INTERIM FINDINGS ON THE EVALUATION OF SPLIT DRUG REGIMENS FOR PULMONARY TUBERCULOSIS - A RANDOMIZED CONTROLLED CLINICAL TRIAL*

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Summary: A randomized controlled clinical trial of three fully oral short course chemotherapy regimens of 6 month duration is being conducted to evaluate split-dose double drug combinations for the treatment of sputum positive pulmonary tuberculosis. Split I and Split II regimens consist of Rifa mpicin and Ethambutol on one day and lsoniazid and Pyrazinamide on the next day, each combination given thrice a week during the initial intensive phase of 2 or 3 months, respectively, followed by Rifampicin and Isoniazid given twice a week during the continuation phase for the next 4 and 3 months; respectively. The control regimen consists of all the four drugs, Rifampicin, Isoniazid, Pyrazinamide and Ethambutol, given together in a single dose thrice a week during the intensive phase of first 2 months, and Rifampicin and Isoniazid twice a week during the continuation phase of next 4 months. Drugs were given under full supervision during the entire chemotherapy period of 6 months. The findings upto the end of chemotherapy for 750 patients suggest that the response is similar in split and control regimens among patients with sensitive organisms and those with resistance to Isoniazid alone. Among patients with organisms resistant to both Isoniazid and Rifampicin, almost all had an unfavourable response. Adverse reactions were low and similar in both split and control regimens.

Introduction

Several highly effective short course chemotherapy regimens have been evolved for the treatment of sputum, positive pulmonary tuberculosis. In most of these regimens, four drugs, viz, Rifampicin(R), Isoniazid(H), Pyrazinamide(Z) and Streptomycin(S) or Ethambutol(E) are given together in a single dose either daily or intermittently in the initial phase. The bulk of the drugs to be consumed in a single dose is, therefore, large and may affect patient compliance. Further, the incidence of adverse reactions such as arthralgia and jaundice is higher with daily regimens.

Hence, a study is being conducted wherein the four drugs are split into two 2-drug combinations, each combination given on alternate days, thus making each combination intermittent. The advantage of the split regimens is that the bulk of the drugs in a tingle dose is less and adverse reactions are expected to be low. These two factors together will presumably help in improving patient compliance.

Study Subjects

The patients were residents of either Madras or Madurai, and had come to the out-patients chest clinics because of symptoms. Patients were eligible for inclusion in the study irrespective of previous chemotherapy, if they were aged 12 years or more, had at least 2 sputum cultures positive for M. *tuberculosis*, even though admission to the study was based on smear positivity, and were willing to attend the centre for supervised chemotherapy for a period of 6 months. Patients with diabetes, hypertension. bleeding diathesis and extra pulmonary tuberculosis were not eligible for the study.

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Regimens

Patients were randomly allocated, stratified on the basis of duration of previous chemotherapy and degree of sputum positivity, to one of the following three fully supervised regimens of 6 months' duration.

In the first regimen, 2RE3HZ3(alt)/4RH2 (split I), during the initial phase, Rifampicin and Ethambutol were given on one day and Isoniazid and Pyrazinamide on the next day, thrice a week for 2 months followed by Rifampicin and Isoniazid twice a week for the next 4 months. The second regimen, 3RE3HZ3 (alt)/3RH2 (split II), was similar to regimen 1, but the initial phase was for 3 months, followed by 3 months in the continuation phase. The third regimen (2REHZ3/ 4RH2) was the control regimen where all four drugs were given together in a single dose thrice a week for 2 months followed by Rifampicin and Isoniazid twice a week for next 4 months. The dosages were same for all the three regimens in both the phases. For patients weighing 40 kg or less, rifampicin 450 mg, Ethambutol 1000 mg and Pyrazinamide 1.5 g were given. For patients weighing more than 40 kg, the dosages were 600 mg, 1200 mg and 2 g, respectively. Isoniazid was given in a flat dose of 600 mg, irrespective of body weight.

Results

The findings of the interim analysis upto the end of chemotherapy are presented here. The population consisted of 750 patients of whom 124 were excluded for various reasons like negative culture on admission, early death, death due to non-tuberculous causes and for having missed 25% or more of chemotherapy. There remained a total of 626 patients in the analysis. Of these, 80% had organisms sensitive to Isoniazid and Rifampicin, 16% of patients had resistance to Isoniazid alone, 0.3% had resistance to Rifampicin alone and 3% of patients had resistance to both Isoniazid and Rifampicin (Table 1).

During chemotherapy, 3 sputum specimens from each patient were examined by culture for *M. tuberculosis* every month. The proportion of patients with negative culture at first month was 29% and 30% in split I and II regimens, respectively and 28% in the control regimen. By second month, it had gone up to 80-83%. From 3rd to 6th month it was 95 - 99%. Thus the speed of sputum conversion was similar in all the regimens (Table 2).

Proportion of patients who received more than 80% of their prescribed chemotherapy was 82% and 85% in split I and II regimens, respectively and 82% in the control regimen. Even though patients had to attend daily for the initial 2 to 3 months in the split regimens, the drug regularity was similar to that of control regimen where they had lo attend thrice a week during this period. (Table 3).

A favourable bacteriological response at the end of chemotherapy was defined as all cultures

Table 1. **Study population**

	2RE3HZ3(alt)/ 4RHZ (Split I)	3RE3HZ3(alt)/ 3RH2 (Split II)	2REHZ3/ 4RH2 (Control)	Total
Total patients	251	250	249	750
Exclusions	43	38	43	124
Total in analysis	208	212	206	626
Sensitive to H and R	173	169	162	504 (80%)
Resistant to H alone	27	36	38	101 (16%)
Resistant IO R alone	1	1	0	2 (0.3%)
Resistant to H and R	7	6	6	19 (3%)

Table 2. **Culture negativity (%) during treatment among patients with initial drug sensitive organisms**

Months after start of treatment	2RE3HZ3(alt)/ 4RH2 (Split I)	3RE3HZ3(alt)/ 3RH2 (Split II)	2REHZ/ 4RH2 (Control)
1	28	30	29
2	80	83	82
3	97	96	96
4	97	99	98
5	95	98	96
6	97	95	98
Range of Patients	171 - 173	168 - 169	161 - 162

Table 3. **Percentage of chemotherapy received during phases I & II**

Treatment received(%)	Number of patients		
	2RE3HZ3(alt)/4RH2 (Split I)	3RE3HZ3(alt)/3RH2 (Split II)	2REHZ3/4RH2 (Control)
≥ 80	195(82)*	204(85)	200(82)
50 - 79	28(12)	24(10)	22(9)
< 50	1(<1)	0(0)	1(<1)
Missed continuously for >1 month	14(6)	13(5)	20(8)
Total	238	241	243

* Percentages in parenthesis

Table 4. **Response at the end of chemotherapy among patients with initial drug sensitive organisms**

Response	Number of patients		
	2RH3ZH3(alt)/ 4RH2 (Split I)	3RE3HZ3(alt)/ 3RH2 (Split II)	2REHZ3/ 4RH2 (Control)
Favourable	163(94)*	158(93)	152(94)
Doubtful	6(3)	9(5)	10(6)
Unfavourable	4(2)	2(1)	0(0)
Total	173	169	162

* Percentages in parenthesis

negative in the last two months of chemotherapy. An unfavourable bacteriological response was defined as 2 or more cultures being positive in the last two months of treatment including one culture in the last month and a least one culture growing 20 colonies or more. In addition, patients who had a change of treatment for persistent culture positivity, or radiographic or clinical deterioration and those who died of tuberculosis were also classified as having had an unfavourable response. Those who did not fit into these criteria were classified as having doubtful response.

At the end of chemotherapy, among patients

with drug sensitive organisms, a favourable response was obtained in 94% and 93% in split I and II regimens, respectively and 94% in the control regimen. It can be observed that the response at the end of treatment is not very much affected by splitting the drugs. All those with doubtful response converted by 7th month without additional chemotherapy. Only 2% and 1% of patients, respectively in the split I and II regimens had unfavourable response (Table 4).

Among those with organisms resistant to Isoniazid alone, favourable response was seen in 78% and 81%, respectively in split I and II regimens and 73% in the control regimen, while unfavourable response was seen in 19%, 14% and 21% respectively in the three regimens. Out of these patients with unfavourable response, one died and all the others had change of treatment for persistent culture positivity (Table 5).

There were 19 patients with organisms resistant to both Isoniazid and Rifampicin. Except one, all the others had an unfavourable response. Two patients who had resistance to Rifampicin alone had a favourable response.

Adverse reactions

Adverse reactions encountered during chemotherapy were mainly gastro-intestinal symptoms, arthralgia, hepatitis and cutaneous reactions. Proportions of patients reporting with any of these complaints were 11%, 18% and 17%, respectively, in the 3 regimens. The difference between split regimens and control regimen was not statistically significant (Table 6). Majority of the adverse reactions were managed symptomatically. Modification of chemotherapy had to be done only in 14 patients. One patient (split I) developed hypersensitivity reaction during the third week of treatment in the form of severe burning all over with hot flushes, when he was receiving Isoniazid and Pyrazinamide. Attempts

Table 5. **Response at the end of chemotherapy among patients with initial H resistant organ**

Response	2RE3HZ3(alt)/4RH2 (Split I)		3RE3HZ3(alt)/3RH2 (Split II)		2REHZ3/4RH2 (Control)	
	No.	%	No.	%	No.	%
Favourable	21	78	29	81	28	74
Doubtful	1	4	2	6	2	5
Unfavourable	5	19	5	14	8	21
Total	27		36		38	

Table 6. **Adverse reactions**

Regimen	Total No. of patients	Patients with complaints						
		Any	Gastro-intestinal	Arthr-algia	Cutan-eous	Giddi-ness	Hcpa-titis	Others
2RE3HZ3 (alt)/ 4RH2 (Split I)	243	27(11)*	9	7	7	3	2	1
3RE3HZ3(alt) 3RH2 (Split II)	244	43(18)	13	19	6	4		3
2REHZ3/4RH2 (Control)	244	41(17)	20	7	9	6	1	4

Percentages in parenthesis

* Includes "flu" syndrome, hypersensitivity reaction and peripheral neuropathy

for desensitization for both Isoniazid and Pyrazinamide failed and the drugs were terminated. Rifampicin was terminated in three patients. One patient (control) developed itching with purpuric rashes during the third week of treatment, second patient (control) had 'flu' syndrome from the second dose of treatment (this patient had received Rifampicin outside before admission to the study) and the third patient (split II) had fever and breathlessness after receiving Rifampicin and Ethambutol combination, developed hypersensitivity reaction while under observation in the clinic after receiving Rifampicin. Nine patients had interruption of drugs, seven for jaundice (2 split I, 4 split II, 1 control). Of these, five patients developed jaundice during the initial intensive phase. Rifampicin and Isoniazid (and Pyrazinamide in the initial phase) were withheld temporarily and reintroduced after subsidence of jaundice without any problem. The other two patients had interruption of the offending drug for severe glossitis in one and itching in the other. For these two patients also, drugs were reintroduced without any problem. One patient (control) had severe gastrointestinal problem and the dosage of the drugs had to be reduced.

Discussion

Several studies have shown that short course regimens using the four drugs viz, Rifampicin, Isoniazid, Pyrazinamide and Streptomycin or Ethambutol during the intensive phase are effective in the treatment of sputum positive pulmonary tuberculosis[1-3]. However, in these regimens patients find it difficult to consume the drugs given either daily or intermittently because of the bulk. An *in vitro* study done at our centre has demonstrated that splitting the 4 drugs REHZ into 2 split drug combinations of RE and HZ may not affect the bactericidal action of the regimens[4]. Further. it has already been reported from experimental murine tuberculosis that split dose alternating regimens are as effective as giving all the 4 drugs together[5]. Thus, it was assumed that anti-tuberculosis drugs given in split combination would be effective in human beings as well.

Hence, the Tuberculosis Research Centre conducted a controlled clinical trial in sputum positive pulmonary tuberculosis where the 3 drug combination was split into two 2-drug combinations, combination given on alternate each days, thus making each combination intermittent.

This study, as far as we are aware, is unique because split drug combinations were used in a controlled clinical trial in sputum positive pulmonary tuberculosis patients for the first time.

The results indicate that in patients with initially drug sensitive organisms, the split regimens have a high sterilizing activity, producing sputum conversion in 80 to 83% by 2 months, which is similar to that in the control regimen. This result compares well with the findings of 80 - 87% conversion in East African patients treated with short course chemotherapy[6-7]. At the end of chemotherapy, a favourable response (all cultures negative in the last two months of chemotherapy) was observed in 93 - 94% in split regimens which is again similar to that in the control regimen (Table 4). This finding is in conformity with the observations from *in vitro* studies, animal experiments and *in vivo* studies[4,5,8,9].

Among patients with bacilli resistant to 'H' alone favourable response was observed in 78% and 81%, respectively, in split I and II regimens which is similar to the 74% in control regimen, whereas in patients with organisms resistant to both Isoniazid and Rifampicin almost all had an unfavourable response.

Adverse reactions were generally low and similar in both split and control regimens. Patients were not questioned about symptoms of drug toxicity, but every spontaneous complaint was recorded after careful questioning by a physican. Main adverse reactions encountered were gastro-intestinal symptoms, arthralgia, hepatitis and cutaneous reactions. Proportions of patients with any of these complaints were 11% and 18% in split regimens and 17% in the control regimen. This is much lower than that observed at the centre in earlier SCC regimens with daily treatment in the initial intensive phase[1]. Modification of chemotherapy (termination, interruption, reduction) were necessary in only 14 cases.

Thus. there does not appear to be any difference either in the efficacy of regimens or toxicity when drugs are administered as split regimens (alternately) compared to giving all the 4 drugs together. All patients are being followed-up to assess the efficacy of the double drug combination regimens with long term follow up for possible relapses. It may be presumed that the relapses would be minimal since the culture negativity rates at the end of 2 months of intensive chemotherapy are of the order of 80 to 83%[8].

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