Original article

A comparative trial of Azithromycin versus Doxycycline for the treatment in Rickettsial Fever

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Abstract:

Introduction: Herewith our aim was to compare efiicacy of azithromycin with doxycycline

Materials and Methods: We conducted a randomized trial from May 2015 to November 2015 to compare azithromycin (10mg/kg/day for 7 days) with doxycycline (4.5mg/kg/day) for the treatment of rickettsial fever.

Results: A total of 40 patients were randomly assigned to receive either azithromycin or doxycycline. Cure was achieved in 20 (100%) of 20 patients in the azithromycin-treated group and in 19 (95%)of 20patients in the doxycycline-treated group (P = .117). The median time to defervescence was 30 h for the azithromycin-treated group and 36 h for the doxycycline-treated group (P = .097). There were no serious adverse events during the study. No relapses occurred in either group during a 1-month follow-up period.

Conclusion: The azithromycin was as effective as doxycycline for the treatment of rickettsial fever. Although tetracyclines are the conventional therapies for the treatment of rickettsial fever, the emergence of strains that respond poorly to doxycycline, in India, has compelled clinicians to seek alternative antimicrobial agents .

Azithromycin attains high intracellular concentrations and is effective against doxycycline-resistant strains of rickettsial fever; thus, it might be a suitable alternative therapeutic agent.

INTRODUCTION

Rickettsial infections are prevalent throughout the world including India. Rickettsial fever is one of the most important endemic infections in rural area (1). Rickettsial diseases pose multiple problems to clinicians since no symptoms or signs are specific enough to make clinical diagnosis. High index of suspicion is required to diagnose it clinically because the serological tests have their limitations like, poor specificity, late positive reaction and cost.(2) Rickettsial infections are caused by a group of micro organisms that phylogenetically occupy a position between bacteria and viruses (obligate intracellular pathogens) . In India, mainly 2 clinical types are seen. (1)

1.Spotted fever: Indian tick typhus (mediterranian spotted fever)–caused by R. coronii

2. Typhus group of fever : Scrub typhus is more common

Although doxycycline is the recommended drugs of choice for the treatment of rickettsial fever, reports of doxycycline-resistant strains have prompted a search for alternative treatments.

Many studies done worldwide show efficacy of macrolides (Azithromycin & Clarithromycin) & Fluoroquinolones.(4,5,6) . Hence we decided to

conduct a double blind prospective study to compare efficacy of doxycycline with azithromycin.

MATERIALS AND METHODS

INCLUSION CRITERIA . Eligible patients were those <12 years of age who exhibited documented fever (axillary temperature, ⩾38.0°C) together with a maculopapular skin rash, bodyache, joint pain and WEIL FELIX showing positive results.

64 patients presenting with fever and a skin rash or an eschar were admitted during study period between May 2015 and November 2015

Of these, 24 patients were not eligible for study entry: 4 patients had already came with history of ingested antibiotics with potential antirickettsial activity, 10 had oral temperatures of <38.0°C, , 4 refused to participate in this study, 2 presented with severe illness—3 was not able to take oral medication because of severe vomiting and 1 withdrew from study due to doxycycline induced gastrointestinal manifestations..

Finally 40 patients who fulfilled the enrollment criteria were randomly assigned to one of the two treatment groups.

Randomization and treatment. After getting written, informed consent; the enrolled patients were randomly assigned to receive one of the two oral treatment regimens.

During hospitalization, the axillary temperature of each patient was measured every 2 hr, and a physical examination was performed at least twice per day. In addition, chest radiography, urinalysis, and hematological and biochemical tests were performed at study enrollment. Complete blood cell counts and serum creatinine levels were measured every 3 days until the patient was discharged.

Patients were hospitalized for at least 5 days and were discharged when defervescence had been achieved and maintained for at least 48 h. Patients were contacted by telephone 1 month after discharge to check for symptoms of relapse.

Analyses of the results. The efficacy of treatment was analyzed basedon an' Intention-to-treat analysis' . The number of patients who completed the treatment—20azithromycin-treated patients and 20 doxycycline-treated patients.

The primary efficacy outcome was the time to defervescence, which was defined as the interval between the time at which the first dose of antibiotic was administered and the time at which the axillary temperature first decreased to <37.3°C and was maintained for >48 h without antipyretics.The secondary efficacy outcome was evaluated according to the following definitions. "Cure" was defined as the resolution of fever within 5 days after initiating the 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 rickettsial fever, in the absence of any other identifiable cause, within 30 days after completing therapy.Patients were assessed for adverse events. "Adverse events" were defined as symptoms or signs that appeared during treatment and had not been reported prior to the administration of the first dose of the antibiotic. Analyses of baseline characteristics and adverse events were done on the intention-to-treat basis.

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RESULTS

Table 1 -Age and sex distribution

	MALE N= 27	FEMALE N= 13
0-1 YR	5	2
1-2 YRS	10	4
2-5 YRS	5	3
5-12 YRS	7	4

40patients completed the treatment, and intention-to-treat analyses involving this population were performed. There were no statistically significant differences between the 2 treatment groups with respect to baseline characteristics.

Table 2 -After randomization :

	AZITHROMYCIN N= 20	DOXYCYCLINE N= 20
0-1 YR	4	3
1-2 YRS	8	6
2-5 YRS	4	4
5-12 YRS	4	7

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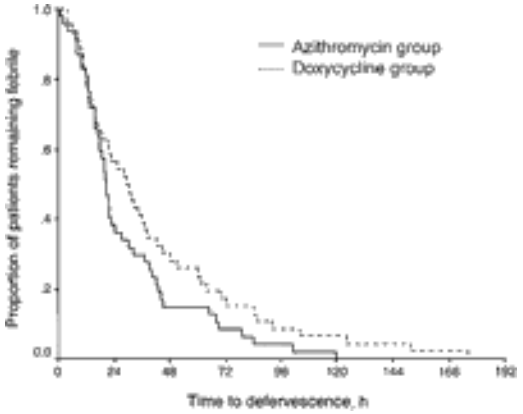
Table 3 -Clinical features :symptoms N ==40

fever	40 (100%)
Maculopapular rash	40 (100%)
Abdominal pain	4 (10%)
Body aches	19 (47.5%)
Joint pains	25(62.5%)

Table 4 – clinical features : signs N=40

Hepatomegaly	30 (75%)
spleenomegaly	26 (65%)
Pedal oedema and puffed face	16 (40%)
eschar	04 (10%)



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In this page Figure 1 Kaplan-Meier curve of the time to defervescence in patients who received azithromycin and patients who received doxycycline.

There were no deaths or serious adverse events in either group. Gastrointestinal reactions were the most frequent adverse events in both groups. Twelve patients in the doxycycline-treated group and 7 in the azithromycin-treated group complained of gastrointestinal reactions, but these individuals completed the study with no alteration of the antibiotic regimen (P > .05). Mild and transient vomiting was observed in 3 doxycycline-treated patients, but they did not disrupt the dosing schedule. There were no abnormal laboratory findings that led to the discontinuation of treatment.

Both antibiotic regimens were highly effective for the treatment of rickettsial fever. No relapses were

observed in either group over a follow-up period of 1 month.

DISCUSSION

The results of the present study revealed that azithromycin was as effective as doxycycline for the treatment of rickettsial fever. The median time to defervescence was shorter for azithromycin-treated patients than for doxycycline-treated patients, but the difference was not statistically significant. Patients who received azithromycin had fewer treatment-related adverse events than did patients who received doxycycline. No relapses occurred in either treatment group during a 1-month follow-up period.

Macrolides have been reported to be effective for the treatment of uncomplicated rickettsial fever in children .(4,5,6)Azithromycin may be better suited than other macrolides for the treatment of rickettsial fever. Azithromycin effectively penetrates human polymorphonuclear leukocytes and macrophages, which are target cells for rickettsia

Moreover, the post antibiotic effects of azithromycin tend to be considerably longer lasting in vivo because azithromycin has substantial tissue-binding ability and exhibits slow leakage from cells . These factors might explain why there were no relapses among the patients who received azithromycin in the present study.

Although the difference was not statistically significant, the prevalence of adverse gastrointestinal events was greater in the doxycycline-treated group, and one doxycycline-treated patient withdrew from the study because of severe vomiting. Nevertheless, the results of the present study suggest that azithromycin is tolerated better than doxycycline.

CONCLUSION

We found that azithromycin was as effective and as safe as doxycycline for the treatment of rickettsial fever in patients.

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