FULLY INTERMITTENT SIX MONTH REGIMENS FOR PULMONARY TUBERCULOSIS IN SOUTH INDIA*

Rani Balasubramanian

Summary : **A large-scale multi-centric study in South India was organised by the Tuberculosis Research Centre, Madras. The regimens consisted of Rifampicin, Isoniazid, Streptomycin and Pyrazinamide, administered under supervision, twice or thrice a week for the first 2 months, followed by different combinations of 2 or 3 drugs administered twice or once a week for the next 4 months. The patients were followed up with intensive bacteriological examination. The response at the end of chemotherapy and the relapse rates during a 4½-year follow-up in approximately 1,000 patients with drug-sensitive organisms initially and 200 patients with organisms initially drug resistant are presented.**

Introduction

The earlier studies from the Tuberculosis Research Centre, Madras, have shown that Short Course Chemotherapy regimens of 5 to 7 months' duration are effective in sputum positive pulmonary tuberculosis. However, there are some limitations, e.g. high incidence of arthralgia and hepatitis in daily chemotherapy and patients having to attend daily for a period of 2 to 3 months. The alternative is to try out fully intermittent chemotherapy, as intermittent regimens are likely to be less toxic. Hence, we undertook a controlled clinical study of 10 fully intermittent regimens of different rhythms in initial phase and various drug combinations and rhythm in continuation phase.

Material and Methods

The present paper incorporates the findings in patients during a follow up period of 54 months after stopping chemotherapy.

The criteria for admission were as follows : Patients had to be *bona fide* residents of Madras or Tambaram, aged 12 years or more. They had not had more than 6 months of previous anti-tuberculosis chemotherapy and had two smears positive for AFB. Patients did not have concomitant renal or hepatic or cardiac disease or diabetes mellitus.

The regimens employed were as follows : Streptomycin + Rifampicin + Isoniazid + Pyrazinamide administered either twice or thrice a week during initial phase for two months, followed by either Rifampicin and Isoniazid twice weekly with or without Streptomycin or Rifampicin and Isoniazid once weekly with or without SM or Streptomycin + Isoniazid twice weekly for 4 months. Patients were allocated at random to one of the ten regimens shown below.

Chart 1.

Initial (2M)	Continuation (4M)
$SRHZ_3$ (Thrice weekly) OR $SRHZ_2$ (Twice weekly)	RH_2, SRH_2 (Twice weekly), RH_1, SRH_1 (Once weekly). SH_2 (Twice weekly),

The dosages of drugs were as shown below :

Chart 2.

Drugs	Dosage
Streptomycin (S)	0.75 gm
Rifampicin (R)	12 mg/kg
Isoniazid (H)	15 mg/kg*
Pyrazinamide (P)	50 mg/kg Thrice Weekly 70 mg/kg Twice Weekly

* Incorporating Pyridoxine 10 mg

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Correspondence: Dr. Rani Balasubramanian, TB Research Centre, Spurtank Road, Chetput, Madras-600 031.

A total of 1,157 patients were admitted to the study. Of these, 81% had organisms sensitive to Streptomycin, Rifampicin and Isoniazid. Only 4 of the 937 drug sensitive patients had unfavourable response. All the others with favourable response, i.e. negative cultures in the last two months, were followed up for a period of 54 months after stopping treatment.

Investigations during follow up included two sputum specimens monthly from 7 to 24 months, three sputum specimens six monthly from 25 to 60 months and chest X-ray annually from 12 to 60 months.

Bacteriological relapse requiring treatment was defined as a total of two or more positive cultures in three consecutive months, at least one with 20 colonies or more and accompanied by at least one positive smear.

Results

The bacteriological response in drug sensitive patients is presented in Table 1. Considering thrice weekly series, the proportion of patients who had relapsed varied from 5% to 7%, the average being 6.2%. In the twice weekly series, it was either 7% or 8% in all except the regimen where Streptomycin & Isoniazid were given twice a week in the follow up phase, where it was 12%. The difference between this and others is not statistically significant. The relapse rates of all the 10 regimens are similar indicating that all are of equal efficacy in patients with sensitive drug organisms irrespective of the differences in the rhythm in the initial phase or number of drugs, that is two or three drugs or rhythm either twice a week or once a week.

Table 1. *Bacteriological relapse in drug sensitive patients*

Continuation 4M	Initial 2 M: $SRHZ_3$ Total patients	$SRHZ_3$ Relapse %		$SRHZ_2$ Total patients	$SRHZ_2$ Relapse %	
S R H_2 9 0	94	6	6.2	89	7	7.9
RH_2		7		90	8	
S R H_1 9 9	96	6		103	7	
RH_1		5		92	7	
SH_2	89	7		95	12	

* Upto 54 Months after stopping treatment

The findings in patients with initial resistance to H or SH are shown in Table 2. Resistance to Streptomycin alone does not pose a problem when patients are treated with short course chemotherapeutic regimens. The unfavourable response and overall failure rates are given according to the drugs in continuation phase. The results of thrice weekly and twice weekly series during initial phase are similar and have, therefore, been combined and presented here. Considering the regimen where SRH_2 was given in continuation phase, the proportion of patients who had unfavourable response was 17% of 36 patients and overall failure rate was 17%. When the same drugs were given without Streptomycin, the unfavourable response occurred in 19% of 26 patients similar to the regimen containing Streptomycin and the overall failure rate was 23% similar to 17%. In contrast, when the same 3 drugs were given once a week, unfavourable response occurred in 30% of 30 patients, the proportion was significantly higher($X^2 = 5.62$ for 1 df $P < 0.02$) than the regimen where drugs were given twice a week and the overall failure rate increased to 47%. And when the same drugs were given without Streptomycin, the failure rate was 44% similar to the regimen where Streptomycin was given in addition. The difference between 46% and 19% is statistically significant. Coming to the regimen where no Rifampicin was given in continuation phase, unfavourable response increased to 59% of 34 patients and failure rate also increased to 74%, a significantly higher proportion than the other 4 regimens. The differences between 74% and 46% ($X^2 = 5.65$ for

Table 2. *Findings in patients with initial resistance to H or SH*

Drugs in continuation phase	Total patients No	Unfavourable response %	Overall failure** %	
SRH_2	36*	17*	17	19%
RH_2	26	19	23	
SRH_1	30	30	47	46%
RH_1	27	41	44	
SH_2	34	59	74	

* Initial resistance to RMP in one patient
** Failure (unfavourable response + relapse)

1 df, P = 0.02) and 74% and 19% (X^2 = 25.0 for 1 df P < 0.001) are highly significant. There was one patient in SRH, series who had initial Rifampicin resistance, and he had unfavourable response. These findings clearly indicate that Rifampicin is essential in treatment of patients with initial drug resistance to H or SH and the response is much better in patients treated with regimens where Rifampicin is given throughout the period of 6 months compared to regimens where Rifampicin is given only during the initial period of 2 months. Among 6 month Rifampicin regimens, there was better response in patients treated with Rifampicin twice a week than among those given once a week. Streptomycin as a third drug in continuation phase has no additional benefit.

To conclude, fully intermittent 6-month regimens are effective in patients with organisms sensitive to anti-tuberculous drugs. In patients with organisms resistant to anti-tuberculous drugs, lower failure rates were observed in 6 months' Rifampicin regimen compared to 2 months' Rifampicin regimen. Among 6 months Rifampicin regimens, better rjesponse was obtained with Rifampicin and Isoniazid given twice a week than once a week. Streptomycin as a third drug in continuation phase has no additional benefit.