Synergistic sulfonamides plus clindamycin as an alternative therapeutic regimen for HIV-associated Toxoplasma encephalitis: a randomized controlled trial

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Abstract

Background: The preferred therapeutic regimen for Toxoplasma encephalitis (TE) is a combination of pyrimethamine and sulfadiazine, and trimethoprim-sulfamethoxazole (TMP-SMX) plus azithromycin is the widespread alternative therapeutic regimen. The synergistic sulfonamides tablet contains TMP, sulfadiazine, and SMX and hypothetically could be used for TE treatment. This study aimed to compare the efficacy and safety of synergistic sulfonamides plus clindamycin (regimen B) with TMP-SMX plus azithromycin (regimen A) for the treatment of human immunodeficiency virus (HIV) associated TE.

Methods: This was an open-labeled, multi-center randomized controlled trial recruited from 11 centers. Each recruited patient was randomly assigned to receive regimen A or regimen B for at least 6 weeks. The overall response was evaluated by assessment of the clinical response of TE-associated clinical features and the radiological response of TE-associated radiological findings. The overall response rate, clinical response rate, radiological response rate, and adverse events were assessed at 2, 6, and 12 weeks. Death events were compared between the two regimens at 6, 12, and 24 weeks.

Results: A total of 91 acquired immunodeficiency syndrome (AIDS)/TE patients were included in the final analysis (44 in regimen A *vs*. 47 in regimen B). The overall response rate, which refers to the combined clinical and radiological response, was 18.2% (8/44) for regimen A and 21.3% (10/47) for regimen B at week 6. The results of clinical response showed that, in comparison with regimen A, regimen B may perform better with regards to its effect on the relief of clinical manifestations (50.0% [22/44] *vs*. 70.2% [33/47], $P = 0.049$). However, no significant differences in radiological response, mortality events, and adverse events were found between the two regimens at week 6.

Conclusions: Synergistic sulfonamides plus clindamycin, as a novel treatment regimen, showed no significantly different efficacy and comparable safety in comparison with the TMP-SMX plus azithromycin regimen. In addition, the regimen containing synergistic sulfonamides may exhibit advantages in terms of clinical symptom alleviation.

Trial Registration: ChiCTR.org.cn, ChiCTR1900021195.

Keywords: Clindamycin; Efficacy; Human immunodeficiency virus/acquired immunodeficiency syndrome; Safety; Synergistic sulfonamides; Toxoplasma encephalitis

Introduction

Toxoplasma encephalitis (TE), caused by the obligate intracellular parasitic protozoan eukaryote *Toxoplasma gondii* (*T. gondii*), is a life-threatening infection in human immunodeficiency virus (HIV)-infected patients. HIV-infected patients are particularly susceptible to TE, especially so among those who are Toxoplasma immunoglobulin G (IgG) seropositive, have a $CD4^+$ T-cell count less than 200 cells/μL, are not on antiretroviral therapy (ART), or are not receiving trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis.[1] The prevalence of co-infection with HIV and *T. gondii* is as high as between 25.1% and 60.7%, and the prevalence rates differ in different countries.[2] In addition, the in-hospital mortality of HIV-associated TE remains as high as 29.9% (29/97), as observed in a cross-sectional study conducted from 2004 to 2009 in Cameroon.[3] Therefore, co-infection with HIV and *T. gondii* continues to be a substantial global public health concern.[4]

The preferred therapeutic regimen for TE advocated by the Department of Health and Human Services (DHHS) of the USA, the European acquired immunodeficiency

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syndrome (AIDS) Clinical Society (EACS), and the British HIV Association is the combination of pyrimethamine and sulfadiazine (P-S).[5-7] Unfortunately, limited availability of both P-S in China prevents the utilization of this regimen locally. The DHHS guidelines recommend that TMP-SMX may be used as a substitute if pyrimethamine is not readily available.[8] At present, TMP-SMX plus either azithromycin or clindamycin is the alternative therapeutic regimen with widespread usage within China.[9]

The synergistic sulfonamides tablet contains TMP, sulfadiazine, and SMX and was first produced in China. As a compound preparation, it has been found that synergistic sulfonamides can safely and effectively be utilized against a wide pathogenic microbial spectrum, with a robust bactericidal effect.[10] We therefore hypothesized that this combination could possibly be used for the management of TE due to its similarity to the compositional elements of TMP-SMX. We subsequently designed the present open-labeled, multi-center, randomized trial to evaluate the efficacy and safety of synergistic sulfonamides combined with clindamycin as an alternative therapy for TE in AIDS patients.

Methods

Ethical approval

This study was approvaled by the Ethics Committee of Chongqing Public Health Medical Center (No. 2019-003-02-KY), and the procedures followed were in accordance with the *Declaration of Helsinki* 1975, as revised in 2000 (available at http://www.wma.net/e/policy/17-c_e.html). The study protocol was approved by the Ethics Committee of each of the 11 study centers involved in the trial before the study commenced, and informed consent was obtained from each enrolled patient and/or their legal guardian(s).

Study design

This was an open-labeled, multi-center, randomized, controlled trial. Patients were recruited from 11 study centers according to strict inclusion and exclusion criteria.[11] The 11 study centers were Chongqing Public Health Medical Center, Beijing Youan Hospital of Capital Medical University, the First Hospital of Changsha, Liuzhou People's Hospital, the Third People's Hospital of Shenzhen, Guiyang Public Health Clinical Center, Public Health Clinical Center of Chengdu, the Third People's Hospital of Kunming, Yunnan Infectious Disease Hospital, the Fourth People's Hospital of Nanning, and Chest Hospital of Guangxi Zhuang Autonomous Region. The primary objective of the study was to evaluate and compare the efficacy and safety of synergistic sulfonamides plus clindamycin as a novel therapeutic regimen, with TMP-SMX plus azithromycin for the treatment of TE in AIDS patients.

Randomization and masking

A specific random number sequence was generated by clinical researchers using Medical Research Platform (http://www.51yyt.org/FrontPage/login.aspx? Inviter=) for each patient with consent, and this number was used to randomly stratify patients into either the synergistic sulfonamides plus clindamycin group or the TMP-SMX plus azithromycin group at a ratio of 1:1.

Inclusion criteria

The inclusion criteria are as follows: (1) participants aged 18 years or older; (2) participants diagnosed with TE based on the following criteria: (a) clinical manifestations such as headache, focal neurological deficit, fever, mental confusion, seizures, psychomotor, or behavioral changes; (b) computed tomography (CT) or magnetic resonance imaging (MRI) scans show cerebral ring-enhancing lesions, especially in the basal ganglia; (c) positive anti-Toxoplasma IgG or IgM antibody test, Toxoplasma antigen test, Toxoplasma deoxyribonucleic acid (DNA) detection by polymerase chain reaction, or *T. gondii* staining; and (d) effectiveness of anti-Toxoplasma treatment; and (3) participants who provided informed consent.

Exclusion criteria

The exclusion criteria are as follows: (1) participants allergic or intolerant to therapeutic medications to be used in this study; (2) participants who had hemoglobin <60 g/L, white blood cell count $<1.0 \times 10^9$/L, neutrophil count $<0.5 \times 10^9$/L, platelet count $<50 \times 10^9$/L, blood amylase $>2 \times$ upper normal limit (UNL), serum creatinine $>1.5 \times$ UNL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or alkaline phosphatase $>5 \times$ UNL, total bilirubin $>2 \times$ UNL, or serum creatine phosphokinase $>2 \times$ UNL; (3) participants who were pregnant or breastfeeding; (4) participants who had used intravenous recreational drugs; and (5) participants who were not Chinese.

Treatment arms

Each patient was randomly assigned to receive either of the following two regimens. Regimen A: TMP-SMX given orally at a dose of 1.44 g every 8 h plus azithromycin given intravenously at a dose of 0.5 g once a day for at least 6 weeks. Regimen B: Synergistic sulfonamides given orally at a dose of 1.44 g every 8 h plus clindamycin given intravenously at a dose of 0.6 g every 6 h for at least 6 weeks.

Outcomes

The overall response was evaluated by assessment of the clinical response of TE-associated clinical features and the radiological response of TE-associated radiological findings, as described previously.[12] The efficacy, including overall response rate, clinical response rate, and radiological response rate were assessed at 2, 6, and 12 weeks. Death events were compared between the two regimens at 6, 12, and 24 weeks. Adverse events including gastrointestinal symptoms, anemia, leukopenia, thrombocytopenia, liver injury, and renal injury were assessed at 2, 6, and 12 weeks.

The overall response rate was defined as the clinical symptomatic response together with radiological response.

Clinical response refers to the situation where patients who had fever, nausea/vomiting, central neurological symptoms such as headache, disorders of consciousness, skeletal muscle symptoms such as twitch and hemiplegia at baseline, and at least one of these TE-related clinical symptoms was improved or resolved after treatment. Also, CT or MRI scans of AIDS/TE patients typically show cerebral ring-enhancing lesions, especially in the basal ganglia. Thus, in our study, radiological response refers to an improved, disappeared, or reduced lesion showed in the results of CT or MRI subsequent to drug treatment compared with imaging results obtained before drug treatment.

Statistical analysis

All data analyses were executed using Statistical Package for the Social Sciences (SPSS) software (Version 25.0, IBM-SPSS, Armonk, NY, USA). Continuous variables were described as median (Q_1, Q_3), depending upon the distribution. The Mann–Whitney *U* test was performed to assess differences between the two therapeutic regimens. Categorical variables were calculated as percentages and were assessed using the Chi-squared test or Fisher's exact test, where appropriate. A *P* value of 0.05 was deemed to indicate statistical significance.

Results

Characteristics of included AIDS/TE patients

Ninety-nine AIDS/TE patients were assessed for eligibility at baseline. Among them, seven had been medicated with TE-related drugs before randomization and one had a history of intravenous recreational drug use and were excluded. Therefore, a total of 91 AIDS/TE patients were included in the final study analysis, and 44 of them were randomly assigned to receive regimen A and 47 were randomly assigned to receive regimen B.

The baseline characteristics of the 91 included patients [Table 1] showed that there were no significant differences in demographic characteristics such as median age (41 [32, 47] years *vs.* 40 [33,48] years, $Z = 0.505$, $P = 0.613$) and gender composition (male, 33/44 *vs.* 36/47, $\chi^2 = 0.032$, $P = 0.859$) between the patients in the two groups. There was also no significant difference in TE-related clinical symptoms between the two groups, such as fever (15/44 *vs.* 16/47, $\chi^2 = 0$, $P = 0.996$), nausea or vomiting (13/44 *vs.* 12/47, $\chi^2 = 0.184$, $P = 0.668$), and disorders of consciousness (5/44 *vs.* 8/47, $\chi^2 = 0.594$, $P = 0.441$). Also, no significant difference was observed with regard to the incidence of other coexisting opportunistic infections between patients given regimen A and regimen B (9 of 44 in regimen A *vs.* 11 of 47 in regimen B, $P = 0.734$). However, significantly more subjects who were assigned to regimen B manifested with headaches than those assigned to regimen A (21/44 *vs.* 35/47, $P = 0.009$).

In addition, the differences in related laboratory test results between the two groups, such as $CD4^+$ T-cell counts, HIV ribonucleic acid (RNA), ALT, AST, creatinine, hemoglobin, leukocytes, and neutrophils were all found to not be significantly different, except for platelet counts. The above results indicate that the main clinical characteristics related to HIV and TE in the two groups were basically similar at baseline, as illustrated in Table 1.

Table 1: Characteristics of AIDS/TE patients at baseline.

Characteristics	Regimen A ($n = 44$)	Regimen B ($n = 47$)	χ^2/Z	*P* values
Gender, male	33 (75)	36 (77)	0.032	0.859
Age (years)	41 (32, 47)	40 (33, 48)	0.505*	0.613
Weight (kg)	56 (50, 64)	55 (49, 65)	0.108*	0.914
Combined with other central nervous system infection	7 (16)	5 (11)	0.551	0.458
Combined with other opportunistic infection	9 (20)	11 (23)	0.115	0.734
Single or multiple focal lesions	9 (20)	6 (13)	0.976	0.323
Clinical manifestations				
Fever	15 (34)	16 (34)	0.000	0.996
Headache	21 (48)	35 (74)	6.866	0.009
Disorders of consciousness	5 (11)	8 (17)	0.594	0.441
Nausea/vomiting	13 (30)	12 (26)	0.184	0.668
Laboratory tests				
Hemoglobin (g/L)	118.5 (97.3, 130.0)	111.0 (96.0, 127.0)	1.108*	0.268
Platelets ($\times 10^9$/L)	177.5 (130.5, 243.0)	151.0 (108.0, 188.0)	2.113*	0.035
Leukocyte ($\times 10^9$/L)	4.6 (3.5, 6.5)	4.6 (3.4, 7.8)	0.266*	0.790
Neutrophils ($\times 10^9$/L)	3.0 (2.0, 4.6)	3.0 (2.1, 6.1)	0.226*	0.821
Creatinine (μmol/L)	58.1 (51.8, 66.1)	55.7 (48.8, 66.7)	0.798*	0.425
ALT (IU/L)	21.0 (14.0, 49.8)	24.5 (13.5, 42.5)	0.327*	0.744
AST (IU/L)	25.5 (19.0, 35.8)	24.0 (18.0, 32.3)	0.662*	0.508
$CD4^+$ T-cell count (cells/μL)	40.0 (11.8, 94.5)	45.0 (15.5, 92.5)	0.106*	0.915
CD4/CD8	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.554*	0.579
HIV RNA log(10)	5.5 (4.7, 5.9)	5.2 (4.2, 5.7)	1.108*	0.268

*Z values. Data are presented as *n* (%) or median (Q_1, Q_3). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CD: Cluster of differentiation; HIV: Human immunodeficiency virus; RNA: Ribonucleic acid.

Medication during the 6-week treatment course

In total, 54 AIDS/TE patients (28 receiving regimen A and 26 receiving regimen B), completed the 6-week follow-up, and among them, 92.8% (26/28) in the regimen A group and 88.5% (23/26) in the regimen B group finished a complete 6-week course of anti-*T. gondii* treatment. Two patients who received regimen A did not complete the prescribed treatment course; one patient ceased the treatment at week 2 due to the development of drug-induced dermatitis, and the dosage of prescribed drugs for another patient was decreased at week 4. With respect to patients in regimen B, three of them did not complete the full anti-*T. gondii* drug treatment, among which one patient stopped the treatment at week 2 due to development of skin rashes, one patient had the dosage of prescribed drugs reduced at week 4, and one patient succumbed to their illness at day 39.

Overall clinical and radiological response at 2, 6, and 12 weeks

In our study, there was no statistical difference in the overall response rate between the two therapeutic groups at 2, 6 (time point of completion of the treatment), and 12 weeks, in both the intention-to-treat (ITT) population and the modified ITT (mITT) population, as shown in Figure 1. Additionally, there were no significant differences in the clinical symptom response rate between the two regimens at 2 and 12 weeks. However, at week 6, the clinical response rate among patients who were prescribed synergistic sulfonamides plus clindamycin was significantly higher than that among those who were prescribed TMP-SMX plus azithromycin (70.2% [33/47] *vs.* 50.0% [22/44], $P = 0.049$ in the ITT analysis; 76.7% [33/43] *vs.* 55.0% [22/40], $P = 0.036$ in the mITT With respect to radiological response, there was no statistically significant difference in the radiological response rate between the two groups at 2, 6, and 12 weeks.

Mortality events and adverse events during follow-up

At 6, 12, and 24 weeks, there was no observed statistical difference between the two regimens with regards to mortality events, as shown in Figure 2.

Skin changes were found in one patient in each group, and this incidence was not statistically significant, with one case of skin rash in the group allocated regimen A and one case of drug-induced dermatitis in the group using regimen B. Gastrointestinal symptoms were common in patients who were treated with either of the therapeutic regimens, but the frequency of these symptoms was not significantly different between the two groups (25.0% in regimen A *vs.* 14.9% in regimen B, $P = 0.226$, at week 6). In addition, no cases of abnormal creatinine levels were found in patients treated with either of the two regimens. Several patients in both groups showed evidence of hepatic dysfunction, with high ALT and AST (>200 IU/L) being observed, but these hepatic changes were analyzed and found to be not statistically significant in a comparison between the two groups. Additionally, abnormal leukocyte counts were frequently observed in both treatment groups. However, hematological adverse reactions including aberrant leukocyte counts, hemoglobin levels, platelet counts, and neutrophil counts were calculated to be mathematically similar between the two groups during the study period, as shown in Table 2.

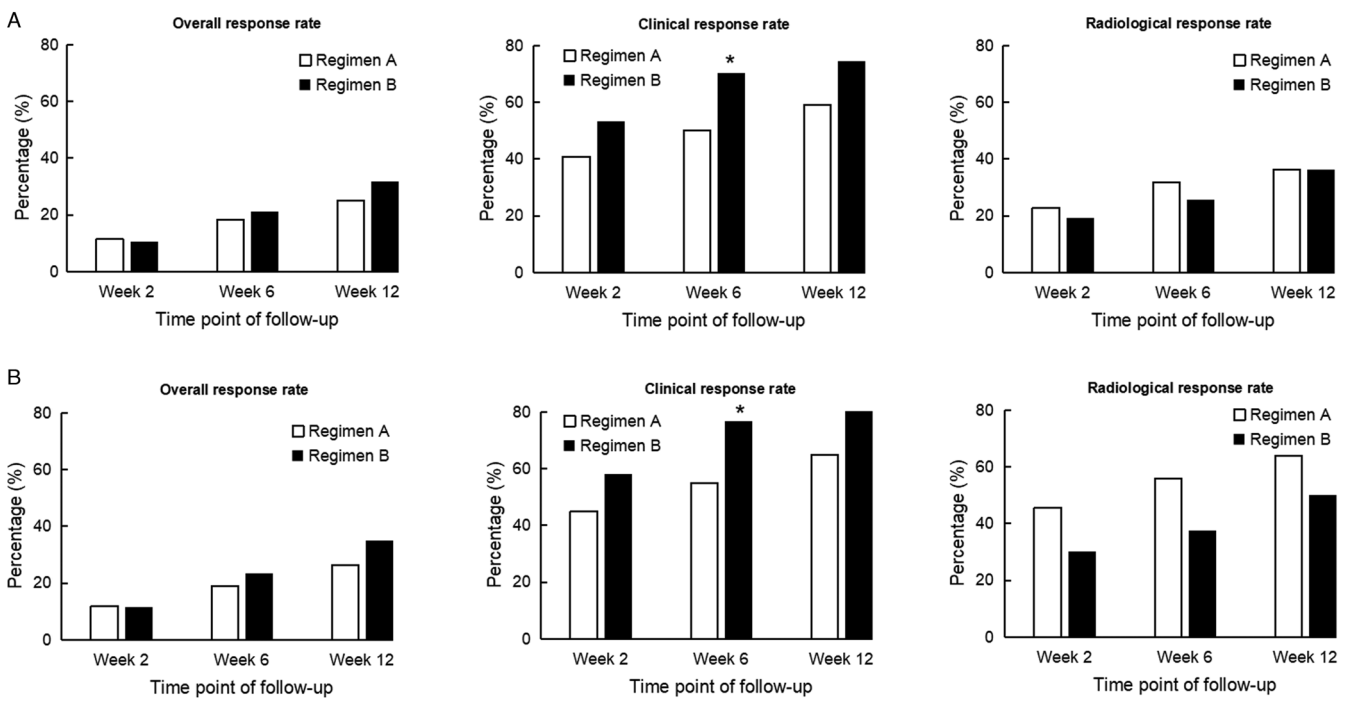

Figure 1: ITT (A) and mITT(B) analysis of overall response rate, clinical response rate, and radiological response rate of the two therapeutic regimens at 2, 6, and 12 weeks. $^{*}P < 0.05$. ITT: Intention-to-treat; mITT: modified ITT.

Discussion

Pyrimethamine plus sulfadiazine is the preferred therapeutic regimen for the treatment of HIV-associated TE and is recommended by several international guidelines.[5-7] However, due to the poor accessibility to these drugs in China, TMP-SMX plus azithromycin or clindamycin are alternative regimens widely utilized in China. In addition, previous studies have confirmed that, in comparison to pyrimethamine plus sulfadiazine, treatment with TMP-SMX resulted in a similar complete or partial clinical response (RR = 0.97, 95% confidence interval [CI]: 0.78–1.21) and a similar skin rash rate (RR = 0.17, 95% CI: 0.02–1.29).[13] Moreover, one meta-analysis demonstrated that when the pooled cure rate was used to evaluate the overall rate of complete disappearance of clinical symptoms for TE after therapy, the pooled cure rates of pyrimethamine-sulfadiazine, TMP-SMX, and pyrimethamine-clindamycin were 49.8% (95% CI: 38.8–60.8%), 59.9% (95% CI: 48.9–70.0%), and 47.6% (95% CI: 24.8–71.4%), respectively, with no statistical difference being found between cure rates for these drug combinations.[14]

In 1976, the synergistic sulfonamide tablet, which consists of SMX, sulfadiazine, and TMP, was first marketed in China as a compound preparation. In order to reduce costs by saving raw materials, the dose of SMX in the synergistic sulfonamide tablet was reduced to half dose in the TMP-SMX formulation.[10] A second sulfonamide drug, sulfadiazine, as a supplementary active ingredient, was added to the pharmacological formulation in the synergistic sulfonamide preparation. It has been shown that synergistic sulfonamides have similar antibacterial effects *in vitro* and *in vivo* to TMP-SMX.[10] However, there is lack of sufficient clinical evidence regarding the efficacy and safety of synergistic sulfonamides for the treatment of *T. gondii* infection. We therefore conducted the present randomized controlled trail in order to compare the efficacy and safety of synergistic sulfonamides plus clindamycin to a preferred alternative regimen recommended by current guidelines, that is, TMP-SMX plus azithromycin.

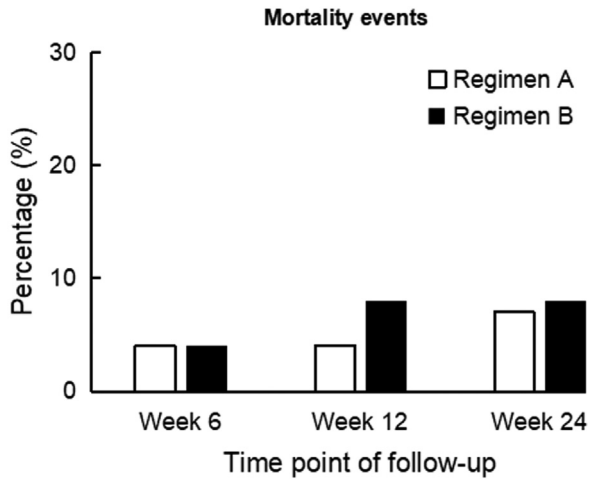

Figure 2: Mortality events for regimen A and egimen B at 6, 12, and 24 weeks.

The results of our study suggest that synergistic sulfonamides plus clindamycin as a new combination treatment regimen displays robust efficacy and safety for the treatment of HIV-associated TE. We observed that the clinical response attributable to synergistic sulfonamides plus clindamycin was 76.7% (33/43), the radiological response was 37.5% (12/32) at week 6. These results were comparable to those observed in previous studies. For example, one randomized controlled trial[15] reported that the calculated clinical response rates of TMP-SMX (10 mg of TMP per kg/day plus 50 mg of SMX per kg/day every 12 h) and of pyrimethamine-sulfadiazine (pyrimethamine 50 mg daily, and sulfadiazine 60 mg/kg of body weight/day) were 62.1% (23/37) and 65.7% (23/35), respectively, among AIDS/TE patients after 1 month of treatment, and the complete radiological response of these two regimens were 62.1% (23/37) and 39.3% (13/33), respectively, at the same time point. With regards to adverse reactions, such as skin rash, gastric disturbances, toxic effects on the liver, toxic effects on the kidneys, leukopenia, neutropenia, pancytopenia, and thrombocytopenia, the results in another study[15] showed that the rate of these adverse events was 12.5% (5/40) among patients with AIDS and TE who were treated with TMP-SMX during the 1 month of acute therapy and the 3 months of maintenance therapy and was 37.8% (14/37) among those who were treated with pyrimethamine-sulfadiazine. Skin rash was the most common adverse event noted in patients treated with pyrimethamine-sulfadiazine. Another randomized controlled study[16] also showed that the adverse events, including drug allergy, severe skin rash, Stevens-Johnson syndrome, bone marrow suppression, pancytopenia, and

Table 2: Adverse effects of the two therapeutic regimens at 2, 6 and 12 weeks.

Characteristics	Adverse events at week 2			Adverse events at week 6			Adverse events at week 12		
	Regimen A ($n = 44$)	Regimen B ($n = 47$)	*P* values	Regimen A ($n = 44$)	Regimen B ($n = 47$)	*P* values	Regimen A ($n = 44$)	Regimen B ($n = 47$)	*P* values
Skin rash/drug-induced dermatitis	1 (2)	1 (2)	1.000	1 (2)	1 (2)	1.000	1 (2)	1 (2)	1.000
Gastrointestinal symptoms	5 (11)	4 (8)	0.917	11 (25)	7 (15)	0.226	11 (25)	7 (15)	0.226
Platelets $<50 \times 10^9$/L	1 (2)	2 (4)	1.000	4 (9)	3 (6)	0.928	4 (9)	2 (4)	0.613
Neutrophils $<0.5 \times 10^9$/L	1 (2)	0	0.974	2 (4)	1 (2)	0.954	2 (4)	1 (2)	0.954
Creatinine >221 μmol/L	0	0	–	0	0	–	0	0	–
AST >200 IU/L	0	0	–	1 (2)	4 (8)	0.398	1 (2)	4 (8)	0.398

Data are presented as *n* (%). AST: Aspartate aminotransferase; –: Not applicable.

thrombocytopenia occurred at a rate of 60.0% (6/10) in patients who were prescribed pyrimethamine-clindamycin (pyrimethamine 50 mg/day plus sulfadiazine 4 g/day or pyrimethamine 100 mg/day plus sulfadiazine 4 g/day) and was 0.0% (0/10) in patients receiving TMP-SMX (trimethoprim 10 mg · kg^{-1} ·day^{-1} plus sulfamethoxazole 50 mg · kg^{-1} · day^{-1}) after receiving 2 to 6 weeks of treatment.

In comparison with TMP-SMX plus azithromycin, synergistic sulfonamides plus clindamycin showed a non-significant different effect on overall response rate, radiological response rate, and adverse events at 2, 6, and 12 weeks. However, 33 of 43 (76.7%) patients who received synergistic sulfonamides in combination of clindamycin had a clinical response at week 6, and at the same time point, only 22 of 40 (55.0%) subjects treated with TMP-SMX plus azithromycin showed a clinical response. Our results show that, in comparison with TMP-SMX plus azithromycin, synergistic sulfonamides plus clindamycin may perform more efficaciously in relieving clinical symptoms in a statistically significant manner ($P = 0.036$ in the mITT population). At 2 and 12 weeks, the differences in clinical response between the two regimens were not observed to be significant. Although the two regimens showed non-significant differences in overall response rates and safety, the regimen containing synergistic sulfonamides showed a slight advantage in terms of control of clinical manifestations.

We acknowledge a few limitations to the present study. Firstly, we did not achieve our target of 200 study participants due to the fact that the number of newly diagnosed HIV-associated TE cases in China has decreased sharply as a result of widespread ART coverage within China. Secondly, the drop-out rate was relatively high at week 6 (40.6%, 37 of 91), and this is likely to introduce a degree of selection bias (especially follow-up bias) to our study when assessing our main outcomes. Thirdly, it would have been more appropriate and valid to detail the efficacy and safety of synergistic sulfonamides if the preferred recommended treatment regimen (pyrimethamine plus sulfadiazine) could have been used in our study as a control regimen.

In conclusion, synergistic sulfonamides plus clindamycin as a novel therapeutic combination regimen for the treatment of AIDS/TE displayed a statistically non-significant difference in efficacy in clinical and radiological responses and a favorable but non-significantly different safety profile on analysis of adverse events. Although in comparison with TMP-SMX plus azithromycin, synergistic sulfonamides plus clindamycin showed a statistically non-significant difference in overall response rate and safety; the regimen containing synergistic sulfonamides may have a small advantage in terms of its effect on controlling clinical symptoms. Whether the preceding observations may be safely extrapolated to non-AIDS populations or to non-Chinese racial populations warrants further study.

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Conflicts of interest

None.

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