Controlled Trial: 5-day Course of Telithromycin versus Doxycycline for the Treatment of Mild to Moderate Scrub Typhus

The Efficacy and Safety of Telithromycin Compared to Doxycycline in Patients with Scrub Typhus

- A 16-week, Prospective, Multi-center, Open-label, Randomized, Controlled Trial

Abstract

Background and Objectives: Introduction-New antibiotics are required to have not only the antibacterial activity against doxycycline-resistant *O. tsutsugamushi* but also lower risk for resistance or any cross-resistance to others. New antibiotics are required that have an antibacterial activity against doxycycline-resistant *Orientia tsutsugamushi*, have a low potential of inducing resistance, and do not induce cross resistance to other antibiotics. An *in vitro* sensitivity study showed that telithromycin was more effective than erythromycin for *Rickettsia, Batonella* and *Coxiella burnetii*. Telithromycin has been reported to have *in vitro* activity against *Rickettsia spp., Batonella spp., and Coxiella burnetii*. We conducted this study to compare the efficacy and safety of telithromycin with that of doxycycline in treating patients with mild-to-moderate scrub typhus. Our study was designed to evaluate the clinical efficacy of telithromycin compared to doxycycline for the treatment of mild or moderate scrub typhus due to *O. tsutsugamushi*.

Patients and Methods: In this 16-week, prospective, open-label, randomized trial, From September 2005 to December 2005 we compared conducted a prospective, open-label, randomized trial comparing the efficacy and safety of a 5-day telithromycin therapy with those of a 5-day doxycycline therapy in patients with the treatment of mild-to-moderate scrub typhus at Chosun University Hospital in Kwangju, Korea or one of its two community-based affiliated hospitals (Jangheung Hospital and Chumdan Hospital) which are all located in southwestern Korea between September and December 2005 at Chosun University Hospital and one of its two community branch-hospitals (Jangheung Hospital and Chumdan Hospital), which are all located in southwest Korea.

Results: A total of 92 patients (47 patients treated with telithromycin and 45 patients-
treated with doxycycline) were randomly assigned to either telithromycin group (n=47) or doxycycline group (n=45). After the treatment, the cure rate was 100% in the telithromycin group and 97.8% in the doxycycline group. The cure rates were 100% and 97.8% for telithromycin and doxycycline, respectively (p>0.05). After the treatment, fever control time was 20.45±12.9 hours in the telithromycin group and 22.60±21.44 hours in the doxycycline group (p>0.05). The time interval required to defervesce after drug administration was 20.45±12.9 hours (mean interval ± SD) in the telithromycin-treated group, and 22.60±21.44 hours in the doxycycline-treated group (p>0.05). Furthermore, there were no significant differences in time elapsed until such symptoms as headache, myalgia and rash have disappeared. There was no significant difference between the treatments in time to symptom resolution (e.g., headache, myalgia, rash). [HE: Need to provide statement re: safety data]

**Conclusions:** In conclusion, the efficacy and safety of a 5-day qd regimen of telithromycin 800 mg were equivalent to those of a 5-day bid regimen of doxycycline 100 mg in patients with scrub typhus. Besides, based on the excellent tissue pharmacokinetics and low risk for resistance, telithromycin is considered as a promising new antibacterial agent for patients with scrub typhus and rickettsiosis. These results suggest that for the treatment of mild to moderate scrub typhus without accompanying complications, the safety and efficacy of 800 mg daily treatment of telithromycin for 5 days may be comparable to that of doxycycline 100 mg bid for 5 days. In addition, telithromycin has a more favorable pharmacokinetic profile than doxycycline and a lower propensity to induce resistance. [HE: both of these comments need to be substantiated in the document] [HE: the study is about scrub typhus—Why do the authors feel that they can extrapolate to all rickettsial infections, especially after an open-label RCT?]

**Key words:** Doxycycline, scrub typhus, and telithromycin, doxycycline

**INTRODUCTION**

A scrub typhus is an endemic disease in Asia, scrub typhus and it is caused by a strict intracellular, gram-negative bacterium, *Orientia tsutsugamushi* (*O. tsutsugamushi*), which is a strict intracellular, gram-negative bacteria. It scrub typhus is an acute febrile illness, whose signs and--that shows-symptoms include such as--fever, headache, chill,
myalgia, and the signs of rash, eschar and lymphadenopathy. In most cases, a recovery is achieved with the early treatment. In some cases, however, nonetheless, some patients develop severe complications such as interstitial pneumonia, acute respiratory distress syndrome, acute renal failure and multiple organ dysfunction occur, which may lead to death. Therefore, a great care must be taken to manage patients with scrub typhus—Thus, this disease requires a cautious medical management (1, 2).

Most cases of scrub typhus rapidly respond to the appropriate antibiotics; for most patients and the fever can be controlled within 48 hours after the initiation of antibiotic treatment (3). To date, chloramphenicol has been the first effective antibiotic—drug for the treatment of scrub typhus—and doxycycline is regarded as a drug of choice, presently used as an optional therapeutic agent. QIn addition, quinolone has also been used experimentally, although its efficacy remains questionable—effectiveness has not yet been sufficiently validated. According to the U.S. Food and Drug Administration (FDA) Fetal Risk Summary, however, chloramphenicol and tetracyclines are classified as Class D drugs which are contraindicated in pregnant women. The FDA also prohibited the use of tetracyclines and quinolone in are not recommended for children. Furthermore, according to a study reported in Thailand, O. tsutsugamushi showed a with resistance to chloramphenicol and doxycycline. It is therefore imperative that has been reported so new antibiotics be promptly developed therapeutic are urgently required (5). According to some After in vitro studies, reports showing that doxycycline-resistant O. tsutsugamushi isolates (from human?) were sensitive to azithromycin and the other new macrolides in vitro (6,7). Since then, it has been reported that children and pregnant women were successfully treated with macrolides antibiotics, including azithromycin (8, 9). In a controlled trial study comparing azithromycin with and doxycycline, the efficacy of a single administration of 500 mg-azithromycin 500 mg was equivalent has been shown to be comparable to that of a 7-day the-daily administration of 200 mg-doxycycline 200 mg for 7 days (10). In However, our previous case report and one clinical trial however, treatment (11, 12) have documented the failure occurred with of treatment and symptoms of relapse after the administration of azithromycin therapy (11, 12). Therefore, azithromycin—so this drug must be used with caution.

New antibiotics are required to have not only the antibacterial activity against doxycycline-resistant O. tsutsugamushi but also, and have a lower risk for potential of inducing resistance or any cross-resistance to others antibiotics.
The first ketolide antibiotic, telithromycin has good antibacterial activity against intracellular bacteria such as *Chlamydia*, *Mycoplasma*, *Legionella* spp. and other diverse ones. An *in vitro* sensitivity study showed that telithromycin has been reported in an *in vitro* sensitivity study to be more effective than erythromycin for *Rickettsia*, *Bartonella* and *Coxiella burnetii* than erythromycin (13). This suggests that therefore, telithromycin is a safe, drug of choice for the treatment of may be considered as an alternative antibiotics that could be safely used for rickettsiosis or Orientia infection.

In a recent preliminary study in Korea which compared the clinical effectiveness of telithromycin with doxycycline on scrub typhus (A recent, preliminary study compared the efficacy of telithromycin with that of doxycycline in Korean patients with scrub typhus?) (14), it has been shown that telithromycin showed a better treatment outcome than doxycycline (14). To date, however, until now, no report written in English literatures have described the efficacy—clinical effectiveness—of telithromycin in treating patients with scrub typhus could be found.

Under the background described above, we conducted this study was designed to compare the efficacy and safety of prove the clinical usefulness of telithromycin by comparing it with that of doxycycline in for treating patients with mild-to-moderate scrub typhus.

**PATIENTS AND METHODS**

**Patient Selection**

In this We conducted a multicenter, prospective study, we Enrolled subjects were the patients with possible scrub typhus. Inclusion criteria were (1) adults—patients—aged ≥18 years or older; (2) a) who have had fever of higher than (temperature: ≥37.5°C; (3) the concurrent presence of together with eschar or a maculopapular skin rash; and (4) the clear presence of more than two symptoms such as ≥2 of the following symptoms:—headache, malaise, myalgia, coughing, nausea, and abdominal discomfort. Each patient was hospitalized at Chosun University Hospital in Kwangju, Korea or one of its two community-based affiliated hospitals (Jangheung Hospital and Chumdan Hospital) which are all located in southwestern Korea was admitted between September, 2005 to and December, 2005 — to Chosun University Hospital or one of its two community branch hospitals (Jangheung Hospital and Chumdan Hospital), which
are all located in southwest Korea.

Exclusion criteria were (1) an inability to take oral medications; (2) pregnancy; (3) hypersensitivity to the trial drugs; (4) a previous history of drug therapy with potential antirickettsial activity (e.g., rifampicin, chloramphenicol, macrolides, fluoroquinolones or tetracyclines) within 48 hours prior to admission; and (5) severe scrub typhus (shock requiring vasopressor therapy for more than one hour, a stuporous or comatose level of consciousness, respiratory failure requiring mechanical ventilation or renal failure requiring immediate dialysis) (4, 10). For the differential diagnosis of scrub typhus from other diseases with similar symptoms (e.g., murine typhus, leptospirosis, hemorrhagic fever with renal syndrome and systemic lupus erythematosus), patients underwent diagnostic tests. We thus excluded patients with concurrent infections who had the risk of causing different clinical outcomes were excluded.

Prior to the study, patients or their guardians submitted a written informed consent from the patients or their guardians (10) and The protocol was approved by the Institutional Ethics Board (IEB) Committee for the Clinical Human Research of Chosun University Hospital.

A diagnosis of scrub typhus was made in cases in which the IFA titer increased more than four times or greater rise in the IFA titer (15, 16). In our patients, we monitored the clinical course on a daily basis. The patients were examined daily during hospitalization and then once a week for four weeks after discharge from the hospital. Patients were contacted by telephone one month after discharge for a check-up for symptoms of relapse.

The Basis of Sample Size Determination Calculation

To compare the bioequivalence study between the equivalence of the two antibiotics, (based on Blackwelder’s methods, (17)) we assumed the cure rate (What about “response rate”?) of doxycycline was assumed to be 90%, and defined an over-20% difference in >20% for the cure rate between the two antibiotic treated-
groups was defined as not being bio-equivalent (17). Type I and II error It was assumed that the type I and type II errors were estimated at 0.05 and 0.20, respectively. In addition, the drop-out rate was estimated at a 20% drop-out and at least a rate, a minimum of 40 patients were required for each group. Therefore, in our series, was required so a total of 80 patients experimental subjects were recruited. *Editor’s Note: A total of 92 patients were finally selected for the present trial, as mentioned in the results section.

Randomization and Treatment Assignment
Eligible patients with a temperature of higher than 37.5°C were randomly allocated to receive one of the two oral regimens in accordance with a protocol. *Editor’s Note: In compliance with the protocol, patients who met inclusion criteria were randomly assigned to two treatment arms: the telithromycin and doxycycline group. Treatment assignment The allocation was determined by the last digit of the resident registration number (whether the last digit of the resident registration number was odd or even?). In other words, patients with the cases with an odd number were received treated by a 5-day course of daily regimen of 200 mg doses of doxycycline 200 mg, and those the cases with an even number did were treated by a 5-day course of daily regimen of 800 mg doses of telithromycin 800 mg.) Treatment Therapy was initiated started immediately after a comprehensive clinical examination was done and the collection of specimens was collected for further laboratory procedure tests.

Outcome Measures (Also, “End Points”)—
In our series, The primary efficacy outcome measure (also, “primary end point”) was the fever clearance time (time to fever clearance?); this was defined as the time from start of appropriate antibiotic therapy to the first instance, the interval between the time of the first dose and the time when the oral temperature fell below 37.3°C and remained that level without antipyretics for at least a minimum of 48 hours. The secondary efficacy outcome measure (also, “secondary end point”) was assessed based on—evaluated according to—the following definitions: (1) “Cure” was defined as fever the resolution of fever within five 5-days after the start of initiating the antimicrobial (antibiotic?) therapy; (2) ”Failure” was defined as the persistence of fever without any identifiable causes; and (3)” Relapse” was defined as the reappearance of fever with—the clinical manifestations of scrub typhus within 30
days after the completion of antibiotic therapy, but without in the absence of any other identifiable causes, within 30 days after completing therapy as previously described previously (10). All patients were evaluated assessed for toxicity (toxic reactions), and "Adverse events (AEs) (Treatment-emergent adverse events [AEs])" were defined as any unfavorable symptoms or signs that occurred appeared during the treatment or those which were and that had not been reported prior to the administration of the first dose of the antibiotic therapy.

Statistical Analysis methods

Pearson’s x² or Fisher’s exact tests were used applied to compare the rates and proportions (Please clarify,) between the two groups. The Mann-Whitney U test was carried out to compare the continuous variables that were not normally distributed. An independent-sample t-test was used to compare the variables that were normally distributed, normally distributed variables. For comparison of the time required to control fever, the Kaplan-Meier survival method was employed to compare the fever clearance time between the two groups. The log-rank test was used to compare for comparison of the cure rate between the two groups. To rule out possible bias, we primarily used the Intent-to-Treat (ITT) population and then performed a protocol (PP) analysis, which can be introduce depending on the choice of population to be analysed (Please clarify.)

Statistical Analysis was done using SPSS®, Version 12.0 for Windows (SPSS, Inc., Illinois, Chicago). *Editor’s Note: All data was expressed as mean±SD (SD: standard deviation).

RESULTS

1. Baseline Demographic characteristics

A total of 163 One hundred sixty three patients visited Chosun University Hospital
and its affiliated hospitals between branches from September and to December 2005 with a chief complaint of fever or rash. Of Among them, 68 patients did not meet inclusion criteria (a history of antirickettial therapy in nine patients; a temperature of lower than 37.5°C in 27 patients; severe complications associated with scrub typhus in nine patients [four cases of shock requiring vasopresor therapy for more than one hour, three cases of stuporous or comatose-level consciousness, two cases of respiratory failure requiring mechanical ventilation and one case of vomiting in which the oral intake was impossible]; and the refusal of participation in 22 patients), were not eligible due to following reasons: 9 patients were treated prior to the visit with antibiotics that had antirickettial activity, the temperature of 27 patients was lower than 37.5 degrees at the time of the visit, 9 patients showed severe scrub typhus-related complications (shock requiring vasopressor therapy for >1 h: 4, a stuporous or comatose level of consciousness: 3, respiratory failure requiring mechanical ventilation: 2, and one patient could not take oral administration due to vomiting), and 22 patients refused to participate in the study. Ninety five patients satisfied the inclusion criteria. Of these patients, however, three had the concurrent diseases; three cases of other concomitant diseases were confirmed (all 3 patients had hemorrhagic fever accompanied by with renal syndrome. Excluding these patients, ) thus, they were excluded from the study. Finally selected 92 patients (n=92) and then assigned them to the 47 patients were treated with telithromycin group (n=47) and the 45 patients were treated with doxycycline group (n=45). In both groups, a 5-day daily administration was done. Between the two treatment groups, age, gender, the duration of symptoms prior to admission and most of the clinical laboratory findings were well balanced; any statistical difference in the demographic characteristics could not be found. *Editor’s Note: “At baseline, there were no significant differences in the demographic and clinical data such as age, sex, the duration of symptoms and laboratory measurements between the two groups”? Baseline characteristics are represented in Table 1. The demographics of the patient population are shown in table 1. Overall, a diagnosis of scrub typhus was made in 82.2% (78/92). That is, an IGM titer was greater than 1:80 or the concentration of serum IgM was elevated by more than four times compared to baseline in % (?/47) of the telithromycin group and % (?/45) of the doxycycline group. Among 92 patients, 78 patients (27 cases among 45 cases of the telithromycin administration group, (82.2%), and 30 cases among 47 cases of the doxycycline administration group, (63 %) [Editor’s Note: The number of patients from each treatment arm was inverted. Please check this.] had an IGM titer greater.
than 1:80 or the elevation of IgG greater than 4 times to be confirmed as having the disease. A definite diagnosis was made in eight patients of the telithromycin group; the loss of follow-up in four patients, different diagnoses in two patients, a history of drug fever in one patient and idiopathic cause in the remaining one patient. Among the telithromycin administered group, 8 patients had not definitely diagnosed as scrub typhus; 4 of them due to the follow up loss, 2 patients due to having different diseases, one patient due to having drug fever, and remaining one case due to undetermined cause. At a follow-up serum test done a week later, however, an IGM titer was less than 10 (unit?) and the concentration of serum IgM was 32 (unit?). Nonetheless, even on the follow-up serum test performed after 1 week, the IgM was less than 10 and the IgG was less than 32. Eight Among the 8 undiagnosed patients of the doxycycline administered group comprised seven cases of the loss of follow-up was seen in seven (7%) and one case (1%) of adult-onset Still’s disease (AOSD) was noted. 7 patients were lost to follow-up, and one patient was confirmed to have an adult onset Still’s disease.

2. Efficacy

After the treatment, Five days after the treatment with telithromycin or doxycycline, the cure rate was 100% in the telithromycin group and 97.8% in the doxycycline group (Table 2). However, this was not statistically significant with no statistical difference. In all patients with For the mild-to-and-moderate scrub typhus, fever clearance was noted following the treatment, after the 5-day treatment with doxycycline or telithromycin, the fever was controlled in all patients. In yet one patient of the doxycycline group, however, patient whose fever clearance was noted 24 hours after the treatment. This patient of doxycycline visited us the hospital once again two—2-weeks later with a chief complaint of fever, rash and pericarditis, in whom no causal relationship was found, and an accurate causality could not be determined. Based on the assumption that the above patient had a relapse, we considered this as recurrence and then administered telithromycin to that patient. However, no treatment responses were noted in this patient, whose symptoms were alleviated. was administered; however, treatment response was not noted and after treatment with steroid, the patient’s symptoms were improved. No definite causal relationship was identified, but The final causality was not clear, and the possibility of viral pericarditis could not be ruled out.

After the treatment, administration of antibiotics, the time required to fever control
Time was 20.45±12.9 hours in the telithromycin treatment group and 22.60±21.44 hours in the doxycycline treatment group. The mean interval was 20.45 ± 12.9 (mean interval ± SD), and that of the doxycycline treatment group was 22.60 ± 21.44 (p>0.05). However, this was not statistically significant. To compare fever clearance time between the two groups, a log-rank test was done using the Kaplan-Meier curve. This also showed no statistical significance. Similarly, a significant difference between two groups could not be detected on the Kaplan-Meier curve after applying a log-rank test to evaluate the time required for controlling fever. Furthermore, there were no significant differences in time elapsed until such symptoms as headache, myalgia and rash have disappeared. In addition, a statistically significant difference could not be detected regarding the time required to control the symptoms such as headache, myalgia and rash (Table 3). A statistical significance was also shown on a per-protocol (PP) analysis as well (data not shown).

3. Adverse Events

No serious adverse events (SAEs) or death were noted following the treatment. Administration of antibiotics were not detected. Adverse events (AEs) were detected in 14.9% (7/47) of the 7 cases among the telithromycin administration group and 24.4% (11/45) of the 11 cases among the doxycycline administration group. Gastrointestinal AEs were also found in both groups; three cases of abdominal discomfort adverse events, a total of 3 patients in the telithromycin administration group and six cases complained of abdominal discomfort, and a total of 6 patients in the doxycycline administration group complained of GI adverse events (two cases of nausea, one case of vomiting, one case of diarrhea and two cases of abdominal discomfort).

Clinically notable laboratory findings were seen in both groups; the hepatic parameters were elevated by more than two times in 8.5% (4/47) of the hepatic function value in 4 patients among the telithromycin administration group and 4.4% (2/45) of the 2 patients among the doxycycline group. In addition, two cases of skin rash and one case of esophageal candidiasis were developed in the doxycycline administration group. Skin rash was developed after the administration of doxycycline, and in one patient, esophageal candidiasis was detected. In all cases, however, all such AEs were of mild-to-moderate severity. In adverse events were of mild or moderate severity, and after the
administration of doxycycline group, excluding one case of except for one patient who complained of skin rash, the administration schedule was not discontinued of the administration of antibiotic was not changed.

**DISCUSSION**

Scrub typhus is an endemic disease on the Pacific coast, particularly in northern Australia and East Asia including Korea. In Korea, the incidence of scrub typhus is continuously rising; on the rise, and a total of 6,787 cases have been reported in 2005 (18). To date, chloramphenicol, tetracycline, and doxycycline have been used as effective antibiotics therapeutics for scrub typhus. However, yet chloramphenicol is no longer in use because of the adverse drug reactions such as fatal aplastic anemia, bone marrow suppression and gray baby syndrome (9, 19). Tetracycline is contraindicated in pregnant women and children aged eight years or younger because it causes of the permanent tooth staining in fetuses and young children.

It has been reported that the new macrolide antibiotics have been used not only for an in vitro assay, but also they were also used at local clinics in for pregnant women and children with scrub typhus or rickettsial infections, whose safety and efficacy have been described in published studies and they were used safely and effectively.(6-9). One of Among the macrolides, azithromycin is a drug of can be used as a first-choice. It has been reported that in patients with mild scrub typhus infection, the effect of a single administration of 500 mg azithromycin is comparable to that of 200 mg daily of doxycycline (10). [Editor’s Note: This statement was already provided in the introduction section. “In a controlled trial comparing azithromycin with doxycycline, the efficacy of a single administration of azithromycin 500 mg was equivalent to that of a 7-day daily administration of doxycycline 200 mg (10).”] –However, treatment failure and recurrence after the administration of azithromycin have been reported (11, 12). [Editor’s Note: This statement was already provided in the introduction section. “In our previous cases and one clinical trial, however, treatment failure occurred with symptoms of relapse after azithromycin therapy (11, 12).”] –According to a previous study comparing a 3-day treatment with azithromycin therapy with or doxycycline therapy in the (azithromycin arm (n=18[8?]) and the cases, doxycycline arm (n=12), –case), there were 2 cases of treatment failure with symptoms of relapse was noted in 25% (2/8) and recurrence among 8 cases of the azithromycin group. Following a full 3-day course of
azithromycin, - Fever persisted over beyond 24 hours after the full 3 days-
azithromycin course in one patient, - and another patient experienced a relapse was seen in another patient. - 3 days after the completion of azithromycin. Further studies are therefore warranted to evaluate, additional studies are required for evaluating the treatment outcome of azithromycin treatment. Furthermore, because of the characteristic of azithromycin of inducing resistance, abuse or misuse of azithromycin may induce resistance. Accordingly, - so azithromycin must should be used cautiously (20).

Telithromycin is the first ketolide antibiotic, telithromycin was that has been produced by the structural modification of macrolides. In comparison with macrolides, the affinity of ketolides to the binding sites in domains II and V of the 50S ribosomal subunit has been improved. Owing to Because of this, ketolides characteristic, it showed antibacterial activity against not only macrolide-resistant bacteria but also various strains bacteria including Chlamydyphila and, Legionella. (21-23). According to in vitro experiments, - of telithromycin showed good antibacterial activity against - on Rickettsia spp., Bartonella spp. and Coxiella burnetii have demonstrated a good antibacterial activity, and its minimal inhibitory concentration (MIC) was lower than that of MIC against such bacteria, as compared to erythromycin. - was confirmed to be lower. These results which suggested that - the possibility of using telithromycin is a useful (effective?) antibiotic in for the treating patients with ment of rickettsiosis and scrub typhus (13). The advantages of ketolide are its pharmacokinetic properties. Ketolide - It is lipophilic, so it is widely distributed widely in fluids, tissues, and intracellular compartments. Its oral absorption rate amounts reaches up to 90%, of which - but 33% undergoes first-pass metabolism. Therefore, - so the actual oral bioavailability is estimated at approximately 57%; this figure is higher it shows better bioavailability than the other macrolides. T-and the absorption rate of ketolides is not influenced by food. After oral administration, Cmax (2.27 mg/L) is attained as early as in one to three hours; After oral administration, it reaches Cmax (2.27 mg/L) as early as in 1-3 hr, its - and the half-life is 12 hours. Ketolides -and can be taken once a day (24–26). In treating patients with A point to be considered for the treatment of O. tsutsugamushi infection, physicians must consider whether the intracellular concentration of ketolides and that of serum ketolides are both sufficient. - [HE: After first use, this should be O. tsutsugamushi] is that both intracellular and serum concentration should be sufficient. In other words, after O. rientia tsutsugamushi inoculation (infection?), the chiggas (Please clarify.) proliferate in the vascular endothelial cells and they subsequently destroy them. - endothelial cells. Ketolides They are then released inside the blood vessels and then present at high concentrations.
An optimal antibiotic must maintain its concentration sufficiently both in peripheral blood and within cells. From this aspect, the concentration of tissue telithromycin in the tissues is high, whose intracellular as well as the extracellular drug-concentration is well maintained; these are the characteristics of antibiotics that can be alternatively used as a useful substitute for the treatment of rickettiosis and scrub typhus (25). Another advantage of telithromycin is that it induces a relatively low risk for level of resistance. T-, and among the macrolide-, lincosamide- and the group B streptogramin-B-class (MLS) of antibiotics, it does not readily induce cross-resistance. In Korea, the 79.7% incidence of penicillin-non-susceptible Streptococci pneumoniae (PNSSp) infection has been reported to be 79.7% (27). The incidence of drug-resistant pneumococci could increase due to the abuse of oral antibiotics such as macrolides and cephalosporin. The elevation of pneumococcal MIC was elevated confirmed after when sequential subcultures were done with subinhibitory concentrations of azithromycin, cefuroxime, and cefaclor (28). In a resistance-selection study based on that applied sequential subcultures with subinhibitory concentrations of MLS agents (macrolide, lincosamide and the streptogramin class), including telithromycin and azithromycin, telithromycin was found to have the lowest resistance selection, in comparison with the other drugs.

Therefore, it has the advantage from the aspect of resistance selection, and it has been reported to have a good antibacterial activity against the in vitro-selected mutants that acquired resistance to other macrolides (20). Please clarify. “Based on this result, it can therefore be inferred that telithromycin has the low risk for resistance. Other in vitro studies have shown that telithromycin has good antibacterial activity against selected mutant strains which are resistant to other macrolides (20).”

In Korea, a preliminary study compared the efficacy of telithromycin with that of doxycycline regarding the fever clearance time require to control fever in the patients with scrub typhus. According to this study, fever clearance time was shorter in the one preliminary Korean study in which the efficacy of telithromycin group than the doxycycline group, and doxycycline had been compared, reported that the telithromycin-group required shorter time. In our series, however, there was no significant statistical difference between the two groups.

The above-mentioned preliminary study was conducted in 23 Korean patients with scrub typhus at two centers. These patients were divided into the telithromycin group (n=12) and the doxycycline group (n=11). This study showed that fever clearance time was 17.7 hours that study on 23 cases (12 cases of telithromycin, 11 cases of doxycycline) who visited two university hospitals, the time required for the control of
Fever in the telithromycin treatment group was 17.7 hours, and 30.7 hours in that of the doxycycline treatment group was 30.7 hours, which was statistically significant; this a significant difference. However, the results of this study must be interpreted in a limited scope because a loading dose was given only to one of the limitations of that study was that only the telithromycin treatment group was given a loading dose (800 mg twice a day on Day 1, the first day of the administration of antibiotics, and then 800 mg once a day from Day 2 on the subsequent day), not in the doxycycline treatment group. Another limitation of this study is further limited by the lack of randomization.

After the treatment, five days after the treatment with telithromycin and doxycycline, the cure rate was 100% in the telithromycin group and 97.8% in the doxycycline group (Table 2). However, this respective, and the difference of cure rates between the two groups was not statistically significant. In our study, for the treatment of mild and moderate scrub typhus patients, after the administration of doxycycline and telithromycin for 5 days, none of patients failed to control their fever. (In our series, no cases of treatment failure were reported) However, 1 patient whose fever was controlled within 24 hours of the administration of doxycycline, at 2 weeks later, the patient again visited the hospital for fever, rash and pericarditis and this patient was classified into the recurrence category, yet any accurate causality could not be confirmed. (In one patient of the doxycycline group, however, fever clearance was noted 24 hours after the treatment. This patient visited us again two weeks later with a chief complaint of fever, rash and pericarditis, in whom no causal relationship was found. Based on the assumption that the above patient had a relapse, we administered telithromycin to that patient.)

Fever clearance time was shorter in our series than the previous. The time required to control fever was relatively shorter in our study than that of the other preliminary study in Korea. This difference can be explained by a case mix in severity of mild-to-moderate scrub typhus in our study. In other words, the previous study subjects in the preliminary study were recruited patients only at from two tertiary hospitals, but we selected patients in a heterogeneous clinical setting (one tertiary care center and two primary clinics). This which suggests that the former study had the more likelihood of selecting severe cases than ours, could have been more likely involved, whereas in our study, the patients were recruited not only from a tertiary hospital but also from primary care setting.

Of interest, in case of doxycycline, there was a (significant or insignificant?) difference in fever clearance time of the doxycycline group between required to control fever in the tertiary hospital and that in the primary medical
institution (28.12±26.67 hours in 25 cases versus 15.70±8.69 hours in 20 cases) were different. In other words, among 45 cases treated with doxycycline, the time required to control fever for the 25 cases treated at the tertiary hospital was 28.12 ± 26.67 (Mean ±SD), and the time required to control fever for the 20 cases treated at the primary medical institution was 15.70 ± 8.69 (Mean ±SD). On the other hand, there was no (significant or insignificant?) difference in fever clearance time of the telithromycin group between the tertiary hospital and primary medical institution (21.04±11.87 hours in 28 cases versus 19.58±14.58 hours in 19 cases). Among all 47 patients who were treated with telithromycin, the time required to control fever for the 28 patients enrolled at the tertiary hospital was 21.04 ± 11.87 (Mean ±SD), and the time required to control fever for the 19 patients enrolled at the primary medical institution was 19.58 ± 14.58 (Mean ±SD). Whereas, in case of telithromycin, the time for fever control between the two different hospital settings was not different; These in regards to such a difference can be attributable to the severity of scrub typhus diseases or the involvement of doxycycline-resistant strains, which deserves further studies, could have been possible reasons but additional studies are needed.

In Regarding the time elapsed until symptoms such as required for the alleviation of headache, myalgia and rash were alleviated, there was no significant difference—a statistically significant difference could not be observed between the two treatment groups (Table 3).

Central nervous system (CNS) involvement is very common frequent in patients with O. tsutsugamushi infection (29). According to one report, among 25 scrub typhus patients, O. tsutsugamushi DNA was could be detected using a via nested PCR in the CSF of six of 25 patients with scrub typhus 6 patients (30). In and most cases, scrub typhus patients complain of headache is a chief complaint, which is assumed to result from CNS involvement. In many cases, headache persists even after fever clearance, and such headache persists even after the control of fever in many cases and the headache is thought to be the result of CNS involvement. In our series, there was no significant difference in time elapsed until headache was alleviated between the two groups. In our study, a statistically significant difference was not detected for the time required to ameliorate headache after the administration of doxycycline or telithromycin.

Gastrointestinal AEs adverse events were more frequent in the doxycycline-treated group. T and the temporary elevation of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels was more frequent in the telithromycin-treated group. However, although these differences did not reach statistical significances. No SAEs or death were noted following the treatment in our series. Serious adverse events
were not detected after each treatment.

In conclusion, we first reported, in English, that the efficacy and safety of a 5-day qd regimen of telithromycin 800 mg were equivalent to those of a 5-day bid regimen of doxycycline 100 mg in patients with scrub typhus. Our study is the first study reported in English literature that has confirmed that for the treatment of mild to moderate scrub typhus without accompanying complications, 800 mg daily treatment of telithromycin for 5 days was a safe and effective treatment, and it was comparable to doxycycline 100 mg bid for 5 days. Besides, further, based on the excellent superior tissue pharmacokinetics and low risk for resistance, profile of telithromycin is considered as and its low potential to induce resistance suggest that it could be a promising new antibacterial agent for patients with treating scrub typhus and rickettiosis.

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Table 1. Baseline Characteristics: Demographic and clinical characteristics of the patients evaluated in a comparative study of telithromycin and doxycycline for the treatment of scrub typhus

Values are mean±SD (SD: standard deviation). AST, a Alanine aminotransferase, ASAT, = aspartate aminotransferase.

* There was no significant difference in baseline characteristics between the two groups. Comparison of the two groups in terms of each characteristic revealed no significant differences (P>.05).

Table 2. Outcomes Measures (Also, “End Points”) of patients who received telithromycin or doxycycline for the treatment of scrub typhus
* There were no significant differences in outcome measures between the two groups (P>.05). Comparison of the two groups in terms of each outcome revealed no significant differences (P>.05).

Table 3. Time elapsed until the symptoms have disappeared. Intervals required for the disappearance of symptoms after the administration of antibiotics for scrub typhus in a comparative study of telithromycin and doxycycline regimens.

Values are mean±SD (SD: standard deviation).

* There were no significant differences in time elapsed until the symptoms have disappeared between the two groups (P>.05). Comparison of the two groups in terms of each outcome revealed no significant differences (P>.05).

Table 4. Adverse events in patients who received telithromycin or doxycycline for the treatment of scrub typhus.

Values are mean±SD (SD: standard deviation). AST, alanine aminotransferase.

Note. ALT: Alanine aminotransferase.

* There were no significant differences in the incidences of adverse events between the two groups (P>.05). Comparison of the two groups in terms of each characteristic revealed no significant differences (P>.05).

Figure 1. The Kaplan-Meier curve plotting fever clearance time of the time to defervescence for patients who received telithromycin or doxycycline for the treatment of scrub typhus.