ORIGINAL ARTICLE

Intravenous Doxycycline, Azithromycin, or Both for Severe Scrub Typhus

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ABSTRACT

BACKGROUND

The appropriate antibiotic treatment for severe scrub typhus, a neglected but widespread reemerging zoonotic infection, is unclear.

METHODS

In this multicenter, double-blind, randomized, controlled trial, we compared the efficacy of intravenous doxycycline, azithromycin, or a combination of both in treating severe scrub typhus. Patients who were 15 years of age or older with severe scrub typhus with at least one organ involvement were enrolled. The patients were assigned to receive a 7-day course of intravenous doxycycline, azithromycin, or both (combination therapy). The primary outcome was a composite of death from any cause at day 28, persistent complications at day 7, and persistent fever at day 5.

RESULTS

Among 794 patients (median age, 48 years) who were included in the modified intention-to-treat analysis, complications included those that were respiratory (in 62%), hepatic (in 54%), cardiovascular (in 42%), renal (in 30%), and neurologic (in 20%). The use of combination therapy resulted in a lower incidence of the composite primary outcome than the use of doxycycline (33% and 47%, respectively), for a risk difference of –13.3 percentage points (95% confidence interval [CI], –21.6 to –5.1; P=0.002). The incidence with combination therapy was also lower than that with azithromycin (48%), for a risk difference of –14.8 percentage points (95% CI, –23.1 to –6.5; P<0.001). No significant difference was seen between the azithromycin and doxycycline groups (risk difference, 1.5 percentage points; 95% CI, –7.0 to 10.0; P=0.73). The results in the per-protocol analysis were similar to those in the primary analysis. Adverse events and 28-day mortality were similar in the three groups.

CONCLUSIONS

Combination therapy with intravenous doxycycline and azithromycin was a better therapeutic option for the treatment of severe scrub typhus than monotherapy with either drug alone. (Funded by the India Alliance and Wellcome Trust; INTREST Clinical Trials Registry–India number, CTRI/2018/08/015159.)

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*A list of INTREST trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Scrub typhus, a life-threatening zoonotic bacterial infection caused by *Orientia tsutsugamushi* and transmitted by trombiculid mite larvae, is a public health challenge that extends beyond the so-called Tsutsugamushi Triangle, the region where this infection has traditionally been endemic in Asia and Northern Australia.[1-5] A billion people are estimated to be at risk in endemic regions, with an estimated 1 million cases and 150,000 deaths annually.[2,5] Scrub typhus typically presents as an acute febrile illness that may be associated with headache, cough, shortness of breath, and altered sensorium. An eschar at the site of the mite bite serves as a highly distinctive diagnostic clue.[6-8] When this infection is untreated, the median case fatality is approximately 6% but can reach 70% in severe disease.[9] Severe disease (including multiorgan dysfunction and shock) develops in approximately one third of hospitalized patients and can lead to death in approximately a quarter of cases despite therapy.[10-12]

Historically, scrub typhus has been treated with doxycycline or chloramphenicol. However, data from sufficiently powered, randomized, controlled trials are lacking, particularly for severe scrub typhus. In recent years, chloramphenicol has been used less frequently because of its toxicity profile, and oral azithromycin is increasingly used for mild scrub typhus. A small, prospective, open-label, randomized trial in South Korea involving patients with mild scrub typhus showed that single-dose azithromycin (500 mg) was as effective as doxycycline (200 mg) daily for a week.[13] In a randomized trial conducted in Thailand that enrolled patients with scrub typhus, leptospirosis, or murine typhus, investigators found that the administration of either 3 days of azithromycin or 7 days of doxycycline led to similar median durations of fever clearance at 48 hours.[14] A recent small trial involving children showed similar fever defervescence with azithromycin and doxycycline.[15] Systematic reviews of available trials showed the use of heterogenous drug regimens and outcome measures, which suggested the need for more comprehensive data.[16-18] In addition, the most appropriate treatment option for severe scrub typhus is unclear.

We conducted the double-blind, randomized, controlled Intravenous Treatment for Scrub Typhus (INTREST) clinical trial to compare the efficacy and safety of three 7-day intravenous antibiotic treatments (doxycycline, azithromycin, or a combination of both) in patients with severe scrub typhus.

A Quick Take is available at NEJM.org

METHODS

TRIAL DESIGN

This multicenter superiority trial was conducted at seven sites across India (Section S1B in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial protocol was reviewed by the institutional review board or ethics committee at each site and by the Oxford Tropical Research Ethics Committee. Participants who were 18 years of age or older provided written informed consent. Those between 15 and 18 years of age provided assent, and consent was obtained from their parents or guardians. The next of kin provided consent for patients who were unable to consent because of altered mental status or severity of illness.

An independent data and safety monitoring board oversaw and periodically reviewed the safety and efficacy of the trial data (Section S1C). The trial drugs were purchased from manufacturers, including intravenous doxycycline (Doxific, Gufic Biosciences), intravenous azithromycin (Azee, Cipla), and placebo multivitamin (Polybion, Merck). The trial was funded by the DBT–Wellcome Trust India Alliance (India Alliance) and the Wellcome Trust, which along with the drug manufacturers had no input into the trial design or conduct, analysis of the data, or writing of the manuscript. The contributions of the authors are described in the Supplementary Appendix. All the authors critically reviewed and provided input into drafts of the manuscript and made the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

PATIENTS

Patients who were 15 years of age or older and had a positive result on a lateral flow assay of a whole-blood sample (Scrub Typhus Rapid, ImmuneMed) or an eschar were screened for

eligibility at the seven participating hospitals. Patients with severe disease and the involvement of at least one organ that led to intravenous treatment were enrolled. Exclusion criteria included treatment with doxycycline, azithromycin, or chloramphenicol for more than 24 hours within 3 days before recruitment; pregnancy or breast-feeding; treatment with antitubercular therapy (because rifampicin has activity against *O. tsutsugamushi*); documentation of immune suppression; treatment with contraindicated concomitant drugs; or any previous adverse reaction to a trial drug.

INTERVENTIONS AND RANDOMIZATION

Patients underwent block randomization in a 1:1:1 ratio. The first group received 200 mg of doxycycline twice daily on day 1 followed by 100 mg twice daily for 6 days. The second group received 500 mg of azithromycin twice daily on day 1 followed by 500 mg daily for 6 days. The third group (combination therapy) received both azithromycin and doxycycline in the doses mentioned above. A computer-generated list with block sizes of nine was used for randomization, with a prespecified pseudorandom number that provides a reproducible randomization list. The randomization list was sent to an independent masking company (Syngene International), where vials of medications were secondarily labeled and numbered with trial identifiers. The drugs for each patient were packed in separate sequentially numbered boxes and delivered to each site in blocks of nine. To maintain blinding, matching placebo infusions were included to make the number of infusions per day identical in all the treatment groups. The treating team, trial management group, and patients remained unaware of the group assignments. The pharmacist at each site assigned medication kits to the patients according to their order of enrollment. Full details regarding the trial conduct are provided in the protocol at NEJM.org.

CLINICAL AND LABORATORY MONITORING

Patients were treated at each site for at least 7 days, with daily assessment of vital signs, oxygen saturation, requirement for supplemental oxygen, ventilation, inotropic support, dialysis, and admission to an intensive care unit (ICU). Patients were also monitored with the use of hematologic tests, biochemical tests, and polymerase-chain-reaction (PCR) assays on buffy-coat blood samples for *O. tsutsugamushi* at baseline and on days 1, 3, 7, and 10 through 14. Persistent complications were assessed and documented on days 3 and 7. Among patients who had died after hospital discharge, 28-day mortality was determined by a telephone call with relatives or other caretakers.

OUTCOMES

The primary efficacy outcome was a composite of death from any cause at day 28, persistent complications at day 7, and persistent fever (oral temperature, ≥37.5°C [99.5°F]) on day 5. Persistent complications at day 7 were defined as the presence of dysfunction in any organ system, including cardiovascular, respiratory, central nervous system, hepatic, or renal, as outlined in the criteria described in Section S1D. Secondary outcomes were death from any cause at 28 days; measures of recovery, including time to fever defervescence (oral temperature, <99.5°F) sustained for 24 hours, duration of ventilation, duration of ICU stay, duration of hospitalization, and the time until recovery to normal sensorium (a score of 15 on the Glasgow Coma Scale, which ranges from 3 to 15, with higher scores indicating greater awareness); and safety. The Common Terminology Criteria for Adverse Events, version 5, was used to grade adverse events.

STATISTICAL ANALYSIS

We determined that the enrollment of 503 patients per group (1509 total) would provide the trial with 80% power to show a between-group difference in the primary outcome of 10 percentage points, assuming that 35% of the patients had a primary-outcome event and allowing for 10% loss to follow-up. The alpha level was adjusted to 0.017 (0.05 divided by 3) to account for three pairwise comparisons with the use of Bonferroni's correction. During a blinded interim review by the data and safety monitoring board, it was determined that a primary-outcome event had occurred in approximately 45% of the patients, so the total sample size was revised to 259 patients per group (777 total), to detect a between-group difference of 14.5 percentage points, a calculation that included a 5% loss to

Table 1. Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Doxycycline (N=265)	Azithromycin (N=263)	Combination Therapy (N=266)	All Patients (N=794)
Age — yr				
Median (IQR)	48 (35–59)	49 (38–60)	46 (35–59)	48 (36–59)
Range	16–87	15–95	15–92	15–95
Male sex — no. (%)	140 (53)	145 (55)	145 (55)	430 (54)
Coexisting illness — no. (%)				
Diabetes mellitus	43 (16)	32 (12)	41 (15)	116 (15)
Systemic hypertension	36 (14)	33 (13)	28 (11)	97 (12)
Cerebrovascular disease	4 (2)	5 (2)	2 (1)	11 (1)
Cardiovascular disease	3 (1)	5 (2)	5 (2)	13 (2)
Chronic lung disease	5 (2)	6 (2)	0	11 (1)
Chronic kidney disease	2 (1)	4 (2)	1 (<1)	7 (1)
Chronic liver disease	0	3 (1)	0	3 (<1)
Smoking history — no. (%)	55 (21)	58 (22)	47 (18)	160 (20)
Alcohol consumption ≥3 days/wk — no. (%)	61 (23)	70 (27)	60 (23)	191 (24)
Duration of fever — days†				
Median (IQR)	7 (5–10)	7 (5–10)	7 (5–10)	7 (5–10)
Range	1–20	1–20	1–15	1–20
Complications — no. (%)				
Cardiovascular‡	110 (42)	105 (40)	119 (45)	334 (42)
Respiratory§	165 (62)	164 (62)	167 (63)	496 (62)
Hepatic: total bilirubin, >2 mg/dl	150 (57)	146 (56)	129 (48)	425 (54)
Renal: creatinine, >2 mg/dl	84 (32)	82 (31)	70 (26)	236 (30)
Neurologic¶	63 (24)	48 (18)	50 (19)	161 (20)
Abnormal sensorium‖	75 (28)	78 (30)	69 (26)	222 (28)
Hematologic: platelets, <20,000/mm^3	30 (11)	41 (16)	39 (15)	110 (14)
Median no. of organs involved (IQR)	2 (1–3)	2 (2–3)	2 (1–3)	2 (1–3)
Positivity for *Orientia tsutsugamushi* on PCR — no. (%)	238 (90)	248 (94)	249 (94)	735 (93)

* To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for creatinine to micromoles per liter, multiply by 88.4. IQR denotes interquartile range, and PCR polymerase chain reaction.
† Data regarding fever duration were available for 261 patients in the doxycycline group, 260 in the azithromycin group, and 262 in the combination-therapy group.
‡ Cardiovascular complications included hypotension (systolic blood pressure, <90 mm Hg), myocarditis, and new-onset arrhythmia.
§ Respiratory complications included an oxygen saturation of less than 92% with infiltrates on chest radiography and a ratio of partial pressure of oxygen to the fraction of inspired oxygen of less than 200.
¶ Neurologic complications (including new-onset seizures, meningitis, and meningoencephalitis) were rated as severe or moderate (<12) on the Glasgow Coma Scale, which ranges from 3 to 15, with higher scores indicating greater awareness.
‖ Abnormal sensorium was defined as a value of less than 15 on the Glasgow Coma Scale.

follow-up. Thus, we planned to recruit a total of 800 patients.

The primary analysis was performed in the modified intention-to-treat population, which included all the patients who had undergone randomization except for 10 patients who had withdrawn consent and 5 who were found to be ineligible, all within 24 hours after randomiza-

Table 2. Primary and Secondary Outcomes (Modified Intention-to-Treat Population).*

Outcome	Doxycycline (N=265)	Azithromycin (N=263)	Combination Therapy (N=266)	Treatment Effect (95% CI)†		
				Combination Therapy vs. Doxycycline	Combination Therapy vs. Azithromycin	Azithromycin vs. Doxycycline
Primary outcome						
Composite of death at day 28, persistent complications at day 7, and persistent fever at day 5 — no. (%)‡				−13.3 (−21.6 to −5.1)	−14.8 (−23.1 to −6.5)	1.5 (−7.0 to 10.0)
No. of patients (%)	124 (47)	127 (48)	89 (33)			
95% CI — percentage points	41 to 53	42 to 55	28 to 39	—	—	—
P value				0.002	<0.001	0.73
Secondary outcomes						
Death at day 28 — no. (%)	29 (11)	32 (12)	35 (13)	1.22 (0.74 to 1.99)	1.09 (0.67 to 1.76)	0.90 (0.54 to 1.48)
Fever defervescence						
Patients — no./total no. (%)	249/254 (98)	238/251 (95)	242/252 (96)			
Median no. of days (IQR)§	4 (4–20)	4 (4–28)	4 (4–24)	0.90 (0.75 to 1.07)	1.00 (0.84 to 1.20)	0.90 (0.75 to 1.07)
Mechanical ventilation						
Patients — no. (%)	108 (41)	118 (45)	112 (42)			
Median duration (IQR) — hr	69 (36–128)	78 (37–132)	70 (37–128)	—	—	—
Inotropic support						
Patients — no. (%)	69 (26)	79 (30)	80 (30)			
Median duration (IQR) — hr	41 (20–59)	41 (17–76)	48 (25–73)	—	—	—
Dialysis						
Patients — no. (%)	14 (5)	12 (5)	8 (3)			
Median no. of days (IQR)	2 (1–3)	2 (1–5)	1.5 (1–3)	—	—	—
ICU stay						
Patients — no. (%)	93 (35)	105 (40)	98 (37)			
Median no. of days (IQR)	4 (2–7)	5 (2–7)	4 (2–7)	—	—	—

Median duration of hospital stay (IQR) — days	8 (7–10)	8 (7–10)	8 (7–10)	—	—	—
Recovery to normal sensorium						
Within 7 days — no./total no. (%)	49/75 (65)	45/78 (58)	42/69 (61)			
Median no. of days (IQR)	3 (1–4)	3 (1–4)	2 (2–4)	—	—	—
O. tsutsugamushi negativity on PCR						
Patients — no./total no. (%)	192/226 (85)	196/240 (82)	203/235 (86)			
Median no. of days (IQR)	3 (3–7)	1 (3–3)	1 (3–3)	1.33 (1.09 to 1.62)	1.03 (0.85 to 1.26)	1.28 (1.05 to 1.57)

* A dash indicates that the calculation was not performed. ICU denotes intensive care unit.
† For the primary outcome, the treatment effect is a risk difference, reported in percentage points. For the secondary outcomes, the treatment effect is reported as a hazard ratio. The widths of the 95% confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
‡ A total of 10 patients (3 in the doxycycline group, 4 in the azithromycin group, and 3 in the combination-therapy group) discontinued the study before day 5 or day 7 but were known to have been discharged alive. Among these patients, the outcome was imputed on the basis of the severity of their complications at the time of discharge.
§ The time until fever defervescence was not applicable in 37 patients because of death, loss to follow-up, or withdrawal of consent before 24 hours after the temperature had been recorded at less than 37.5°C (99.5°F).

tion. We also performed a sensitivity analysis in the full intention-to-treat population, which included the 15 patients who had not been included in the modified intention-to-treat population, with imputed worst-case and best-case outcomes. For patients in the modified intention-to-treat population who had discontinued the trial before day 5 or day 7 but were known to have been discharged alive, missing outcomes were imputed on the basis of the severity of their complications at the time of discharge. An unadjusted generalized linear model with a binomial distribution and identity-link function was used to calculate risk differences in the composite outcome along with the corresponding 95% confidence intervals. We used a Cox proportional-hazards model in a time-to-event analysis of death, fever defervescence, and positivity on PCR assay for *O. tsutsugamushi* DNA. In a sensitivity analysis, we used the Fine and Gray model to consider the competing risk of death in time-to-event analyses of fever defervescence. In addition, Kaplan–Meier curves were plotted, and the proportional-hazards assumptions were tested with the use of the chi-square test based on Schoenfeld residuals.

We also performed a per-protocol analysis that excluded patients who had not received at least 4 days of treatment (>50% of doses) or whose outcome data were missing. Adverse events were evaluated in the safety population, which included all the patients who had received at least one dose of a trial drug. Adverse events were compared between groups with the use of Fisher's exact test. In this analysis, the alpha level was 0.05. The widths of all 95% confidence intervals have not been adjusted for multiplicity. Limited nonprespecified post hoc analyses of subgroups of the primary outcome and recovery of abnormal laboratory results are provided in Table S5. All statistical analyses were conducted with the use of Stata 17 software (StataCorp). The statistical analysis plan was finalized before the database lock (see the Supplementary Appendix).

RESULTS

TRIAL POPULATION

From September 27, 2018, to February 11, 2022, a total of 1684 patients were screened for eligibility, and 809 underwent randomization. Ten patients withdrew consent on day 0 and were taken home by relatives. Five patients

with nonsevere typhus who had undergone randomization were found to be ineligible and were withdrawn from the trial. These patients were included in a sensitivity analysis in the intention-to-treat population (Table S2). Thus, the modified intention-to-treat population consisted of 794 patients (265 in the doxycycline group, 263 in the azithromycin group, and 266 in the combination-therapy group). The per-protocol population consisted of 755 patients (257 in the doxycycline group, 244 in the azithromycin group, and 254 in the combination-therapy group) after the exclusion of the patients who had withdrawn consent during the trial, had been lost to follow-up, had died before receiving a trial drug, or whose treatment was provided in an open-label method.

The patients in all three groups had similar demographic and clinical characteristics at baseline (Table 1). The median age was 48 years (range, 15 to 95 years), and 54% were male patients. The most common coexisting illnesses were diabetes mellitus (in 15%) and systemic hypertension (in 12%). Nearly all the patients (783 of 794 [99%]) presented with fever (median duration, 7 days). Complications were identified in the following percentages of patients: respiratory, 62%; hepatic, 54%; cardiovascular, 42%; renal, 30%; and neurologic, 20%. Microbiologic confirmation on PCR assay was available in 735 patients (92.6%).

In the modified intention-to-treat population, adherence to medication was 98% in the doxycycline group, 97% in the azithromycin group, and 97% in the combination-therapy group. The reasons for nonadherence were consent withdrawal on day 0 and death before receipt of the first dose.

PRIMARY OUTCOME

A primary-outcome event occurred in 89 of 266 patients (33%; 95% confidence interval [CI], 28 to 39) in the combination-therapy group as compared with 124 of 265 patients (47%; 95% CI, 41 to 53) in the doxycycline group, for a risk difference of –13.3 percentage points (95% CI, –21.6 to –5.1; P=0.002), and as compared with 127 of 263 patients (48%; 95% CI, 42 to 55) in the azithromycin group, for a risk difference of –14.8 percentage points (95% CI, –23.1 to –6.5; P<0.001) (Table 2 and Fig. 1A). No significant difference in primary-outcome events was found between the azithromycin group and the doxycycline group (risk difference, 1.5 percentage points; 95% CI, –7.0 to 10.0; P=0.73). The results in the sensitivity analysis were similar to those in the primary analysis (Table S2).

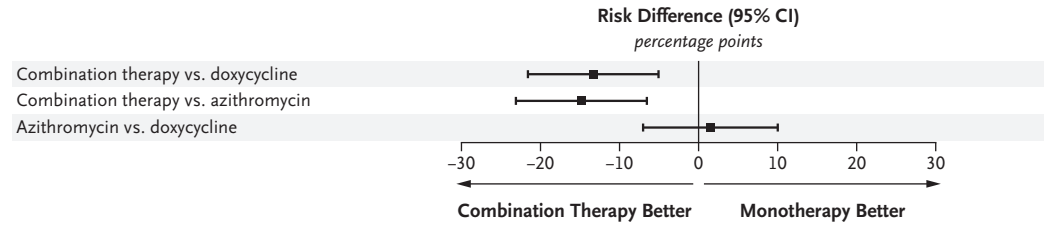
In the per-protocol analysis, a primary-outcome event occurred in 31% of the patients (95% CI, 26 to 38) in the combination-therapy group, in 46% (95% CI, 40 to 52) in the doxycycline group, and in 45% (95% CI, 39 to 52) in the azithromycin group (Table S1 and Fig. S1B), values that were similar to those in the modified intention-to-treat analysis.

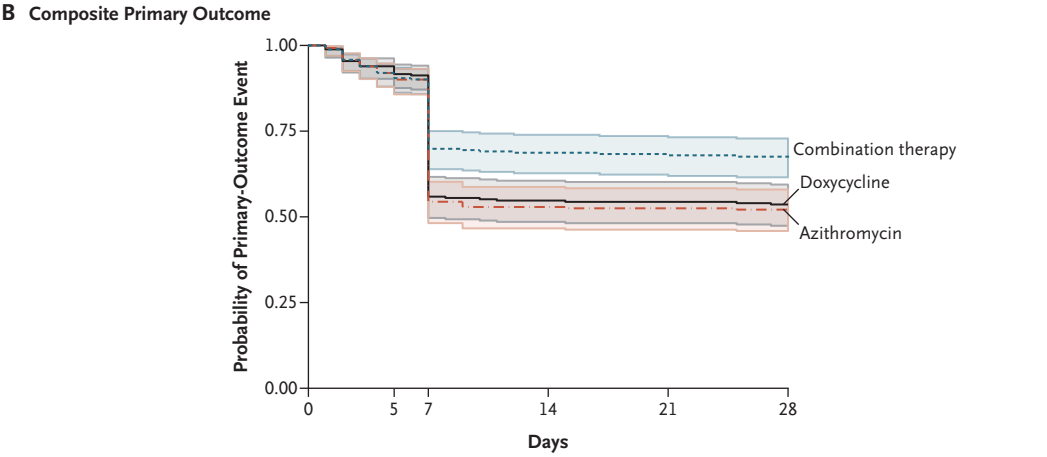
The Kaplan–Meier plots of the time between randomization and a primary-outcome event diverged between the combination-therapy group and the two monotherapy groups at day 7 in both the modified intention-to-treat analysis and the per-protocol analysis, which suggests that the between-group differences in the primary-outcome events were mainly due to persistent complications by day 7 (Fig. 1B, Fig. S1A, and Table S5).

SECONDARY OUTCOMES

The 28-day mortality was similar in the three groups, with incidences ranging from 11 to 13% (Table 2), as were the Kaplan–Meier plots of the time until death (Fig. 2A). The median time until defervescence and Kaplan–Meier plots of the time until defervescence after adjustment for the competing risk of death were also similar (Fig. 2B), as were the requirement for inotropic support, duration of ventilation, and duration of stay in the hospital and ICU. The median durations of dialysis and of abnormal sensorium in patients with a score on the Glasgow Coma Scale of less than 15 on admission were marginally lower in the combination-therapy group.

As compared with the doxycycline group, the time until bacterial DNA clearance of *O. tsutsugamushi* (PCR negativity) was shorter in both the combination group (hazard ratio, 1.33; 95% CI, 1.09 to 1.62) and the azithromycin group (hazard ratio, 1.28; 95% CI, 1.05 to 1.57) (Table S3 and Fig. 2C). The time until PCR negativity was similar in the combination group and the azithromycin group (hazard ratio, 1.03; 95% CI, 0.85 to 1.26).





No. at Risk					
Combination therapy	262	241 236	180	179	177
Azithromycin	261	240 235	138	137	136
Doxycycline	263	247 240	144	143	141

Figure 1. Composite Primary Outcome.

Panel A shows the risk differences in the primary efficacy outcome (a composite of death at day 28, persistent complications at day 7, and persistent fever at day 5) in the doxycycline group, the azithromycin group, and the combination-therapy group (which includes both drugs) in the modified intention-to-treat analysis, as reported in percentage points. Panel B shows Kaplan–Meier curves comparing the time until the primary efficacy outcome in the three groups. The shaded areas indicate 95% confidence intervals.

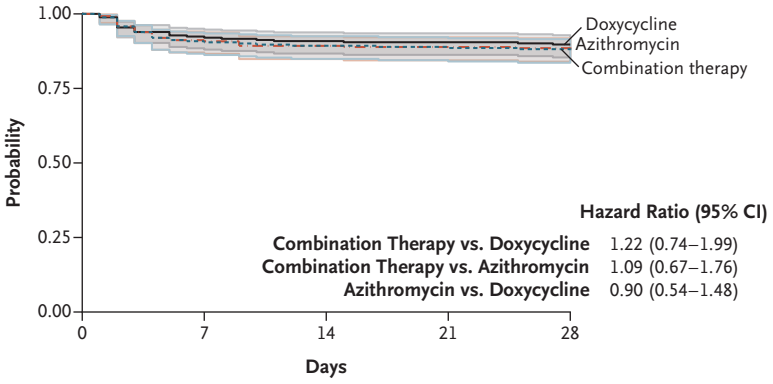
ADVERSE EVENTS

The between-group difference in the occurrence of adverse events was not significant, and the incidences of serious adverse events were similar in the three groups (Table 3). Events of grade 3 or higher were marginally more common in the azithromycin and combination-therapy groups (11% each) than in the doxycycline group (8%), but the differences were not significant. Life-threatening events were reported in 3 patients (1%) in the doxycycline group and in 5 patients (2%) in the azithromycin group. One patient in the combination-therapy group had altered behavior and an episode of self-limiting generalized tonic–clonic seizures, which was considered to be possibly treatment-related. The assigned treatment was discontinued in 42 patients (5%): 13 patients (5%) in the doxycycline group, 17 patients (7%) in the azithromycin group, and 12 patients (5%) in the combination-therapy group.

DISCUSSION

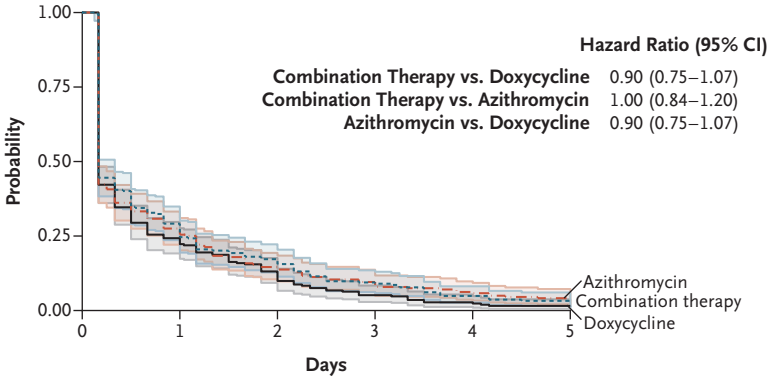
In this trial involving patients with severe scrub typhus, we found that combination therapy with intravenous doxycycline and azithromycin was superior to monotherapy with either drug with respect to the primary composite outcome of death at day 28, persistent complications at day 7, and persistent fever at day 5 in both the modified intention-to-treat and per-protocol populations. The superiority of combination

A Survival at Day 28



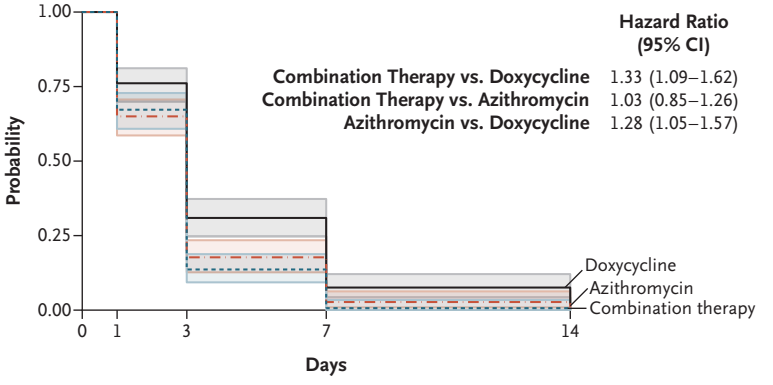
No. at Risk					
Combination therapy	262	238	234	233	231
Azithromycin	261	238	233	232	231
Doxycycline	263	243	239	238	236

B Persistent Fever



No. at Risk						
Combination therapy	252	71	42	23	12	8
Azithromycin	251	67	35	23	15	10
Doxycycline	254	61	33	13	7	4

C PCR Positivity for *Orientia tsutsugamushi*



No. at Risk					
Combination therapy	235 235	133	20	1
Azithromycin	240 240	121	26	3
Doxycycline	226 226	155	53	8

Figure 2 (facing page). Key Secondary Outcomes.
Shown are Kaplan–Meier curves comparing three key secondary outcomes in the three trial groups, including the risk of death at day 28 (Panel A), persistent fever at day 5 (Panel B), and positivity for *Orientia tsutsugamushi* on polymerase-chain-reaction assay (Panel C). The shaded areas indicate the 95% confidence intervals, which have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

therapy was mainly due to a reduced incidence of persistent complications at day 7, when the frequencies of respiratory, renal, hepatic, and central nervous system complications were lower in the combination-therapy group than in either of the monotherapy groups. As has been shown in other studies, no difference in the primary outcome was noted between the monotherapy groups.[13-15]

Severe scrub typhus is associated with substantial complications and death.[9-12,19,20] Common manifestations resulting in organ involvement include acute respiratory distress syndrome, hepatitis, hypotension or shock, meningoencephalitis, and renal failure.[12,19-22] In a post hoc analysis in our trial, complications requiring organ support (e.g., ventilatory assistance, supplemental oxygen, or dialysis) were fewer by day 7 in the combination-therapy group than in the monotherapy groups, whereas the resolution of hepatic and renal involvement was more frequent (Table S4).

Why a combination of doxycycline and azithromycin should be more clinically effective in the treatment of severe scrub typhus than either of the drugs alone is a matter of speculation. Through different mechanisms, the two drugs inhibit messenger RNA translation at the bacterial ribosome. Azithromycin binds the 23SrRNA of the 50S ribosomal subunit at the polypeptide exit tunnel, and doxycycline prevents aminoacyl-tRNA binding to the 30S ribosomal subunit.[23,24] The combination of the two drugs may result in a more complete blockade of protein synthesis with a consequently greater effect against *O. tsutsugamushi*. Better bacterial control during the critical first week of infection may result in prevention and faster resolution of severe manifestations of illness.

Because *O. tsutsugamushi* is an intracellular organism that proliferates and survives in endothelial cells and macrophages, adequate intracel-

Table 3. Safety Outcomes.*

Outcome	Doxycycline (N=263)	Azithromycin (N=261)	Combination Therapy (N=262)	All Patients (N=786)	P Value†	
					Combination Therapy vs. Doxycycline	Combination Therapy vs. Azithromycin	Azithromycin vs. Doxycycline
	number of patients (percent)						
Grade 3 or higher adverse event							
Any	21 (8)	29 (11)	29 (11)	79 (10)	0.24	1.00	0.24
Possibly treatment-related‡	0	0	1 (<1)§	1 (<1)	NA	NA	NA
Serious adverse event							
Any	30 (11)	36 (14)	31 (12)	97 (12)	0.89	0.52	0.43
Death	27 (10)	30 (11)	31 (12)	88 (11)	0.58	1.00	0.68
Life-threatening event¶	3 (1)	5 (2)	0	8 (1)	NA	NA	NA
Prolongation of hospitalization	0	1 (<1)	0	1 (<1)	NA	NA	NA
Any drug discontinuation	13 (5)	17 (7)	12 (5)	42 (5)	1.00	0.35	0.46

* The safety population included all the patients who had received at least one dose of a trial drug. NA denotes not applicable.
† P values were calculated with the use of Fisher's exact test.
‡ The investigators made the determination regarding whether an adverse event was possibly related to a trial drug.
§ One patient had altered behavior and an episode of self-limiting generalized tonic–clonic seizures, which was considered to be possibly treatment-related. The patient recovered fully and survived.
¶ In the doxycycline group, one patient had a seizure and cardiac arrest, one had pulmonary edema, and one had severe hypotension. In the azithromycin group, three patients had respiratory failure, one patient had a cardiac arrest secondary to hypoxia, and one had hypotension, myocarditis, and acute respiratory distress syndrome.

lular antibiotic concentrations are essential.[25,26] Both antibiotics have excellent tissue penetration, and azithromycin accumulates intracellularly to concentrations that are 100 times as high as those in plasma.[23,27,28] This penetration of azithromycin into eukaryotic and prokaryotic cells explains its broad spectrum of activity, specifically against intracellular pathogens. The more rapid clearance of *O. tsutsugamushi* DNA from the buffy coat in both of the azithromycin-containing regimens may reflect this factor and explain why adding azithromycin to doxycycline (the usual drug of choice for rickettsial infections, including scrub typhus) leads to improved clinical outcomes in severe disease.

Because the clinical care of the critically ill patients in our trial was complex, the masked treatment in approximately 2% of the patients was discontinued and made open-label by treating physicians. Children and pregnant women were excluded from the trial. The use of doxycycline was previously thought to be relatively contraindicated in early childhood, but the consensus on this recommendation has changed and such use is now considered to be reasonable in children under 8 years of age, especially in the context of life-threatening disease.[29,30] Generalizing the safety findings of our trial to young children and pregnant women is not possible, although such extrapolation may be reasonable for the efficacy findings.

This trial provides evidence that combination therapy with intravenous doxycycline and azithromycin is a better therapeutic option for the treatment of severe scrub typhus than monotherapy with either drug.

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APPENDIX

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