Original Article

EVALUATION OF A NON-RIFAMPICIN CONTINUATION PHASE (6HE) FOLLOWING THRICE-WEEKLY INTENSIVE PHASE FOR THE TREATMENT OF NEW SPUTUM POSITIVE PULMONARY TUBERCULOSIS

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Summary

Setting: Tuberculosis Research Centre, Chennai and Madurai, South India.

Objective: To assess response to treatment, relapse and emergence of MDR TB in newly diagnosed patients with sputum-positive tuberculosis using an intermittent intensive phase followed by a non-rifampicin continuation phase.

Design: Patients were treated in a controlled clinical trial with $2HRZE_3/6HE$ with thrice-weekly direct dosing in the intensive phase and once-weekly with six doses self-administered in the continuation phase. Clinical and bacteriologic evaluation was done every month for 24 months.

***Results*:** The overall outcome was good, with 92% favourable response (cure) and 4.8% relapse in 450 patients including 103 who did not receive extension of intensive phase for positive smear, 38 with initial H-resistant cultures, 4 with MDR TB and 15 who received less than 75% of chemotherapy. In 392 patients with drug-susceptible cultures, 96%were cured and only 4% relapsed. There was no emergence of MDR TB among failures and relapses; toxicity was low.

Conclusion: Newly-diagnosed Category I patients can be effectively treated with this regimen without emergence of MDR TB. It has immense potential in programmes where directly observed therapy cannot be ensured throughout, and when rifampicin is contraindicated in HIV-TB patients who require concomitant therapy with anti-retroviral drugs. **[*Indian J Tuberc 2007; 54:84-90*]**

Key Words: New sputum positive tuberculosis, intermittent intensive phase, non-rifampicin continuation phase, emergence of multi-drug resistant TB, HIV-TB.

INTRODUCTION

The control of tuberculosis assumes importance and urgency particularly in disease endemic countries which bears most of the burden of the disease. In several African nations, the co-existing pandemic of HIV/AIDS has multiplied the problem of treating TB in patients with HIV. In addition, increasing number of patients with multi-drug resistant tuberculosis (MDR TB) poses further challenges to control programmes.

The globally recommended DOTS strategy of the World Health Organization (WHO) for newly-diagnosed sputum positive patients (Category I), gives an option to use a daily or thrice-weekly initial intensive phase of HRZE/S* for two months followed by four months of RH either daily or thrice-weekly, or HE daily for six months in the continuation phase[1]. Daily regimens with 2SHRZ in the intensive phase followed by HT* for six months[2] and 2HRZE followed by HE for six months[3] have been studied and found to be effective in controlled clinical trials. However, the efficacy of thrice-weekly intensive phase followed by HE in the continuation phase has not been evaluated in controlled trials. A thrice-weekly rhythm has the advantage of easy implementation as directly observed therapy (DOT), especially during the critical initial intensive period of treatment. A daily rhythm using HE in the continuation phase has the advantage that, even if given once-weekly, patients are more likely to remember to take the drugs daily. Since rifampicin is not administered in this phase, the possibility of emergence of multi-drug resistance (MDR), among patients already harbouring H-resistant bacilli, is minimized. This regimen, if effective, will be of use in areas where directly observed treatment is difficult throughout the

* H = isoniazid; R= rifampicin; Z = pyrazinamide; E = ethambutol; S=streptomycin; T= thioacetazone. The number before the letters denotes duration in months

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treatment phase or when rifampicin cannot be used, as in patients with HIV-TB who require concurrent anti-retroviral and anti-tuberculosis treatment.

The primary objectives of this study were to a) evaluate outcome of $2HRZE_3/6HE$ by quantifying treatment failures and relapses, and b) assess the emergence of MDR TB.

In addition, we examined the impact of extension of the intensive phase by 12 doses in patients who had a positive smear at 2 months by comparing outcome with a group of patients who did not receive extension. The results of this part of the study will be published separately.

PATIENTS AND METHODS

Patients aged 12 years or more, who attended chest clinics of the Tuberculosis Research Centre (TRC) were assessed for inclusion to this study. Those who had at least two sputum smears positive for acid–fast bacilli (AFB)* and who had not received prior chemo-therapy for tuberculosis for one month or more were recruited. Criteria for admission were as in previous studies by the TRC[4]. In addition, patients with severe visual defects other than refractory error were excluded.

The study was approved by the Scientific Advisory Committee of the TRC and by the Institutional Ethics Committee. All participants gave informed consent, after information regarding the study regimen and procedures was given to them in their own language.

Intervention

Patients received an initial intensive phase of the four-drug combination consisting of H (600mg), R (450mg), Z (1500mg) and E (1200mg) three times a week for 24 doses. Patients weighing 60 kilogram or more at intake, received 600mg of R. A maximum period of one month was allowed for compensation of any doses missed during this phase. Each dose was given under the direct observation of a clinical nurse.

All patients received 6HE daily in the continuation phase: H (300mg) and E (800mg) supplied to the patient on a once weekly basis. The first dose was administered under direct observation and the remaining six doses for the week supplied for self-administration. Missed doses were not compensated during this phase.

For the first 226 patients the continuation phase was started irrespective of the smear results at the end of intensive phase. As a result 103 patients did not receive additional 12 doses despite having a positive smear. For the next 241 patients, the initial phase was extended by 12 doses for 112 patients with positive smear at two months as recommended in the WHO guidelines[1]. The two groups have been analyzed together as well as separately. Since there was no statistically significant difference between the groups the overall results are presented in this paper.

Pre-treatment investigations

A chest radiograph PA view, examination by smear and culture for *Mycobacterium tuberculosis* of four sputum samples (2 overnight;2 spot collections) and drug-susceptibility testing for H, R, E and S on two pre-treatment cultures were undertaken. Identification tests were carried out on all positive cultures. Hepatic and renal functions and haematological parameters were assessed. A detailed clinical examination, including tests for visual acuity and colour differentiation using the Ishihara chart were carried out.

Investigations during treatment and follow-up

Patients were reviewed every month by a physician. Three sputum specimens (two overnight, one spot) were examined by smear and culture for *M. tuberculosis* every month until the end of the treatment phase. One positive culture at each month was tested for drug susceptibility to H, R and E.

A chest radiograph was taken at end of 1st month and end of treatment phase for all patients. An additional radiograph was taken if the sputum

* Only those with at least two positive cultures were included in the analysis

was reported as positive by smear at four months or later, or if clinical symptoms warranted one, as judged by the physician.

All patients were closely monitored for adverse drug reactions (ADRs), and any modification of the study regimen was recorded. Whenever a complaint suggestive of ADR was made, a team of physicians assessed the patient and detailed examination was carried out and all findings documented.

From the end of treatment until the 24th month, two sputum samples (one overnight, one spot) were collected each month and subjected to smear and culture for *M. tuberculosis*. A chest radiograph was taken at 12 and 24 months and reviewed by a physician.

General Management

Patients were treated on a domiciliary basis. During the initial intensive phase, they attended three times a week to have their treatment under direct observation in the clinic. During the continuation phase they attended once-weekly. A health care worker carried out surprise home visits and pill-counts. If any excess packets of HE were found, they were retrieved and these doses were documented as "missed" on the treatment card maintained at the clinic. If patients failed to attend on the allotted day in either phase of treatment, their homes were visited and all attempts made to retrieve them.

Patients were re-questioned for additional information about prior chemotherapy at the first monthly examination, and when any drug resistance was reported.

Bacteriological procedures

Sputum smears were examined by fluorescence microscopy[5] and specimens were processed for culture by a modified Petroff's method using Lowenstein-Jensen medium. Positive cultures were confirmed as *M. tuberculosis* employing key identification tests[6], and drug susceptibility tests to H, R and E by the minimal inhibitory concentration method[7] and S by resistance ratio method[7] were carried out. The definitions of drug resistance were the same as in previous studies for H[8] and R[8].

Definitions used

Favourable response (Cure): If all six cultures were negative during the last two months of chemotherapy or if a culture was positive during the last two months but became negative subsequently without additional chemotherapy.

Unfavourable response: When (a) two or more cultures were positive in the last two months of treatment, including at least one in the last month, with at least one culture growing 20 colonies or more, or (b) persistent bacteriological positivity or radiographic and / or clinical deterioration warranting change of chemotherapy, or (c) death due to tuberculosis during the treatment phase or (d) change of treatment due to adverse drug reactions.

Bacteriological relapse requiring treatment

Two or more cultures positive for *M. tuberculosis* in a 2-month period, at least one with a growth of 20 colonies or more and associated with a positive smear, occurring during the follow-up period.

RESULTS

A total of 467 patients were admitted to the study between December 1998 and May 2001. Eight patients did not fulfill eligibility criteria: cultures negative for *M. tuberculosis* (4), prior anti-TB treatment for more than one month (2), and identified to have severe visual defect after recruitment (2). Nine others were excluded due to non-availability of smear results at the end of two months. Of the remaining 450 patients, 70% were male, mean age was 31.4 years (range 13 to 65) and mean weight was 41.5 kg. (27.4 to 74.2). Smear grading was 2 plus or more in 70 % of patients and culture grade was 3 plus in 80%. Pre-treatment cultures were susceptible to both H and R in 408 (91 %), resistant to H in 38 (8.4%) and HR in 4 (0.9%) patients.

Overall results

Response to treatment and relapse during follow-up

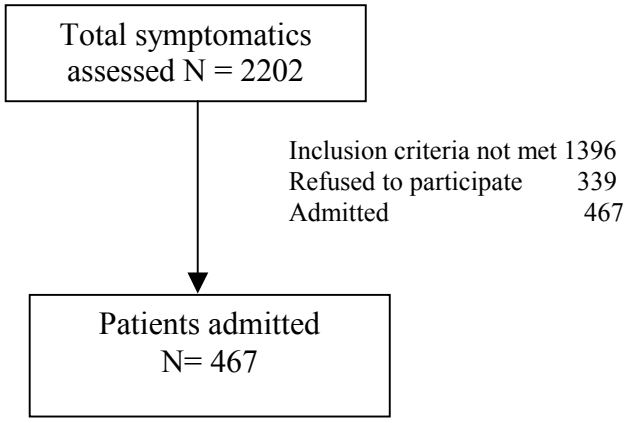
At the end of treatment, 413 (92 %) of 450 patients had a favourable response (cure). Thirty-seven patients had an unfavourable response (29 bacteriological failure, 4 TB deaths, two change of treatment due to adverse drug reactions, and two developed extra-pulmonary TB while on treatment). Of the 413 patients with favourable response (cure), 20 (4.8%) relapsed during the follow-up (Figure 1).

Emergence of drug resistance

In all, 57 patients either failed or relapsed (Figure 1). Four of them had pre-treatment MDR TB. None of the remaining 53 patients emerged with R-resistance or developed MDR TB at the time of failure or relapse. Seven had emergence of single drug resistance to H.

Sub-group analysis

Of the 392 patients who had initially susceptible organisms to H and R and had received 75% or more of prescribed chemotherapy, 378 (96%) had a favourable response at the end of treatment. Six patients were excluded from relapse analysis (four non-TB deaths, one treated for Hansen's disease with a R-containing regimen and one default), although the last available sputum specimens were negative in all these patients. Of the remaining 372 followed upto 24 months, 15 (4%) relapsed (Table 1). Among 37 patients with cultures initially resistant to H, 21 (57%) had a favourable response and 3 had



Exclusions	8
Ineligible:	
Cultures negative for *M. tuberculosis*	4
Previous Rx ≥ 1 month	2
Severe visual defect	2
Eligible	459
Sputum not available at 2 months	9
No. in analyses	**450**
Favourable response (cure) at the end of treatment	413 (92%)
Unfavourable response	37 (8%)
Relapses	20 (4.8%)

Figure: Schematic presentation of all eligible patients in the controlled clinical trial to evaluate the efficacy of a non-rifampicin continuation phase following a thrice-weekly intensive phase in the treatment of newly diagnosed smear positive pulmonary tuberculosis, South India.

a bacteriologic relapse. Of 4 patients who had organisms resistant to both H and R, three had an unfavourable response and one relapsed. The remaining 17 patients had received less than 75% of the study regimen and, therefore, not included in the efficacy analysis.

Adverse reactions

Symptoms suggestive of any adverse drug reactions were reported by 87 (19%) patients: gastro-intestinal reactions by10%, arthralgia 4.6%, cutaneous reactions 5.2%, giddiness 1.3% and hepatotoxicity 0.4%. Reactions were considered severe in two: Z terminated in one patient with severe itching and H in another for jaundice. In all other patients, the reactions were mild. None had ocular toxicity.

DISCUSSION

The findings of this study indicate that the regimen with 6HE in the continuation phase following a thrice-weekly intensive phase can be used to treat new sputum-positive TB patients (Category I). The treatment-outcome in patients with initially drug-susceptible disease was good, with a cure rate of 96% and 4% relapse (Table 1). This finding assumes importance for TB control programmes considering that the vast majority - 80% or more - of patients in this category harbour bacilli susceptible to both H and R[9-11]. An earlier study by TRC[3], which evaluated a similar regimen with a daily intensive phase (2HRZE/6HE), showed 96% cure and 4% relapse in 245 patients with drug-susceptible cultures who received less than one month of prior chemotherapy. These findings indicate that intensive phase with intermittent treatment did not compromise efficacy of the regimen in these patients. An intermittent intensive phase has the advantage that it can be more easily implemented as DOT under TB control programme conditions. Although the outcome in the presence of initial H-resistance was not as good (Table 1), none of the failures or relapses had emergence of additional R-resistance. Recently an international multi-centric study, comparing a daily 8-month regimen and an intermittent intensive phase 8-month regimen, has also reported similar results[12]. However, emergence of drug resistance was not looked into in that study.

Adverse reactions such as hepatitis and arthralgia were less with the thrice-weekly intensive phase used in this study compared to the daily rhythm in the earlier study[3] (0.4% vs 4%; 5% vs 25%, respectively). However, gastro-intestinal reactions were more common (10% vs 3%).

Further, in this study, none of the 53 failures and relapses had developed MDR TB. A programme-based study from Malawi [13] also reports that none of the failures to first line treatment with 6HE in the continuation phase following either 2SHRZ or $2HRZE_3$ had MDR TB. Another study from Vietnam however, reports a higher rate of MDR TB among patients who failed on Category I regimens under programme conditions using the same continuation phase[14]. This

Table: Response at the end of treatment and relapse in patients who received more than 75% of chemotherapy in the control clinical trial, Chennai, South India

Drug susceptibility Profile*	Total patients	Favorable response at end of treatment		Total patients	Relapses	
		No.	%		No.	%
Susceptible to HR	392	378	96	372	15	4.0
Resistant to H	37	21	57	21	3	14.0
Total	429	399	93	393	18	4.6

* 4 MDR: 3 failed and one relapsed

is at variance with the findings of our studies and the report from Malawi. A recent report from Bangladesh[11] indicates that there has been a significant decrease in MDR TB after 1995 when 2HRZE/6HT was introduced as the Category I regimen in the national programme, further supporting our finding.

In a recent analysis of results of an earlier study by TRC[15], we examined the emergence of MDR TB among patients treated with HR_2 in the continuation phase following the same intermittent intensive phase. Of 1043 patients 10% had either failed or relapsed, and of these 13 (12%) emerged with MDR TB. Higher rates of emergence of MDR TB have been reported from Thailand[10] and Peru[16] using HR in the continuation phase under programme conditions.

It is evident, therefore, that patients who fail on regimens with a non-rifampicin continuation phase, even from among those with initially H-resistant bacilli, can be successfully treated with the current re-treatment regimen of 2SHRZE/1HRZE/5HRE recommended by WHO, as there was no emergence of MDR TB. This is an important finding for TB control programmes.

A limitation of this study was that we did not use a concurrent control. We, however, have historical controls from recent trials done in the same setting. The efficacy of daily HRZE followed by HE in the continuation phase[3] and $HRZE_3$ followed by HR_2 have been demonstrated[17]. Our intention was to evaluate a regimen with an intermittent intensive phase with HE in the continuation phase.

In the current context of increasing proportions of HIV seropositivity among patients with tuberculosis, greater numbers of such patients may require treatment for both diseases. Malawi has reported 77% HIV sero-prevalence among TB patients[18]. The UNAIDS is projecting a rapidly expanding epidemic of HIV/AIDS across Asia, which also has the highest burden of TB. There is evidence to suggest drug interactions between rifampicin and both protease inhibitors and nevirapine,[19-22] resulting in sub-optimal serum levels, which could increase the chances of emergence of resistance to these drugs. Our study regimen with 6HE in the continuation phase can therefore be given safely with anti-retroviral therapy after the intensive phase of treatment for tuberculosis. However, only one patient in the current study was HIV positive and had a favourable outcome. Clearly, more studies are needed to establish its utility in HIV positive patients.

This regimen with a non-rifampicin continuation phase ($2HRZE_3/6HE$), with an overall favourable response (cure) of 92% and a relapse rate of under 5%, has the following advantages: a) the thrice-weekly intensive phase is eminently suited for directly observed therapy, which is a key component of the DOTS strategy under TB control programmes worldwide, b) with once-weekly supply in the continuation phase it can be used in regions where DOT cannot be ensured throughout the treatment phase, c) with virtually no emergence of MDR TB, the failures and relapses of this regimen can be successfully treated with the current re-treatment (Category II) regimen and d) for the increasing numbers of patients requiring concomitant chemotherapy for HIV and TB, anti-retroviral therapy can be started as soon as the rifampicin containing initial intensive phase is completed.

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