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EFFECTIVE SHORT COURSE CHEMOTHERAPY FOR TUBERCULOSIS IN DRUG SENSITIVE CASES : HOW EFFECTIVE ARE THEY IN DRUG RESISTANT CASES?

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ABSTRACT

In general, most of the short-course regimens, whether they contained pyrazinamide (non-rifampicin regimen) or also contained rifampicin (rifampicin regimen) were found to be effective in patients with initially drug-sensitive bacilli. In contrast, their efficacies varied in patients with initial drug resistance to isoniazid alone or to streptomycin and isoniazid. The reasons for the varying efficacies of different short-course regimens and their implications are discussed.

Introduction

The current trend in the treatment of tuberculosis is short-course chemotherapy. Numerous short-course regimens with varying durations and drug combinations are known and their efficacies even in drug-sensitive patients differ considerably. It is therefore, necessary to identify the regimens which will be very effective (at least 95% effective) in drug-sensitive patients and to find out how effective these regimens are in patients with initial drug resistance to isoniazid alone or to isoniazid and streptomycin.

Under these circumstances, it is to be stressed that initial drug resistance to isoniazid alone or to streptomycin and isoniazid is widely prevalent in our country (1,2). The treatment of drug-resistant patients with drugs namely, cycloserine, ethionamide and pyrazinamide is not very satisfactory (3-5). The current trend in the treatment of tuberculosis is short-course chemotherapy (6, 7). There are numerous short-course regimens with varying durations (three to nine months) and different drug combinations. It is important to know the regimens that will be effective even in patients with initial drug resistance to isoniazid alone or to streptomycin and isoniazid.

The data presented in this paper belong to published results of clinical trials on short-course chemotherapy conducted in two African (East Africa and Algeria) and three Asian (Hong Kong, Singapore and India) countries during the past two decades. Although these trials were not concurrent, the methodology adopted, the bacteriologic procedures employed and the assessment of results were broadly similar.

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Results

Drug-sensitive patients

Before considering the drug-resistant patients, it is necessary to know the short-course regimens that will be effective in patients with initially drug-sensitive bacilli. The minimum duration of an effective non-rifampicin regimen is about seven months (8). Thus, a regimen consisting of streptomycin, isoniazid and pyrazinamide given daily for two months and then twice-weekly for five months (total duration seven months) had an unfavourable response during chemotherapy in none (0%) of 269 drug-sensitive patients and a bacteriological relapse after stopping chemotherapy in seven (3%) of 269 patients during17 months of follow-up (9). Therefore, the overall failure rate (unfavourable response plus bacteriological relapse) was 3% of 269 patients, the efficacy being about 97% (Table1).

The minimum duration of an effective regimen containing rifampicin for two months initially, besides the above-mentioned three drugs (rifampicin regimen) is about five months (8). Thus, a regimen consisting of two months of daily rifampicin, isoniazid, pyrazinamide and streptomycin followed by three months of twice-weekly streptomycin, isoniazid and pyrazinamide (total duration five months) resulted in an unfavourable response in none (0%) of 129 drug-sensitive patients, and a bacteriological relapse in seven (5%) of129 patients, in 19 months of follow-up (9), an efficacy of about 95% (Table 1). The results were similar even if the initial daily

TABLE -1

Efficacies of a seven-month regimen without rifampicin and two five-month regimens containing rifampicin for two or three months initially

Duration (Months)		Regimen	Drug-sensitive			Initially resistant to H or SH		
Rif	Total		Total pts	Overall failure* %	Effi-cacy %	Total pts	Overall failure* %	Effi-cacy %
0	7	SHZ daily 2 mths, then SHZ twice-weekly 5 mths	269	*3*	*97*	34	*59*	*41*
2	5	SHRZ daily 2 mths, then SHZ twice-weekly 3 mths	129	*5*	*95*	25	*20*	*80*
3	5	SHRZ daily 3 mths, then SHZ twice-weekly 2 mths	230	*4*	*96*	31	*13*	*87*

S=Streptomycin, H=Isoniazid, R = Rifampicin, Z = Pyrazinamide

* Unfavourable response during chemotherapy plus Bacteriological relapses after stopping chemotherapy (See text for details)

chemotherapy with four drugs was given for three months (instead of two) 4% of 230 patients being the overall failures (1), an unfavourable response in 0% of 230 and a bacteriological relapse in 4% of 187 patients and the efficacy being about 96% (Table 1).

Consequently, non-rifampicin or rifampicin regimens of durations more than seven or five months respectively were all effective in drug-sensitive patients.

Drug-resistant patients

Initial drug resistance to streptomycin alone:-

The management of patients with initial resistance to streptomycin alone did not pose a problem and such a resistance did not influence the response to treatment (11,12)

Initial drug resistance to isoniazid alone or to streptomycin and isoniazid:-

Considering the seven-month non-rifampicin regimen referred to earlier, 20 (59%) of 34 patients with initial resistance to isoniazid alone or to streptomycin and isoniazid had an unfavourable response and none (0%) of 14 patients had a bacteriological relapse during a follow - up of 17 months (9). Thus, the overall failure rate was 59% of 34 patients and hence an efficacy of about 41% (Table 1).

In the case of the five-month regimen containing rifampicin for two months initially (rifampicin, isoniazid, pyrazinamide and streptomycin daily for two months, followed by streptomycin, isoniazid and pyrazinamide twice-weekly for three months), four (16%) of 25 drug-resistant patients had an unfavourable response and one (5%) of 21 patients had a relapse in 19 months of follow-up (9). The proportion of patients who were overall failures was 20% of 25 patients and therefore the efficacy of the regimen was about 80% (Table1). The other five-month regimen containing three months of daily rifampicin (rifampicin, isoniazid, pyrazinamide and streptomycin daily for three mounths followed by streptomycin, isoniazid and pyrazinamide twice-weekly for two months) gave better results, two (7%) of 31 patients having an unfavourable response, and two (7%) of 28 patients raving a bacteriological replapse in 19 months of follow-up (10). In all, 13% of 31 patients were overall failures and this regimen had an efficacy of about 87% (Table 1).

Table 2 presents six - month regimens containing rifampicin and isoniazid throughout, having an efficacy of more than 90% in drug sensitive and drug resistant patients.

TABLE -2

Six - month regimens (containing rifampicin and isoniazid throughout) highly effective in drug-sensitive or drug-resistant patients

Duration (Months)		Regimen	Drug-sensitive to H and S			Initially resistant to H or SH		
Rif	Total		Total pts	Overall Failures* %	Efficacy %	Total pts	Overall failures %	Efficacy %
6	6	SHRZ or EHRZ daily 2 months, then HR daily 4 months, or,	412	*2*	*98*	31	*7*	*93*
6	6	SHRZ daily 2 months, then HR thrice-weekly 4 months, or,	216	*1*	*99*	14	*0*	*100+*
6	6	SHRZ or EHRZ thrice-weekly 6 months	335	*2*	*98*	30	*3*	*97*
Total			963	*2*	*98*	75	*4*	*96*

S=Streptomycin, H=Isoniazid; R=Rifampicin; Z = Pyrazinamide; E= Ethambutol

* Unfavourable response during chemotherapy plus bacteriological relapses after stopping chemotherapy (See text for details)

+ Based on 14 patients only (small numbers)

Six-month regimens containing rifampicin, isoniazid, pyrazinamide and streptomycin (or ethambutol) daily for two months followed by rifampicin and isoniazid daily or thrice-weekly for four months or six-month thrice-weekly (fully intermittent) regimens containing rifampicin, isoniazid, pyrazinamide and streptomycin (or ethambutol) throughout gave excellent results, an unfavourable response occurring in none (0%) of 75 drug-resistant patients and a bacteriological relapse in three (4%) of 68 patients followed up for 18-24 months (13-17). The proportion of overall failures was 4% of 75 patients, equivalent to an efficacy of about 96% (Table 2).

Discussion

In drug-sensitive patients, the efficacy of a seven-month non-rifampicin regimen consisting of streptomycin, isoniazid and pyrazinamide given daily for two months, then twice-weekly for five months (9), was about 97% (Table 1) and it was similar to the efficacies of two five-month regimens containing rifampicin in addition for two or three months initially, namely about 95-96% (9,10). Therefore, the response in drug-sensitive patients is independent of rifampicin.

Considering patients with initial drug resistance to isoniazid alone or to streptomycin and isoniazid, the seven month non-rifampicin regimen, consisting of streptomycin, isoniazid and pyrazinamide given daily for two months and twice weekly for five months, had an overall failure rate of 59% among 34 patients (Table 1) the efficacy being about 41% (9). The inference is that pyrazinamide given daily for two months and then twice-weekly for five months was inadequate as a companion drug to streptomycin and isoniazid in drug-resistant patients (Item A, Table 3).

In contrast, the addition of daily rifampicin for just two or three months initially considerably enhanced the efficacy of streptomycin - isoniazid - pyrazinamide combination (Table 1), the proportion of patients who were overall failures being 20% for the two - month rifampicin series (9), and 13% for the three-month rifampicin series (10), the efficacies being about 80% and 87% respectively (Item B, Table 3). The response was still better when rifampicin was given for six months.

Thus, six-month regimens containing rifampicin, isoniazid, pyrazinamide and streptomycin or ethambutol) given daily for two months, followed

TABLE - 3

Factors influencing the efficacies of short-course regimens in patients with initial drug resistance to H alone or to SH

Item	R duration (Months)	Drugs(s) besides SH in the regimen		Efficacy %
		Initial phase	Continuation phase	
A	0	Z daily 2 months	Z twice-weekly 5 months	*41*
B	2 or 3	RZ daily 2 or 3 months	Z twice-weekly 3 or 2 months respectively	*80-87*
C	6	RZ or RZE* daily 2 months	R daily or thrice-weekly 4 months	*96*
		← RZ or RZE* thrice-weekly 6 months @ →		
D	6	← R daily 6 months @ →		*74*
E	6	RZ twice - or thrice - weekly 2 months	R twice - weekly 4 months	*77*
F	6	RZ twice - or thrice - weekly 2 months	R once - weekly 4 months	*56*

S = Streptomycin; H = Isoniazid; R = Rifampicin; Z = Pyrazinamide; E = Ethambutol;

* - Ethambutol instead of Streptomycin

@ - Throughout the period

by rifampicin and isoniazid daily or thrice-weekly for four months or six-month thrice-weekly regimens comprising rifampicin, isoniazid, pyrazinamide and streptomycin (or ethambutol) gave excellent results (Table 2). Only 4% of 75 drug-resistant patients were overall failures (unfavourable response rate 0%, relapse rate 4%) when treated with the just-mentioned regimens (13-17) the efficacy being about 96% (Item C, Table 3). These results were similar to those obtained in drug-sensitive patients treated with the same regimens (Table 2), the overall failures being 2% of 963 patients, corresponding to about 98% efficacy (13-17). Thus, these findings clearly demonstrate that rifampicin is not only absolutely necessary for drug-resistant patients but also has to be given sufficiently long, preferably for six-months (but see below)

In fact, the Committee on Treatment of the International Union Against Tuberculosis and Lung Disease has recommended that for populations with a high prevalence of initial drug resistance, in particular to isoniazid, the regimen of choice is a six month daily regimen consisting of rifampicin, isoniazid, pyrazinamide and ethambutol (or streptomycin) for two months followed by rifampicin and isoniazid for four months (18).

Contrary to expectations, a few six-month regimens despite containing rifampicin throughout did not yield satisfactory results in patients, with initial drug resistance, indicating that the response was not dependent solely on the rifampicin duration. Thus, a six-month daily regimen of streptomycin, isoniazid and rifampicin (19-21) had an overall failure rate of 26% among 54 patients (an unfavourable response in 15% of 54 patients and a relapse in 15% of 39 patients), the efficacy being about 74% (Item D, Table 3) The omission of pyrazinamide was the probable reason because when daily pyrazinamide was added to the three drugs for two months initially 7% of 30 patients were overall failures (unfavourable response rate 0% relapse rate 8%), the efficacy being about 93% (13, 14, 16).

Further, six-months regimens consisting of rifampicin, isoniazid, pyrazinamide and streptomycin given twice - or thrice -weekly for two months, followed by rifampicin and isoniazid twice-weekly for four months (22) had an efficacy of about 77%; but when rifampicin and isoniazid were continued once-weekly the efficacy dropped to about 56% (Items E and F, Table 3). In other words once-a-week rhythm in the continuation phase definitely affected the response adversely. In the case of the regimen with twice-weekly rhythm in the continuation phase, it is difficult to say whether the twice-weekly rhythm in the continuation phase or twice/thrice-weekly rhythm in the initial phase was the culprit. A study in Singapore (16) showed that none of 14 patients was an overall failure when treated with a similar regimen, except that the rhythm was daily for two months and thrice-weekly for four months.

Whether the rhythm of administration of drugs during the initial phase (usually two months) influences the efficacy can be answered on the basis of an indirect evidence. A five-month regimen consisting of two months of daily chemotherapy with streptomycin, isoniazid, rifampicin and pyrazinamide (followed by three months of twice-weekly streptomycin, isoniazid and pyrazinamide) had an efficacy of about 80% (9). In a six - month regimen containing two months of twice- or thrice-weekly chemotherapy with the same four drugs (followed by four months of twice - weekly rifampicin and isoniazid,) the efficacy was about 77% (22). It is of interest to note that the five-month regimen, notwithstanding two disadvantages, namely rifampicin duration of two months only and total duration of five months, was as potent as the six-month regimen containing rifampicin throughout. Therefore, there is a strong suggestion that the daily rhythm of the five-month regimen was able to make up for the two deficiencies. In addition, the similarity of efficacies, namely about 80% and 77%, of the two regimens with varying rifampicin durations, namely two and six months respectvely, is a proof that the response is not governed only by the rifampicin duration. A study in Poland on a six-month regimen consisting of isoniazid, rifampicin (without pyarzinamide) given initially daily for two months and once weekly for the next four months was not effective even in 87 drug sensitive patients followed for 18 months, 18 (21%) relapsed, the efficacy being 79%. Efficacy on drug-resistant patients was not provided in this study.

The highly effective six-months regimens (containing rifampicin and isoniazid throughout) referred to earlier (Table 2) have certain limitations, namely frequent attendance at the clinic, a high incidence of jaundice (24-27) and arthralgia (28-30) among Indian patients. Therefore, these regimens may be uncceptable under field conditions.

It is concluded that there is a need to evolve regimens (preferably oral) that are effective even in patients with initial drug resistance have low drug toxicity and require less frequent attendance at the clinic.

Fully self-administered daily regimens of six to eight months' duration involving minimal attendance at the clinic (once a fortnight or once a month) will be welcomed by one and all, provided that solutions to the problems of drug toxicity (high with daily regimens) and irregularity in drug consumption are found out.

Further studies are called for with respect to intermittent regimens. Since six-month regimens containing four months of twice-weekly rifampicin and isoniazid were ineffective (22), an eight-month twice-weekly regimen consisting of rifampicin,. isoniazid, pyrazinamide and ethambutol initially for three months, followed by rifampicin and isoniazid for five months needs evaluation. In addition, the implications of giving one dose under supervision and supplying one dose for self-administration during each clinic attendance calls for further probing.

Regimens with once-weekly rhythm in the continuation phase also needs further exploration. But in order that efficacy is not compromised, an eight-month regimen containing rifampicin, isoniazid, pyrazinamide and ethambutol twice-weekly for four months initially followed by rifampicin and isoniazid once weekly for four months can be investigated.

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