,000 km^2 area of the Asia-Pacific rim, extending from Afghanistan to China, Korea, the islands of the southwestern Pacific and northern Australia [1]. It is estimated that 1 billion people are at risk for scrub typhus and ca. 1 million cases occur annually [2]. A systematic review of 76 studies showed that the median mortality from untreated scrub typhus is 6% with a wide range of 0–70% [3].

Prior to 1986, scrub typhus was confined to south of 31° north latitude in China, where scrub typhus is described as 'summer type' because its main epidemic season is summer. Summer-type scrub typhus is generally caused by Karp, Kato and JG strains, among others [1]. The associated complications are relatively severe and include pneumonitis, acute respiratory distress syndrome, acute renal failure, myocarditis and septic shock [4]. After the first report of scrub typhus in Shandong Province in 1986, epidemic foci of scrub typhus have been confirmed in 15 provinces and municipalities in northern China [5–7]. Previous investigations indicated that scrub typhus cases mainly occurred from September to December with a peak in October in northern China. Therefore, scrub typhus in northern China is called autumn–winter type. Kawasaki is the prevalent genotype of *O. tsutsugamushi* in northern China, including Shandong Province, Anhui Province and Jiangsu Province (this study). The associated complications in northern China are relatively mild.

Although doxycycline and azithromycin are the recommended drugs for the treatment of scrub typhus, various *O. tsutsugamushi* strains have different antibiotic susceptibilities [8,9]. Moreover, doxycycline-resistant strains have been isolated in northern Thailand [10]. Therefore, the efficacy of these antibiotics for the treatment of scrub typhus in northern China needs to be validated. In this paper, a retrospective analysis was conducted to compare the efficacy of azithromycin with that of minocycline, an analogue of doxycycline, for the treatment of mild scrub typhus.

2. Materials and methods

2.1. Patients and treatment

This study was performed retrospectively from data collected at the Affiliated Hospital of Nantong University, a 2016-bed tertiary care university hospital located in Jiangsu Province, northern China.

* Corresponding author. Department of Emergency Medicine, Affiliated Hospital of Nantong University, 20 Xisi Road, Nantong, Jiangsu 226001, China. Fax: +86-51385052085.
E-mail address: yanboshen123@163.com (Y. Shen).

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Clinical examination was performed by four authors (MZ, TW, XY and YS). Diagnosis of scrub typhus was confirmed by immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) using a recombinant 56-kDa protein to detect specific IgM produced in scrub typhus infections. The sensitivity and specificity of the assay are 86% and 84%, respectively [11]. The assay was performed on serum samples using a Scrub Typhus Detect IgM ELISA Kit (InBios Inc., Seattle, WA) as per the manufacturer's instructions. An optical density (OD) above the mean OD plus three times the standard deviation of healthy donor serum was considered positive. Patients with organ failure were excluded from the analysis. Organ failure was assessed using the Sepsis-related Organ Failure Assessment (SOFA) score [12]. Patients were randomly assigned to treatment with oral minocycline (Wyeth Pharmaceuticals Inc., Suzhou, Jiangsu, China; 200 mg initially, followed by 100 mg every 12 h for 7 days) or intravenous (i.v.) azithromycin (Shenyang No. 1 Pharmaceutical Inc., Shenyang, Liaoning, China; 500 mg once daily for 5 days). Intravenous azithromycin was chosen because oral azithromycin is not available in the Affiliated Hospital of Nantong University. All patients in this study were hospitalised and treatment compliance was supervised by nurses. Oral temperature was monitored every 2 h. Patients were discharged when defervescence had been achieved and maintained for ≥48 h. Patients were contacted by telephone 1 month after discharge to check for symptoms of relapse.

2.2. Analysis of the results

'Time to defervescence' was defined as the interval between the time at which the first dose of antibiotic was administered and the time at which the oral temperature first decreased to <37.3 °C and was maintained for ≥48 h without antipyretics. 'Cure' was defined as defervescence within 120 h after initiating antimicrobial therapy. 'Failure' was defined as the persistence of fever without any identifiable cause. 'Relapse' was defined as the reappearance of fever and clinical manifestations of scrub typhus, in the absence of any other identifiable cause, within 30 days after completing therapy. 'Adverse events' were defined as symptoms or signs that appeared during treatment and had not been reported prior to administration of the first dose of antibiotic.

2.3. Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows v.23.0 (IBM Corp., Armonk, NY). Fisher's exact test was used to compare rates and proportions because the sample size was small. The Shapiro–Wilk method was used to test the distribution for normality ($P > 0.05$ for normal distribution; $P \leq 0.05$ for non-normal distribution). Mann–Whitney *U*-test was used to analyse continuous variables that were not normally distributed. Independent sample *t*-test was used to compare continuous variables that were normally distributed. Time to defervescence was compared by the Kaplan–Meier survival method, and the difference between the two regimens was analysed with the log-rank test. All *P*-values were two-tailed, and a *P*-value of ≤0.05 was considered statistically significant.

3. Results

From August 2013 to January 2016, scrub typhus was diagnosed in 93 patients, which was confirmed by a highly specific IgM ELISA [11]. Among these patients, 19 were excluded from the analysis (2 were pregnant, 1 was under 16 years old, 4 had renal or respiratory failure before treatment, 1 was transferred to another hospital and 11 had taken agents with potential antirickettsial activity within 48 h prior to admission). The remaining 74 patients (40 receiving oral minocycline and 34 receiving i.v. azithromycin) were analysed in this study.

Table 1
Demographic, clinical and laboratory characteristics of patients who received minocycline or azithromycin for the treatment of mild scrub typhus.

Characteristics	Treatment group		*P*-value[a]
	Minocycline ($n = 40$)	Azithromycin ($n = 34$)	
Demographics			
Age (years) [median (range)]	67 (17–80)	71 (19–86)	0.191
Sex (no. female/male)	20/20	15/19	0.647
Duration of fever before admission (days) [median (range)]	7 (2–14)	8 (5–13)	0.338
Duration of fever before treatment (days) [median (range)]	8 (5–14)	9 (6–13)	0.104
Clinical characteristics			
Maximum body temperature (°C) [median (range)]	39.5 (38.5–40.2)	39.3 (38.1–40.3)	0.174
Eschar or ulcer [*n* (%)]	40 (100)	34 (100)	1.000
Headache [*n* (%)]	13 (33)	16 (47)	0.237
Fatigue [*n* (%)]	23 (58)	24 (71)	0.333
Myalgias [*n* (%)]	13 (33)	11 (32)	1.000
Chill [*n* (%)]	28 (70)	25 (74)	0.800
Rash [*n* (%)]	34 (85)	29 (85)	1.000
Laboratory parameters			
WBC count ($\times 10^9$/L) [median (range)]	6.6 (1.6–13.6)	7.0 (1.2–12.6)	0.220
hs-CRP (mg/L) [median (range)]	76 (10–138)	82 (13–156)	0.413
Total bilirubin (μM) [median (range)]	10.2 (4.3–29)	11 (4.3–27.0)	0.338
Direct bilirubin (μM) [median (range)]	3.7 (0–12.0)	4.6 (0.1–16.0)	0.168
ALT (IU/L) [median (range)]	65 (12–181)	67 (23–123)	0.416
AST (IU/L) [median (range)]	65 (11–132)	69 (22–146)	0.155
Serum creatinine (μM) [median (range)]	61 (32–97)	66 (50–150)	0.318

WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] *P*-values were calculated using Mann–Whitney *U*-test for continuous variables that were not normally distributed, independent sample *t*-test for continuous variables that were normally distributed, and Fisher's exact test for rates and proportions.

There were no statistically significant differences between the two treatment groups with respect to baseline characteristics (Table 1). Common clinical manifestations among the 74 patients were eschar or ulcer (100% and 100% in the minocycline and azithromycin treatment groups, respectively), fatigue (58% and 71%), chill (70% and 74%) and rash (85% and 85%). Analysis of the laboratory results revealed that most patients had a normal white blood cell count but an elevated high-sensitivity C-reactive protein (hs-CRP) level, which is consistent with a previous report from northern China [5]. Most patients had normal total bilirubin and direct bilirubin levels, but had high alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. This is also consistent with the previous reports from northern China [5,6].

Both antibiotic regimens were effective for the treatment of scrub typhus (Table 2). A total of 40 patients treated with minocycline and 33 patients treated with azithromycin defervesced within 120 h after initiating the antimicrobial therapy ($P = 0.459$). Only one patient was still febrile 120 h after azithromycin treatment and became afebrile after changing to minocycline. A significantly higher proportion of patients were afebrile in the minocycline regimen than in the azithromycin regimen within 48 h of the first dose of antibiotic ($P = 0.040$). The median time to defervescence obtained by the Kaplan–Meier method was 16 h for the minocycline-treated group and 24 h for the azithromycin-treated group. A log-rank test on the time to defervescence confirmed a statistically significant difference between the two groups ($P = 0.003$) (Fig. 1). The duration of hospitalisation was also significantly shorter for the