Fixed-dose combination versus separate drug formula for pulmonary and extrapulmonary tuberculosis

Maha M. El-Kholy, Samiaa H. Sadek, Osama Mahran

Introduction The prescription of an effective and well-tolerated antituberculosis (TB) treatment regimen is an important step in the management of TB.

Objective The aim of the present study was comparison between fixed-dose combination (FDC) anti-TB drugs and separate drug formula (SDF) not only in pulmonary tuberculosis (PTB) but also in extrapulmonary tuberculosis (EPTB).

Patients and methods A total of 240 patients with TB were included in the present study: 122 patients had PTB and 118 had EPTB. Both patients with PTB and those with EPTB were divided into two groups according to receiving FDC or SDF. All patients had baseline clinical and laboratory data, including blood picture, liver function tests, renal function tests, erythrocyte sedimentation rate, uric acid, and chest radiography. Follow-up clinical, laboratory, and radiology assessments were done during the course of treatment. Patients who received FDC and those who received SDF were compared for clinical, laboratory, radiological improvement, and sputum conversion in PTB during the course of treatment; moreover, they were compared for drug tolerance, compliance with treatment, and development of adverse effects.

Results Both FDC and SDF in PTB and EPTB had comparable effect with respect to clinical improvement, and also sputum conversion in PTB; significant change in liver function was observed in PTB among those who received FDC, but better radiological clearance was detected with SDF. Both regimens were comparable with respect to compliance and adverse effects, except for more gastric disturbance with FDC.

Conclusion SDF is recommended in patients with borderline liver function, gastrointestinal troubles, and presence of extensive radiological infiltrate.

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Department of Chest, Assiut University Hospitals, Assiut, Egypt

Correspondence to Samiaa H. Sadek, Department of Chest, Faculty of Medicine, Assiut University, Assiut University Hospital, Assiut University, Assuit 71111, Egypt Tel: + 20 100 676 9597; fax: +20 882 333 327; e-mail: samiaa_sadek@yahoo.com

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Introduction

Tuberculosis (TB) is considered a public health problem as it does not only threaten the life of the patients but also affects the community. The WHO documented that the incidence of TB worldwide in 2015 was 10.4 million cases, with 5.9 million cases were in men and one million cases in children [1]. It also reported 1.4 million deaths owing to TB, with 480 000 cases having developed multidrug-resistant TB in 2015 [1]. The aims of treating TB are achievement of patient cure and decreasing incidence of transmission to other personnel. Any body organ can be involved by TB, and the principle line of treatment is the same for both pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB) [2]. Treatment strategy for infection with susceptible strains involves initiation phase of 2 months with four-drug regimen [rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol], followed by maintenance phase of 4 months with two drugs only (RIF and INH). Regimen containing RIF and INH was proved by many randomized controlled study to be effective in all EPTB when used for 6–9 months, except for TB meningitis which needs extended duration of up to 12 months [3,4]. The fixed-dose combination (FDC) regimen had been introduced in the management of TB instead of separate drug formula (SDF) aiming to simplify treatment and reduce error, in addition to improvement of adherence and compliance to treatment regimen [5]. Some studies have evaluated FDC versus SDF in the management of PTB [6,7], but to the best of our knowledge, no study has previously evaluated FDC regimen versus SDF in EPTB in our locality, so this study was performed aiming at evaluating efficacy, safety, compliance, and adverse effects of FDC versus SDF in both PTB and EPTB.

Patients and methods

The present cohort observational study was conducted in Assiut University and Chest Hospitals. A total of 257 patients with TB were recruited from outpatient clinic; 17 patients were excluded as they did not complete the course of treatment. The remaining 240 patients were included: 122 patients with PTB and 118 patients with EPTB.

Ethical approval

Informed written consents were obtained from all patients according to the National Ethics Committee.

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Patients were subdivided into two groups: those who received FDC and those who received SDF. PTB cases in the present study included 88 patients diagnosed as having smear-positive PTB (a case with PTB with one or more sputum smear positive for acid-fast bacilli in the presence of a functional external quality assurance system with blind rechecking) [8], and 34 patients diagnosed as smear-negative PTB (a case which fulfill the following criteria: at least two smear negative for AFB, radiology consistent with active TB, no response to a course of broad spectrum antibiotics, and decision by clinician to start anti-TB treatment) [8]. The cases of EPTB were diagnosed according to WHO, 2013 [8] criteria (evidence of *Mycobacterium tuberculosis* in one specimen, or histology, or strong clinical criteria of active EPTB associated with decision by clinician to start anti-TB therapy) [8].

All patients in our study had the following data collected: clinical data including history of fever and anorexia, and in case of PTB, and some cases of EPTB, history of cough and hemoptysis, and baseline laboratory data including complete blood picture, liver function tests, renal function, uric acid level, and erythrocyte sedimentation rate (ESR). In the case of PTB, baseline chest radiography was obtained with subsequent classification into minimal, moderate, and far-advanced TB [9].

All patients were followed, while they received anti-TB treatment, for monthly clinical improvement, and also for sputum conversion for negative AFB in case of smear-positive PTB cases. Follow-up laboratory data were obtained every 2 months. In addition to assessment of development of adverse effects of drugs, adherence and compliance with treatment were also recorded.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM Corp. Released2011; IBM SPSS Statistics for Windows, Version 20.0; IBM Corp., Armonk, NY) software. The results were expressed as mean±SD or frequencies. Independent Student's *t*-test was done for comparison between two groups, and *P* values of less than 0.05 were considered significant. Figures were done using Microsoft Excel, 2010 (Microsoft Corporation, Redmond, WA, USA).

Results

A total of 257 patients were included in the present study; 17 patients were excluded as they were lost to follow-up. Regarding demographic data, 122 patients had PTB, and 118 patients had EPTB. Patients in both groups were characterized by young age (32.43±9.44 and 30.36±7.94 for PTB and EPTB, respectively), predominance of male sex, and smoking habit (Table 1). With respect to clinical data of patients with PTB, we did not observe significant differences between patients who received FDC and those who received SDF. Sputum conversion to negative for AFB (acid fast bacilli) was comparable for both groups. For patients with EPTB, no significant differences were detected with respect to clinical variables for patients who received FDC and those who received SDF (Table 2). Patients with PTB and EPTB in the present study were characterized by leukocytosis, anemia, and upper limit of normal platelet count, which improved significantly during the course of treatment with FDC regimen as well as SDF (Fig. 1). Although liver function tests were within normal range during the course of treatment for both regimens in PTB and EPTB, significant increase in their level from baseline to the sixth month of course of treatment was more common with FDC regimen especially in PTB group (Fig. 2). Abnormal increase in AST level was observed only in six cases with PTB and four cases with EPTB, with no significant difference between those who received FDC or SDF. Both FDC and SDF significantly decreased ESR during course of treatment of patients with PTB and those with EPTB. Blood urea nitrogen significantly increased with treatment except for FDC in PTB; although uric acid level showed some significant changes up and down in both groups with SDF and FDC, it was still within normal range. Moreover, serum creatinine level significantly increased in both groups that received either FDC or SDF but was within normal range (Fig. 3). FDC and SDF in PTB produced significant radiological improvement but larger percentage of complete radiological resolution was

Table 1 Demographic of the studied groups

Variables	Pulmonary tuberculosis (*n*=122)	Extrapulmonary tuberculosis (*n*=118)	*P* value
Age (years)	32.43±9.44	30.36±7.94	NS
Sex [*n* (%)]			
Male	78 (63.9)	74 (62.7)	NS
Female	44 (36.1)	44 (37.3)	NS
Weight (mean±SD) (kg)	55.62±10.67	59±14.75	NS
Smoking habits [*n* (%)]			
Smokers	74 (60.7)	70 (59.3)	NS
Nonsmokers	48 (39.3)	48 (40.7)	NS

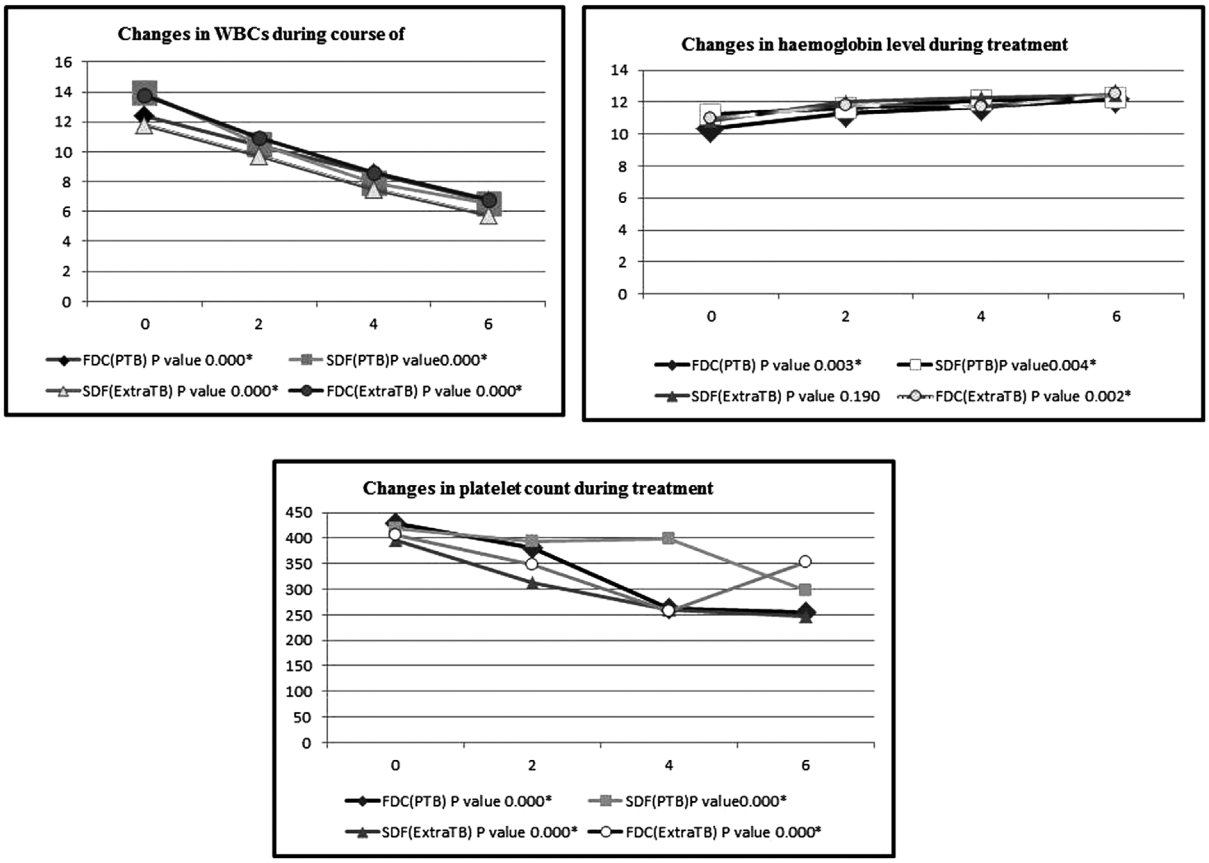
$P<0.05$, significant.

Table 2 Clinical data and sputum conversion of the studied groups during the course of treatment

Variables	Time	PTB (122 patients) [*n* (%)]		EPTB (118 patients) [*n* (%)]		P_1	P_2
		FDC (60)	SF (62)	FDC (58)	SF (60)		
Fever	Baseline	56 (93.33)	62 (100)	22 (37.9)	20 (33.3)	NS	NS
	2 Months	16 (26.7)	20 (32.3)	10 (17.2)	12 (20)	NS	NS
	4 Months	2 (3.3)	2 (3.2)	6 (10.3)	8 (13.3)	NS	NS
	6 Months	0 (0)	0 (0)	2 (3.4)	0 (0)	NS	NS
Anorexia	Baseline	54 (90)	56 (90.3)	58 (100)	59 (98.3)	NS	NS
	2 Months	36 (60)	24 (38.7)	18 (31)	16 (26.7)	NS	NS
	4 Months	4 (6.7)	2 (3.2)	6 (10.3)	2 (3.3)	NS	NS
	6 Months	0 (0)	0 (0)	2 (3.4)	0 (0)	NS	NS
Cough	Baseline	58 (96.7)	62 (100)	26 (44.8)	30 (50)	NS	NS
	2 Months	42 (70)	46 (74.2)	16 (27.5)	12 (20)	NS	NS
	4 Months	18 (30)	20 (32.3)	4 (6.9)	2 (3.3)	NS	NS
	6 Months	2 (3.3)	3 (4.8)	0 (0)	0 (0)	NS	NS
Hemoptysis	Baseline	26 (43.3)	20 (32.2)	–	–	NS	–
	2 Months	14 (23.3)	12 (19.4)	–	–	NS	–
	4 Months	0 (0)	0 (0)	–	–	NS	–
	6 Months	0 (0)	0 (0)	–	–	NS	–
Sputum positive for AFB	Baseline	46 (76.7)	42 (67.7)	–	–	NS	–
	2 Months	9 (15)	10 (16.1)	–	–	NS	–
	4 Months	0 (0)	0 (0)	–	–	NS	–
	6 Months	0 (0)	0 (0)	–	–	NS	–

AFB, acid-fast bacilli; EPTB, extrapulmonary tuberculosis; FDC, fixed-drug combination; PTB, pulmonary tuberculosis; SF, separate formula; P_1 significance between FDC and SF for PTB; P_2 significance between FDC and SF for EPTB.

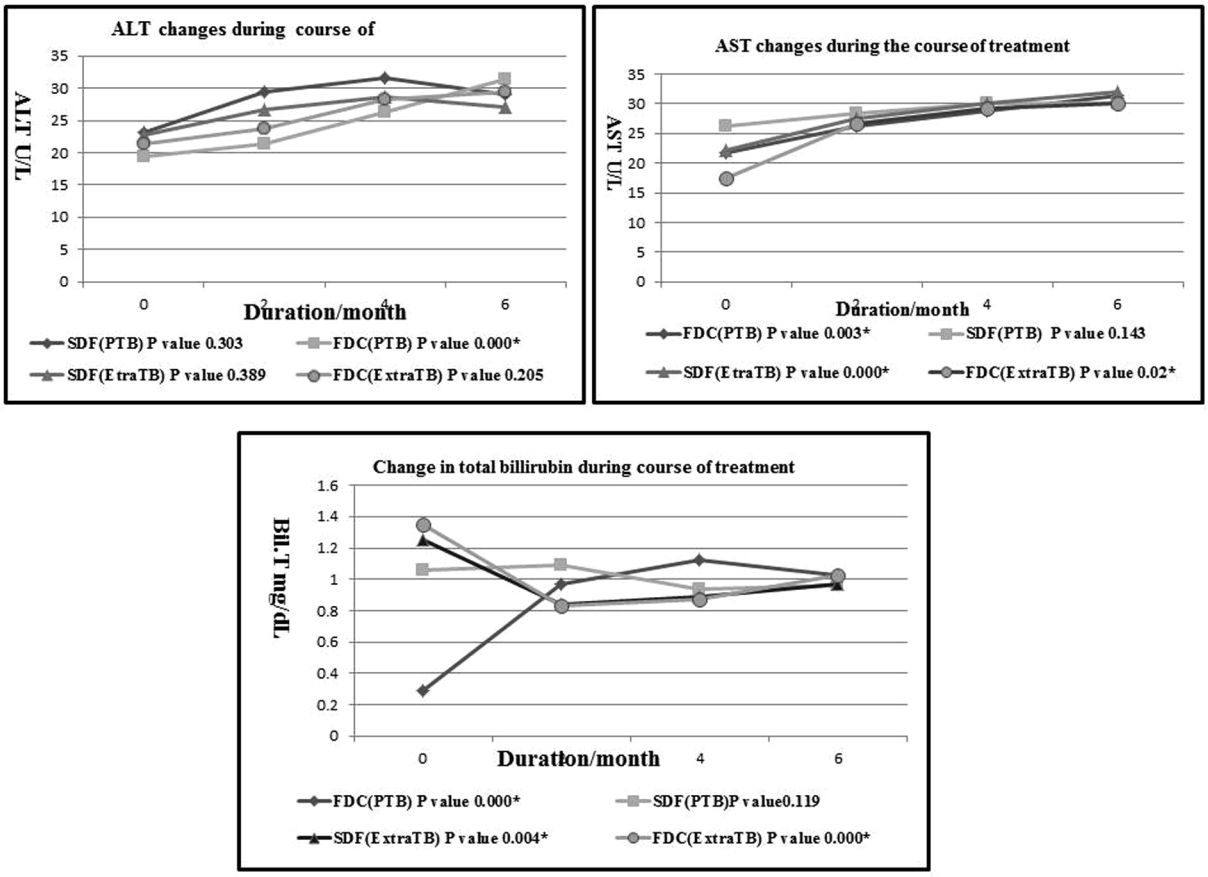
Figure 1



Changes in blood picture during course of treatment.

observed at 6 months of treatment in those who received SDF compared with those who received FDC (Fig. 4). Both FDC and SF had comparable incidence of adverse effects except for gastrointestinal

Figure 2



Changes in liver function tests both in PTB and ETB during the course of treatments.

Table 3 Important antituberculosis drugs-induced adverse effects

Side effect	Total (%)	FDC (%)	SF (%)	*P* value
Gastrointestinal tract	41.7	54.5	26	0.025*
Arthralgia	16.7	15.2	18.5	NS
Vertigo	13.3	18.2	11.1	NS
Itching	13.3	12.1	11.1	NS

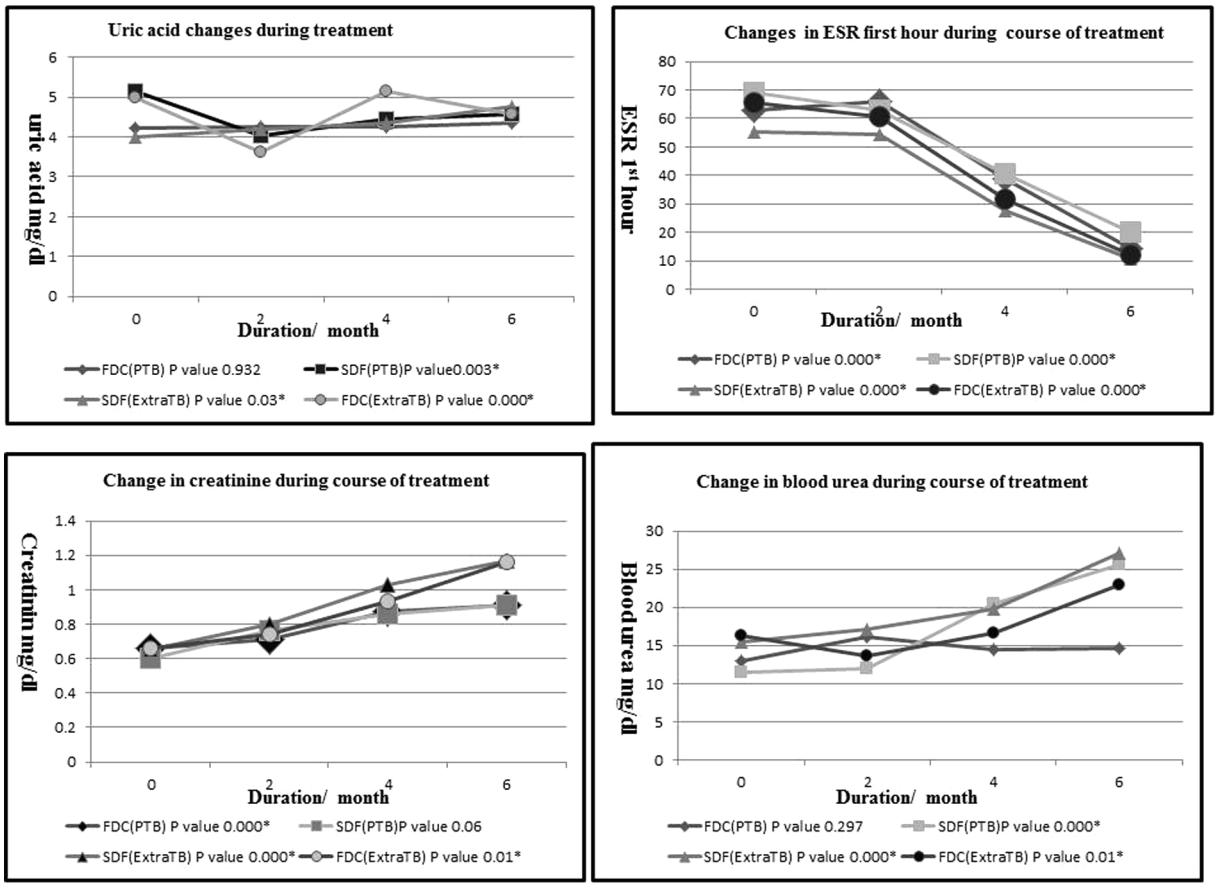
FDC, fixed-drug combination; SF, separate formula; *Significant.

tract (GIT) adverse effects, which were more common with FDC than SF (Table 3).

Discussion

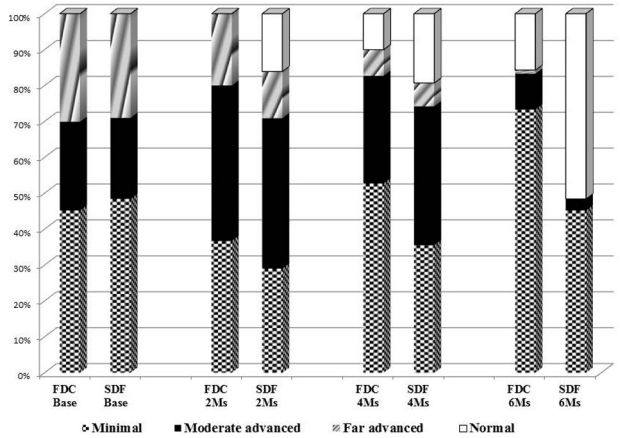
The choice of effective anti-TB treatment is a major public health challenge since the discovery of TB. The goals of introduction of FDC anti-TB drugs were simplification of drug supply, improvement of compliance, effective treatment, and minimizing both incidence of drug resistance and adverse effects [10]. Demographic data of the present study revealed that PTB and EPTB were more common in males, younger age, and smokers. This result is in agreement with WHO [1] facts, which documented that 56% of infected patients with TB are males, and despite affecting all age groups, it mostly affects adults in their productive years. Hassmiller [11] documented that smoking not only increased risk of development of TB but is also associated with development of severe forms of disease, and TB-related death. Both FDC and SDF produce comparable effects regarding clinical improvement in PTB and EPTB, and treatment satisfaction; moreover, sputum conversion in PTB was comparable in those who received either FDC or SDF in the current study. Randomized controlled trials documented that both FDC and SDF had comparable efficacy with respect to clinical improvement and treatment satisfaction [12,13]. Another study documented similar effects of FDC and SDF in term of sputum smear or culture conversion and also adverse effects [14], and this is in agreement with our results. Leukocytosis and anemia with near or exceeding upper limit of normal platelets characterized both patients with PTB and EPTB at baseline in the current study, which improved significantly with treatment with either FDC or SDF. Yaranal *et al.* [15] observed leukocytosis in about 26% of patients with TB because of infection. Moreover, mild leukocytosis was observed in other studies of TB [16,17]. The mechanism of anemia associated with TB was reported in many studies [16,18,19]; they suggested that it related to blunted

Figure 3



Changes in renal function, uric acid, and ESR during course of treatment in both groups.

Figure 4



Graphic presentation of radiological response of PTB with FDC compared to SDF.

both erythropoietin response of bone marrow and erythropoietin response to anemia, and also release of various cytokines such as tumor necrosis factor α, which subsequently suppresses erythropoietin production. In addition, a study reported elevated serum ferritin in all patients with TB as an acute phase reactant [19]. The previous studies also documented thrombocytosis in TB, and attributed that to increased inflammatory mediators and cytokines especially interleukin 6 [16,18,19]. The current study documented more significant rise in liver enzymes and bilirubin with FDC regimen especially in PTB; similar results were reported by Wu *et al.* [20] and attributed this to concomitant use of RIF and INH which aggravated hepatotoxicity. Both PTB and EPTB had raised ESR level which decreased significantly with both FDC and SDF in the present study. Yaranal *et al.* [15] reported that 99% of patients with TB in their study had raised ESR level, and also other studies documented that raised ESR level was associated with disease activity and its decline was associated with disease regression and with negativity of sputum in case of PTB [21,22]. The changes in renal function with anti-TB treatment in the present study correlated with other studies [23,24], which documented increase in uric acid and creatinine level that return to normal once drug stopped and attributed this to changes in protein metabolism and excretion by kidney because of anti-TB treatment. Moreover, Edalo *et al.* [25] reported significant increase in plasma level of urea, creatinine, and uric acid with administration of anti-TB drugs, and also they documented significant increase in liver enzymes and bilirubin level. Both FDC and SDF produced significant radiological improvement, but

complete radiological clearance was more common with SDF in the present study. The less radiological improvement associated with FDC may be related to lower bioavailability of RIF secondary to chemical reaction with INH in the presence of gastric acidity, and this leads to lower peak plasma concentration of RIF in case of FDC compared with SDF [26,27]. This current study revealed comparable adverse effects with both SDF and FDC except for more GIT symptom, which was more common with FDC group. Several studies did not document significant difference between FDC and SDF with respect to adverse effects, adherence, and compliance with treatment [20,27]. The reported higher level of gastrointestinal adverse effects with FDC in the present study may be attributed to the administration of multiple drugs at once with FDC, whereas in SDF, drugs were received at different timing relative to meals, so as to decrease GIT symptoms.

Conclusion

Both FDC and SDF in either PTB or EPTB had comparable effects regarding clinical improvement, compliance, and adverse effects, except for some more common change in liver function, and GIT upset with FDC regimen; moreover, radiological clearance was better with SDF in case of PTB. So we recommend using SDF in cases with borderline liver function, history of GIT upset, and those with extensive radiological infiltration.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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