The outcome of different forms and regiments of antituberculous drugs in Assiut Governorate

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

Objective
To compare the outcome of fixed-dose combination (FDC) therapy versus standard treatment (ST) in treatment of pulmonary tuberculosis (PTB) and extrapulmonary TB in Assiut Governorate.

Patients and methods
In this prospective cross-sectional analytic study, 120 patients were included. Overall, 60 had PTB based on sputum-positive acid-fast bacilli, and 60 had extrapulmonary TB based on biopsy or culture from the affected sites. Patients were classified into two groups: 80 patients received FDC in the form of four-drug combinations in the intensive phase and the two-drug combination therapy in the continuation phase (group 1) and 40 patients received ST in the form of four separate drugs in the intensive phase and the two separate drugs in the continuation phase (group 2). Follow-up of clinical data, laboratory markers, sputum conversion in PTB during the course of treatment, drug tolerance, compliance, and developing of adverse effect was done in both groups.

Results
There is no statistically significant difference between both groups regarding improvement of the fever and anorexia and weight loss ($P > 0.05$ for each). Moreover, there are no statistically significant changes in the sputum conversion between both groups after 2, 4, and 6 months, respectively. There is a statistically significant increase in the percentage of the patients, with increase of alanine aminotransferase, aspartate aminotransferase, and bilirubin level along the course of the treatments in patients receiving FDC and ST ($P < 001$) but still within normal limits, and there is no need to stop or change the therapy. No significant difference between the two groups regarding the adverse effects such as nausea, vomiting, anorexia, blurred vision, peripheral neuropathy, arthralgia, and skin rash is recorded.

Conclusion
Both FDC and ST have comparable results, with no superiority of either one over the other.

Keywords:
antituberculous drugs, antituberculous regimen, fixed-dose combination, standard treatment, tuberculosis, treatment

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Introduction

Tuberculosis (TB) is a global disease affecting one-third of the world's population [1]. It is the second commonest cause of death from infectious disease, after HIV/AIDS. There were an estimated eight to nine million new cases of TB in 2000, fewer than half of which were sputum-smear positive, the most infectious form of the disease [2]. TB a multisystem disease with different presentations and manifestations is the most common cause of infectious disease-related mortality worldwide. Despite the availability of a highly effective 6-month chemotherapy regimen, worldwide control of TB is severely impeded by poor treatment completion rates that threaten the emergence of multidrug resistance[3].

The success rates achievable with these drugs are significant but require complex and long treatment protocols. Lack of compliance and other factors represent significant hurdles to the optimized the use of existing drugs, which could play a significant role in the emergence of drug-resistant TB.

Fixed-dose combinations (FDCs) of drugs have been advocated as a way of preventing the emergence of drug resistance attributable to inappropriate drug intake. In addition, they can reduce the risk of incorrect dosage, simplify drug procurement, and aid in ensuring adherence [4]. This study was designed to compare

the effectiveness, tolerability, compliance, and adverse effect of FDC and standard treatment (ST).

Patient and methods

This prospective cross-sectional analytic study included 120 patients: 60 had pulmonary tuberculosis (PTB) and 60 had extrapulmonary tuberculosis (EPTB). PTB was diagnosed using sputum direct smear sample (early morning repetitive sample of sputum not saliva examined with Ziehl–Neelsen stain) and/or culture on Lowenstein–Jensen medium. EPTB was diagnosed by pleural biopsy, laparoscopy-guided peritoneal biopsy, lymph node biopsy, or endometrial biopsy according to site.

A total of 80 patients received the four-drug combination in the intensive phase (2 months) and two-drug combination therapy in the continuation phase (4 months) (group 1), and 40 patients received standard TB therapy in the form of four separate drugs in the intensive phase and the two separate drugs in the continuation phase (group 2). FDC included rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol hydrochloride 275 mg in each tablet without any interruption based on National Tuberculosis Program 2012 [2] in the intensive phase. The continuation phase included isoniazid 75 mg + rifampicin 150 mg in each tablet. The number of tablets were given according to the patient's body weight.

Compliance of the patient with the treatment was assessed by weekly follow-ups. The patients were asked if they were taking their medication regularly every time they came to gets their weekly treatment. Patients signed informed consent. IRB of Assiut Faculty of Medicine approved the study, with registration number 17101106.

Inclusion criteria

Newly diagnosed patients with PTB and EPTB and patient above 18 years old were the inclusion criteria.

Exclusion criteria for giving fixed-dose combination

Previous recent anti-TB medications more than one month, patients with history of reactivation or relapse, patients with history of renal problem and hepatic problems, patients with history of optic neuritis, patients with acute gout arthritis or history of gout arthritis, patients with TB meningitis, patients with malignancy, and pregnant women were the exclusion criteria.

All patients had clinical assessment including history of fever, anorexia, cough, hemoptysis, and baseline laboratory data, including complete blood picture, liver function tests, renal function, and uric acid level.

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 (SPSS, version 20, Norman Nie Dale Bent, Hadlai "Tex" Hull,2010, Chicago, IL, Owner IBM) software. The results were expressed as number and percentage 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.

Results

Demographic and clinical data were presented in Tables 1 and 2, where there was no statistically significant difference between the two groups regarding fever, anorexia, weight loss, and sputum conversion. Regarding the kidney function, there was a statistically significant increase in the percentage of patients with high blood urea nitrogen (BUN) and creatinine in patients receiving FDC and ST along the course, with *P* value of less than 0.001; however, it still within normal limit, and there was no need to stop or change the therapy. BUN and uric acid significantly increase along the course of the treatment in patients receiving FDC and ST but still were within normal limits.

There were no statistically significant changes in the sputum conversion between both groups after 2, 4, and 6 months, correspondingly ($P > 0.05$) (Table 3).

Table 4 shows the adverse effects of fixed dose versus ST in patients receiving anti-TB treatment. There was no statistical difference between the two groups regarding the adverse effects such as nausea, vomiting, anorexia, blurred vision, peripheral neuropathy, arthralgia, and skin rash.

Discussion

The current study was designed to compare the effectiveness, tolerability, compliance, and adverse effect of FDC and ST. Demographic data of the present study revealed that in group 1, more than half of our patients with TB were smoker, including 57.5% in PTB and 52.5% of the cases with EPTB, and in group 2, 70% in

Table 1 Demographic data of the study groups

Variables	Fixed dose combination (*n*=80)		Standard treatment (*n*=40)		Total number of patients
	Pulmonary TB (*n*=40)	Extrapulmonary TB (*n*=40)	Pulmonary TB (*n*=20)	Extrapulmonary TB (*n*=20)	
Age (years)	36±10.7	38±5.6	37±7.8	34±3.3	
Sex					
Male	24 (60)	21 (52.5)	13 (65)	11 (55)	74
Female	16 (40)	19 (47.5)	7 (35)	9 (45)	46
Weight (kg)	52±8.7	50±10.7	50±6.6	51±9.7	
Smoking habits					
Smokers	23 (57.5)	21 (52.5)	14 (70)	10 (50)	68
Nonsmokers	17 (42.5)	19 (47.5)	6 (30)	10 (50)	52

Data expressed as *n* (%) and mean±SD. FDC+, fixed dose combination; TB, tuberculosis.

Table 2 Clinical data and of the study groups during the course of fixed dose and standard treatment

Variables	Time	Total number of patients		*P*
		FDC (*n*=79)[a]	ST (*n*=40)	
Fever	Baseline	53 (67.08)	28 (70)	0.135
	After 2 months	11 (13.9)	6 (15)	0.628
	After 4 months	2 (2.5)	3 (7.5)	0.610
	After 6 months	0	0	
Anorexia	Baseline	73 (92.4)	30 (75)	0.329
	After 2 months	31 (39.2)	14 (35)	0.472
	After 4 months	2 (2.5)	3 (7.5)	0.820
	After 6 months	0	0	
Weight loss	Baseline	66 (83.54)	32 (80)	0.430
	After 2 months	44 (55.69)	20 (50)	0.682
	After 4 months	12 (15.1)	7 (17.5)	0.270
	After 6 months	3 (3.7)	2 (5)	0.154

Data expressed as *n* (%). FDC+, fixed-dose combination; ST, standard treatment. [a]One female patient died after one month due to reparatory acidosis and cardiac arrest in the department.

Table 3 Sputum conversion in pulmonary tuberculosis in both fixed dose and standard treatment

Variables	Time	Pulmonary TB (60 patients)		*P*
		FDC (*n*=40)	ST (*n*=20)	
Positive sputum	Baseline	31 (79.5)	15 (75)	0.122
	After 2 months	5 (12.5)	3 (15)	0.330
	After 4 months	0	0	-
	After 6 months	0	0	-

Data expressed as *n* (%). FDC+, fixed dose combination; ST, standard treatment; TB, tuberculosis.

Table 4 Side effects of fixed dose versus standard treatment in patients receiving antituberculosis treatment

Side effects	Total	FDC	ST	*P*
Nausea	25 (21)	13 (22)	12 (30)	0.245
Anorexia	36 (30.25)	20 (33.9)	16 (40)	0.144
Vomiting	7 (5.88)	4 (4.5)	3 (7.5)	0.221
Blurred vision	11 (9.24)	6 (10.1)	5 (12.5)	0. 321
Peripheral neuropathy	18 (15.1)	10 (16.9)	8 (20)	0.533
Arthralgia	24 (20.1)	13 (22%)	11 (27.5)	0.522
Skin rash	33 (27.7)	19 (32.2)	14 (35)	0.632
No side effects	3 (2.52)	2 (3.38)	1 (2.5)	0.135

Data expressed as *n* (%). FDC+, fixed-dose combination; ST, standard treatment. *P* value significant if less than 0.05.

PTB and 50% in extrapulmonary were smokers. This agrees with Yen *et al*. [5] who reported that smoking not only increases the risk but also increases the risk of recurrence and developing a severe form of it.

Regarding sex of the patients, most of patients were males. Approximately 60% of patients with PTB and 52.5% of the cases with EPTB were male in patients with fixed treatment, and 65% in patients with PTB and 55% in EPTB in ST This agrees with Avdeeva *et al*. [6] and Katherine *et al*. [7]. The mean body weight was 52.0 ± 8.7 kg for the pulmonary group and 50.00 ± 10.9 kg in the extrapulmonary group in patients with fixed dose and 50 ± 6.6 in PTB and 51 ± 9.7 in extrapulmonary in patients with standard therapy. This is owing to the anorexia, which is a common symptom of TB.

The mean age for the pulmonary group was 36 ± 10.7 years and 35 ± 8.4 years in the extrapulmonary group. This agrees with Avdeeva *et al*. [6], who found that TB is more common in the age between 14 and 34 years in high-prevalence regions.

Both regimens showed more or less similar results regarding the fever and anorexia improvement through the course of the treatment. This was in concordance with Gravendeel *et al*. [8], who showed comparable results with using FDC and ST.

Both regimens showed comparable results regarding sputum conversion in patients with PTB. This agreed with Su and Perng [9].

The current study demonstrated a statistically significant increase in the percentage of patients with increased aspartate aminotransferase, alanine aminotransferase, and bilirubin levels receiving FDC and ST along the course of the treatment. However, the increase was still within normal range, and there was no need to stop the medications for any of the patients. This is in agreement with Su and Perng [9], who showed increase in the liver enzymes in patient received ST compared with those who received FDC. This is also in contrast with Wu *et al*. [10] who found that patients who received FDC showed higher increase in the liver enzymes compared with patients who received ST for the treatment of the TB. This is because the mean body weight of the patients in our study was lower than the mean body

weight in their study, so the number of tablets taken by the patients for the FDC in our study was less than the number of tablets taken by the patients in their study. They also mentioned that at the higher body weight, the concentration of the INH is higher in those who receive FDC treatment than those who receive ST of the TB. This could explain the difference in the results between this study and their study.

Regarding the hemoglobin levels, there was a statistically significant increase in the percentage of patients with normal hemoglobin levels in patients receiving FDC and ST along the course of the treatment.

This is in agreement with Lee *et al*. [10], who found that more than 31% of the patients diagnosed with TB have anemia at the time of diagnosis. The current study also found that the patients were at the lower border of normal hemoglobin or anemic at the time of the diagnosis. This could be owing to anorexia caused by the TB, which causes a chronic inflammation as well.

Regarding white blood cells (WBCs), there was a statistically significant increase in the percentage of patients with normal WBCs in patients receiving FDC and ST along the course of the treatment.

This agrees with Tozkoparan *et al*. [11] who found variation in the WBC count, with predominant increase in 60% of patients at the time of diagnosis. Moreover, this agrees with Al-Omar *et al*. [12], who found leukocytosis with neutrophilic state was predominant in patient with PTB and those neutrophils release preformed toxin and proteolytic enzymes from the TB granule.

Regarding the platelet count, there was a statistically significant increase in the patients with normal platelet counts in patients receiving FDC and ST. This comes in agreement with Tozkoparan *et al*. [11] who found that thrombocytosis decreased significantly with the use of the anti-TB chemotherapy by using mean platelet volume and red cell distribution width as a good indicator for platelet count improvement. Moreover, Kassa *et al*. [13] found that the levels of platelets in the patients with TB were significantly lowered after completion of the intensive phase of TB treatment.

Regarding renal function, there is a statistically significant increase in the percentage of patients with increased BUN and creatinine levels in patients receiving FDC along the course of the treatment. Moreover, there was an increase in the percentage of patients with high creatinine levels in patients receiving ST.

This agrees with Adebisi *et al*. [14], who reported that renal adverse effects in patients with TB on anti-TB drugs come from that using the chemotherapy, which causes hyperuricemia, which in turn causes increase in the creatinine levels. This also agrees with the study of Lienhardt *et al*. [15] in which they stated that pyrazinamide increases the levels of serum uric acid.

Pyrazinamide affects the serum uric acid early and affects handling of urate, urea, and creatinine by the kidneys. It was also reported in Nigeria that among patients with TB on anti-TB drugs with pyrazinamide, 51.6% developed hyperuricemia [14]. Moreover, Antony *et al*. reported that pyrazinamide causes hyperuricemia, as pyrazinamide and ethambutol are two anti-TB drugs that have been reported to induce hyperuricemia [16]. Pyrazinamide is a strong urate retention agent, causing a greater than 80% reduction in renal clearance of uric acid at a 300-mg therapeutic daily dose [17].

The current study showed slight raise in the level of the BUN in the patient who receive ST as well as patients received FDC. This comes in agreement with Edalo *et al*. [18] who reported a significant increase in plasma level of urea, creatinine, and uric acid with administration of anti-TB treatments. The raise in the serum BUN serum creatinine and uric acid did not necessitate any of the patients in the current study to stop the medications or change the regimens.

Regarding adverse effects, FDC showed comparable results to ST. This is in agreement with Wu *et al*. [10], who showed potential advantages associated with the administration of FDCs compared with separate-drug formulations. This also disagrees with Sagwa *et al*. [19] who demonstrated a higher incidence of gastrointestinal tract-related adverse effects.

Conclusion

The current study concluded that both FDC and ST have comparable results, with no superiority of either one over the other.

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Conflicts of interest

There are no conflicts of interest.

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