

## SHORTENING SHORT COURSE CHEMOTHERAPY : A RANDOMISED CLINICAL TRIAL FOR TREATMENT OF SMEAR POSITIVE PULMONARY TUBERCULOSIS WITH REGIMENS USING OFLOXACIN IN THE INTENSIVE PHASE

Tuberculosis Research Centre  
(Indian Council of Medical Research), Chennai

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### Summary:

**Background:** The recommended 6-month regimens for the treatment of pulmonary tuberculosis are highly effective in the setting of clinical trials, yet cumbersome to implement under practical conditions. Shorter treatment regimens would ease drug administration for both patients and providers: an effective regimen of 3 or 4 months' duration would have significant practical advantages for tuberculosis control.

**Methods:** The study subjects were HIV negative adults with newly diagnosed sputum smear and culture positive pulmonary tuberculosis. Eligible patients were randomly allocated to one of four regimens: (a) Ofloxacin, Isoniazid, Rifampicin, and Pyrazinamide daily for 3 months; (b) regimen(a), followed by Isoniazid and Rifampicin twice a week for 1 month; (c) regimen(a), followed by Isoniazid and Rifampicin twice a week for 2 months; or (d) Ofloxacin, Isoniazid, Rifampicin, and Pyrazinamide daily for 2 months, followed by Isoniazid and Rifampicin twice a week for 2 months. Each dose was administered under direct observation. The patients were assessed clinically and bacteriologically every month during and after treatment. Follow up will continue for 5 years; the results up to 24 months after treatment are presented here.

**Results:** A total of 529 patients were admitted to the study. Data for efficacy analysis are available for 416 patients: 113 were excluded primarily because of limited compliance. At the end of treatment, only 4 (1%) of 360 patients with initially drug-susceptible tuberculosis had an unfavourable bacteriological response (> 1 positive culture in the last 2 months of treatment), one patient in each regimen. Over a follow-up period of 2 years, 7 (8%) of 83, 3 (4%) of 81, 2 (2%) of 86, and 12 (13%) of 91 patients relapsed in regimens (a) through (d), respectively. Most (79%) of the relapses occurred in the 6 months following the cessation of treatment. Of the 47 patients with tuberculosis initially resistant only to Isoniazid, 2 (4%) had an unfavourable bacteriological response at the end of treatment. However, bacteriological relapse occurred in 8 (19%) of 43 such patients who were assessed for relapse. Intention to treat analysis i.e. after including those who had inadequate therapy, of 469 patients (which had 53 patients who received inadequate chemotherapy), showed that only 4 (3%) of 120, 6 (5%) of 115, 5 (4%) of 118 and 3 (3%) of 116 patients in the 4 regimens had an unfavourable bacteriological response at the end of treatment. Adverse reactions attributable to the anti-tuberculosis medications were observed in 3 (1%) (regimen d) to 44% (regimen c) of the patients, but a majority of the reactions were mild and manageable with symptomatic measures. Only 5% of patients had a reaction that required modification of the regimen.

**Conclusions:** Regimens of 4 or 5 months' duration that contain Ofloxacin and other first-line anti-tuberculosis agents for at least three months can achieve high cure rates and low 24-month relapse rates in newly diagnosed patients with smear positive pulmonary tuberculosis without causing significant adverse reactions. These results indicate that Ofloxacin containing regimens of 4-5 months achieve >95% efficacy with no increased incidence of adverse reactions and minimal relapses, permitting shortening of short-course chemotherapy.

**Key Words:** Tuberculosis, Chemotherapy of tuberculosis, Short course chemotherapy, Ofloxacin, Fluoroquinolones, Clinical trials

## INTRODUCTION

One of the long-term goals in tuberculosis control has been to shorten the period of treatment while maintaining high rates of cure with low rates of relapse. The current, widely used 6-month

regimens are highly effective in the clinical trial setting, yet are cumbersome to implement under control programme conditions. Shorter duration treatment regimens would facilitate drug administration, for both patients and treatment providers; an effective, fully oral regimen of 3 or 4

**Correspondence:** Dr PR Narayanan, Director, Tuberculosis Research Centre, Mayor VR Ramanathan Road (Spurtank Road), Chetput, Chennai 600031, Fax :91 044 8228894. Email [pmarayanan@vsnl.com](mailto:pmarayanan@vsnl.com)

months' duration would have significant practical advantages for patients as well as tuberculosis control programmes. In a previous randomized clinical trial, a 3-month regimen of daily Streptomycin, Isoniazid, Rifampicin, and Pyrazinamide resulted in a nearly 100% favourable outcome at the end of treatment (all sputum cultures negative); yet 20% of the patients relapsed in the subsequent 21 months.<sup>1</sup> Based on that experience, as well as the results of *in vitro* studies demonstrating the bactericidal activity of Ofloxacin<sup>2</sup>, we conducted a randomized, controlled clinical trial to assess the efficacy of regimens using Ofloxacin in the intensive phase for the treatment of smear-positive pulmonary tuberculosis.

## OBJECTIVES

To study the efficacy of 3-, 4-, and 5-month regimens using Ofloxacin in the intensive phase for the treatment of smear positive pulmonary tuberculosis, in terms of the proportions of patients who become culture negative at the end of treatment and the proportion of patients who relapse during follow-up after treatment. The month by month sputum culture conversion and the occurrence of adverse reactions to the drugs used in the regimens were also studied.

## METHODS

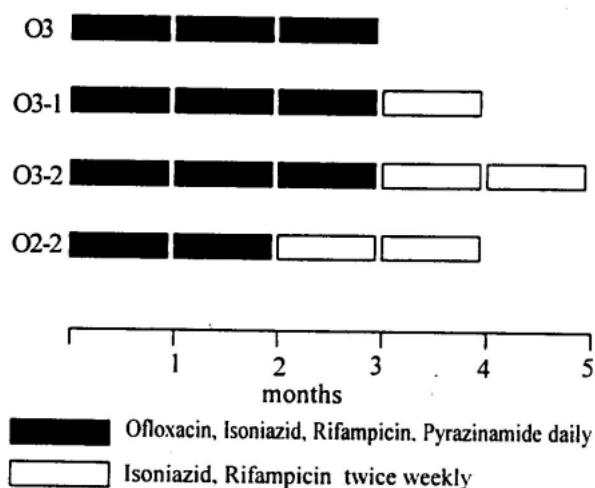
### Patients :

The study was conducted at our centres in two cities in south India. Chennai and Madurai. Study subjects were adult patients, at least 20 years old who had newly diagnosed smear positive pulmonary tuberculosis and lived within a designated area of our centres. For admission to the study, the patients were required to consent to undergo all the investigations, attend the health centre daily for supervised outpatient treatment and allow home visits by centre staff. Those with previous treatment for tuberculosis exceeding 15 days were not eligible, nor were those with concomitant hypertension, diabetes mellitus, epilepsy, or serious forms of extra-pulmonary tuberculosis. Patients with fewer than two positive sputum cultures initially, and those who were HIV sero-positive were excluded. Informed consent was obtained from all the patients.

### Regimens and randomisation:

Eligible patients who had at least two sputum smears positive for acid-fast bacilli were randomly allocated to one of the following four regimens, stratified on the degree of sputum smear grading of the penultimate home sputum specimen (first stratum - 0 or 1+ ; second stratum - 2+ or 3+ ):

- (O3) - Ofloxacin, Isoniazid, Rifampicin, and Pyrazinamide daily for 3 months
- (O3-1) - Regimen a, followed by Isoniazid and Rifampicin twice a week for 1 month
- (O3-2) - Regimen a, followed by Isoniazid and Rifampicin twice a week for 2 months
- (O2-2) - Ofloxacin, Isoniazid, Rifampicin, and Pyrazinamide daily for 2 months, followed by Isoniazid and Rifampicin twice a week



**Figure 1** : Treatment regimens

Restricted random allocation sequences were generated by a statistician using random number tables, separately for the two strata and sealed envelopes were used to assign the regimens. Patients were enrolled in the study by the physicians, and when ready for allocation, the case sheet was sent to the statistician who drew the regimen from sealed envelopes depending on the stratum to which the patient belonged.

The medication dosages were: Ofloxacin 400 or 600 mg, Rifampicin 450 or 600 mg, and Pyrazinamide 1.5 or 2 g, depending on body weight (<40 kg or ≥40 kg); and Isoniazid 300 mg (daily

treatment) or 600 mg (twice-weekly treatment), irrespective of body weight. All drugs were administered under supervision as a single dose. Patients who missed clinic visits were visited at home and strongly encouraged to attend the clinic for treatment.

Pre-treatment screening included four sputum specimens (two spot specimens and two overnight collections), which were examined by fluorescence microscopy<sup>3</sup> and cultured for mycobacteria by the modified Petroffs method.<sup>4</sup> Positive cultures were identified as *Mycobacterium tuberculosis* by standard methods.<sup>5,6</sup> Drug susceptibility tests were performed on Lowenstein Jensen medium using a 4 mg/ml bacterial suspension by the resistance ratio method (Streptomycin) or the minimum inhibitory concentration method (Isoniazid, Rifampicin and Ofloxacin).<sup>7-10</sup> The definitions of drug resistance for Rifampicin, Streptomycin and isoniazid were the same as used in previous studies<sup>1, 11</sup>; for Ofloxacin, drug resistance was defined as growth on 4 mg/l of the medium.<sup>10</sup> The following investigations were also done: posterior-anterior chest radiograph; urine examination for albumin, glucose, bile pigments, acetyl Isoniazid, and Rifampicin; total and differential leucocyte counts, haemoglobin estimation, total erythrocyte and platelet counts; liver function (bilirubin, alanine transaminase, aspartate transaminase, alkaline phosphatase); renal function (serum urea and creatinine); serum uric acid; random blood glucose; and ELISA for HIV antibody.

A physician examined the patient every month and recorded adherence to treatment, any adverse drug reactions and the clinical response. Sputum specimens were examined every month by microscopy and culture, three (two overnight and one spot) during the treatment phase and two (one overnight and one spot) during the follow-up phase. One positive sputum culture was tested each month for susceptibility to Isoniazid, Rifampicin and Ofloxacin. Sputum specimens were given identification laboratory numbers, and bacteriological investigations were carried out by technicians who were blind to the clinical status of the patient and the regimen. A chest radiograph was obtained during the first month and at the end of treatment. Patients who had clinical deterioration or had adverse reactions to anti-tuberculosis drugs were examined by a team of physicians and any decision to change or modify the regimen was made collectively. At the

end of treatment, every case was reviewed by a panel consisting of two physicians, a bacteriologist and a statistician. Follow-up was designed to last 5 years; the results up to 24 months after treatment are presented here.

#### *Outcome:*

Primary outcome was recorded as follows:

*a) Bacteriological status at the end of treatment:* The response to treatment was classified as "favourable" if all six sputum cultures in the last 2 months of treatment were negative; as "unfavourable" if one, or more, of the three cultures was positive in each of the last 2 months of treatment; and as "doubtful" if one or two cultures were positive in the last month of treatment but all the three cultures from the preceding month were negative.

*b) Bacteriological relapse:* Among patients with a favourable or doubtful response at the end of treatment, bacteriological relapse was defined as a total of two or more positive cultures for *Mycobacterium tuberculosis* in any two consecutive months. Retreatment was started if one of the positive cultures yielded 20 colonies or more and if one of the smears was positive.

Secondary outcome was recorded as follows:

*a) Sputum culture conversion at two months:* The proportion of patients who became sputum culture negative at the end of two months of treatment.

*b) Adverse reactions to anti-tuberculosis drugs:* The proportion of patients who developed adverse reactions attributable to the drugs in the treatment regimen

#### *Sample size :*

The sample size was calculated on the following basis. The efficacy of a 3-month regimen previously studied by the Tuberculosis Research Centre<sup>1</sup> was 80%. and we anticipated an efficacy of 95% for the current regimens. With a type I error of 0.05, and a type II error of 0.20, the approximate sample size for each regimen was calculated to be 115. Allowing for a 15% attrition in patients over 5-year follow-up period, the final sample size was calculated to be  $115 + 17 = 132$  or about 130 patients for each regimen.

*Statistical analysis:*

Proportions of patients with primary and secondary outcomes (for patients with initially drug susceptible and drug resistant tuberculosis separately), in the four regimens, were compared using  $X^2$  test, and p value with 95% CI was calculated.

Efficacy analysis was done for 416 patients who received at least 75% of the prescribed chemotherapy. Intention-to-treat analysis was done for 469 (92%) of the 512 patients who fulfilled the eligibility criteria and were admitted to the study.

The study protocol was cleared by the Scientific Advisory Committee and by the Institutional Ethical Committee of the Tuberculosis Research Centre.

**RESULTS**

The study commenced in November 1995 and recruitment of cases was completed in November 1998. A total of 529 patients were admitted to the study. Of these, 113 patients were excluded from analysis of efficacy of the regimens for the following reasons: 17 did not fulfill the eligibility criteria (11 had only one or no positive sputum cultures initially, 3 had received previous anti-tuberculosis treatment for more than 15 days, 2 were HIV sero-positive and 1 was less than 20 years of age); 51 received less than 75% of the prescribed treatment, 30 were lost to treatment for more than 1 month continuously, 2 died of non-tuberculosis causes during treatment, 1 died 11 days after starting treatment, 8 required a change in the regimen (5 because of adverse drug reactions and 3 due to pneumothorax), 2 refused treatment, and 2 received treatment for tuberculosis from a private practitioner after admission to the trial. We present data on the remaining 416 patients: 360 with tuberculosis initially susceptible to Isoniazid, Rifampicin and Ofloxacin, and 56 with tuberculosis initially resistant to one or more drugs (47 to Isoniazid, 7 to Isoniazid and Rifampicin, 1 to Isoniazid, Rifampicin, and Ofloxacin, and 1 to Ofloxacin alone).

Intention-to-treat analysis on 469 patients (404 with tuberculosis initially susceptible to all the drugs, and 65 with tuberculosis initially resistant to

one or more drugs) is also given which includes 53 of the 81 patients who either received less than 75% of the prescribed chemotherapy (48) or missed treatment for more than 1 month continuously (5). The other 28 patients in these categories did not have data that permitted assessment of bacteriological response at the end of treatment (Figure 2).

The baseline demographic and clinical characteristics of the 469 patients of intention-to-treat group were similar among the four treatment groups (Table 1). Male patients comprised 369 (79%) of the total, and those aged 20 to 39 years, 326 (70%) of the total. The mean body weight was 42.1 kg (range 30.0 - 65.8 kg); 173 patients (37%) weighed less than 40 kg, and only 11 (2%) weighed 55 kg or more. Most patients had extensive, cavitory tuberculosis and 246 (52%) had 3+ or 3+ sputum smears.

**Table 1** : Characteristics of 469 smear positive pulmonary tuberculosis patients according to drug regimen allocated

Characteristics	Regimen			
	O3 (n=120)	O3-1 (n=115)	O3-2 (n=118)	O2-2 (n=116)
<b>Sex</b>				
Male	95	91	94	89
Female	25	24	24	27
<b>Age</b>				
<40yrs	85	81	78	82
>=40yrs	35	34	40	34
<b>First home Sp. smear</b>				
Neg or 1+	55	57	57	54
2+ or 3+	65	58	61	62

**Patients with drug-susceptible tuberculosis***Response to treatment and Efficacy analysis:*

A total of 360 patients had tuberculosis that was initially susceptible to all the drugs used. Of these, 88 patients each were assigned to regimens O3, O3-1, and O3-2, and 96 to regimen O2-2. Figure 3 presents the proportion of patients, month by month, who had negative cultures for all three monthly sputum specimens. Culture negativity by

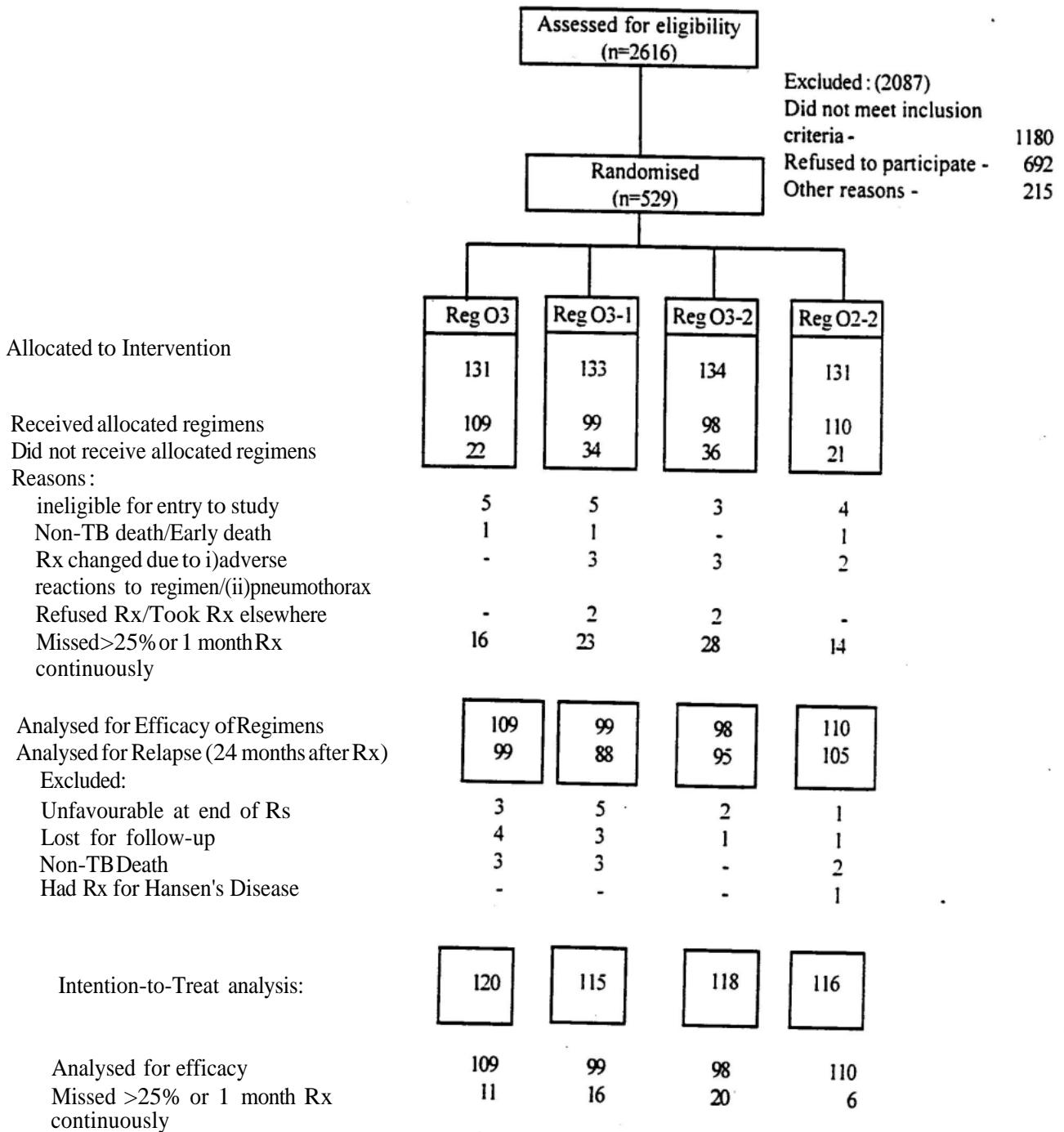
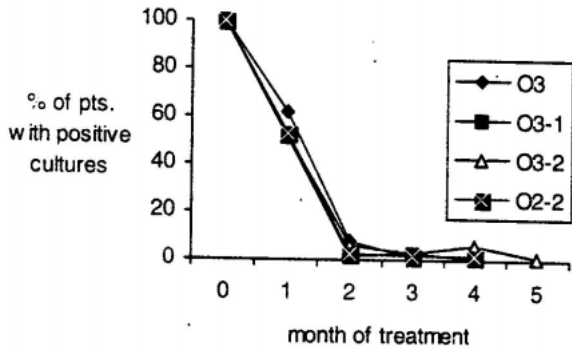


Figure 2 : Flow diagram of patients from eligibility to analysis stages

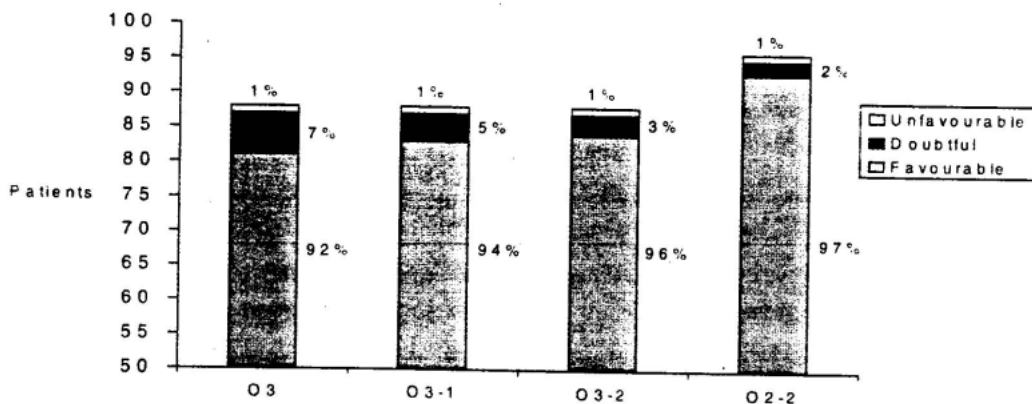
the second month ranged from 92% to 98%. In all the four groups, 98% to 99% of patients had three negative cultures in the last month of treatment.



**Figure 3:** Month by month sputum culture conversion in 360 patients with tuberculosis initially susceptible to Isoniazid, Rifampicin and Ofloxacin (efficacy analysis)

had an unfavourable bacteriological response, 7 who died of non-tuberculosis causes, 7 who were lost to follow-up and 1 who needed treatment for Hansen's disease), 341 patients were followed for 24 months after completing treatment. Of the 341 patients, 24 (7%) had bacteriological relapse requiring retreatment: 7 (8%) of 83 in the O3 regimen (95% CI 3-17%), 3 (4%) of 81 in the O3-1 regimen (95% CI 1-10%), 2 (2%) of 86 in the O3-2 regimen (95% CI 1-8%), and 12 (13%) of 91 in the O2-2 regimen (95% CI 7-22%) (Table 2). In the relapsed patients, in 19 (79%), the relapse occurred in the first 6 months of follow-up, and only one patient relapsed after 12 months. Eighteen of the 24 patients who relapsed received more than 90% of the prescribed chemotherapy and only 3 received less than 80%.

Sputum culture drug susceptibility patterns were consistent with pre-treatment values in 22 of the 24 patients, but in the remaining 2 patients the



**Figure 4:** Response at end of treatment in 360 patients with tuberculosis initially susceptible to Isoniazid, Rifampicin and Ofloxacin (efficacy analysis)

Four patients, one in each regimen, had an unfavourable response at the end of treatment: one died in the second month of treatment (regimen O3-1) and 3 had persistent positive sputum cultures that remained susceptible to all the drugs (Figure 4). Of the 15 patients who had doubtful response, all but one (regimen O3) subsequently had cultures that became negative and remained so through the 24 months of follow-up.

*Bacteriological relapse:*

After the exclusion of 19 patients (4 who

cultures at relapse were newly resistant to Isoniazid. These two patients had received 96% and 99% of the prescribed chemotherapy. The difference in the relapse rates between patients who received regimen O3-2 (2%) and those who received O2-2 (13%) was statistically significant (p=0.02). Also statistically significant was the difference in relapse rates between those who received 3 months of the intensive Ofloxacin-containing phase (regimens O3, O3-1, or O3-2, for which the mean relapse rate was 12/250, or 5%), and those who received only 2 months of the intensive phase (regimen O2-2, for which the relapse rate was 12/91, or 13%) (p=0.02).

*Isolated positive sputum cultures :*

Forty-five patients had a single positive sputum culture during the follow-up period (9 in the O3 regimen, 12 in the O3-1 regimen, 16 in the O3-2 regimen and 8 in the O2-2 regimen). In 12 patients these cultures occurred in the period up to 12 months, in 14 in the period 13-18<sup>th</sup> month and in 19 patients in the period 19-24<sup>th</sup> month from the start of treatment. In all these patients, the sputum cultures in the months following the positive cultures were negative. One patient (regimen O3-1) produced one positive culture each in the 14<sup>th</sup> and 19<sup>th</sup> months. The subsequent cultures were negative.

**Patients with tuberculosis initially resistant only to Isoniazid***Response to treatment*

The bacteriological response to treatment and the rates of relapse are shown in Table 3 for patients with tuberculosis initially resistant only to Isoniazid. Of 47 such patients, 2 (one each in regimens O3 and O3-1) had an unfavourable bacteriological response at the end of treatment. Both received only 79% of the prescribed chemotherapy but did not develop

additional resistance during treatment. Two patients in the O3 regimen (both of whom subsequently relapsed) and one in the O3-1 regimen were classified as having a doubtful response to treatment.

*Bacteriological relapse :*

A total of 43 of these patients were followed for 24 months after treatment. Relapse occurred in 8 patients: 3 of 15 in the O3 regimen, 2 of 9 in the O3-2 regimen, and 3 of 12 in the O2-2 regimen. There were no relapses among the 7 patients in the O3-1 regimen. However, the numbers are small. All of the relapses occurred in the 12 months following the cessation of therapy - 5 in the first 6 months and 3 subsequently. All the 8 patients who relapsed had received between 84% and 100% of the prescribed chemotherapy. In 6 of the 8 patients, the drug susceptibility pattern of the sputum cultures at relapse was consistent with the pre-treatment pattern (Isoniazid resistant), but two had cultures that were susceptible to all the drugs.

*Isolated positive sputum cultures .*

Six patients had a single positive sputum culture during the follow-up period (2 in the O3 regimen, 1 in the O3-2 regimen and 3 in the O2-2

**Table.2 :** Outcome in 341 patients initially susceptible to Isoniazid, Rifampicin and Ofloxacin followed up for 24 months according to regimen (efficacy analysis)

Regimen	Total patients	Relapse		Month of relapse post-treatment		
		(n)	%	1-6	7-12	13-19/21
O3	83	7	8	5	1	1
O3-1	81	3	4	3	0	0
O3-2	86	2	2	2	0	0
O2-2	91	12	13	9	3	0

**Table3 :** Response to treatment and relapse during follow-up in 47 patients initially resistant to isoniazid according to regimen (efficacy analysis)

Reg.	Patients	Favourable	Doubtful	Unfavourable	Assessed for relapse	Relapse (n)	Month of relapse	
							1-6	7-12
O3	18	15	2	1	15	3	1	2
O3-1	8	6	1	1	7	0	—	—
O3-2	9	9	0	0	9	2	1	1
O2-2	12	12	0	0	12	3	3	—

regimen). In 4 patients these cultures occurred in the period up to 12 months, in 1 in the period 13-18<sup>th</sup> month and in 1 patient in the period 19-24<sup>th</sup> month from the start of treatment. In all these patients, the sputum cultures in the months following the positive cultures were negative.

### Patients with tuberculosis initially resistant to Isoniazid and Rifampicin

Of 7 patients with initial resistance to isoniazid and Rifampicin, 5 had an unfavourable bacteriological response at the end of treatment (one each in regimens O3 and O3-2, and three in regimen O3-1). One patient (regimen O2-2) relapsed in the fifth month. Another patient, who had resistance to isoniazid, Rifampicin and Ofloxacin, responded well to treatment (regimen O2-2) and has continued to have negative sputum cultures through 24 months of follow-up.

One patient with resistance to Ofloxacin alone (regimen O3) had a favourable response at the end of treatment, but died in the nineteenth month of follow-up for reasons unrelated to tuberculosis.

### Intention-to-treat Analysis

The Intention-to-treat analysis was done for 469 patients (416 in efficacy analysis plus 53 patients who either received less than 75% of the prescribed treatment (48) or missed more than one month of treatment continuously (5). Of these 469 patients (404 with drug susceptible tuberculosis, 56 with initial

resistance to isoniazid alone, 7 with initial resistance to Isoniazid and Rifampicin, 1 with initial resistance to Isoniazid, Rifampicin and Ofloxacin and 1 with initial resistance to Ofloxacin alone), 120, 115, 118 and 116 were assigned to regimens O3, O3-1, O3-2 and O2-2 respectively. Eighteen patients, consisting of 4 (3%) in regimen O3, 6 (5%) in regimen O3-1, 5 (4%) in regimen O3-2 and 3 (3%) in regimen O2-2, had an unfavourable bacteriological response at the end of treatment. Five of these 18 patients had initial resistance to Isoniazid and Rifampicin. (Table 4).

### Adverse reactions to Drugs:

Adverse reactions attributable to anti-tuberculosis drugs occurred in 31% (regimen O2-2)-44% (regimen O3-2) of the 512 patients who were eligible for admission to the study (Table 5). This analysis, thus, includes patients who were excluded from the efficacy analysis. Modification of the treatment regimen was required in only 24 (5%) of all the patients. Arthralgia was reported by 25% to 36% of patients in the four regimens, but only four patients required a change in the regimen: temporary withholding of Pyrazinamide in three patients, and a reduction of the dose in one. Patients who received 2 months of pyrazinamide were less likely to develop arthralgia (25%) compared with patients who received 3 months of Pyrazinamide (36%), though this difference was not statistically significant (P=0.08).

**Table 4 :** Response to treatment in 469 smear positive patients irrespective of compliance according to regimen (intention-to-treat analysis)

Reg.	Susceptible to all drugs				Resistant to one/more drugs				All patients			
	Pts n	Fav n	Doubt n	Unfav n (%)	Pts n	Fav n	Doubt n	Unfav n	Pts n	Fav n	Doubt n	Unfav n (%)
O3	97	90	6	1 (1)	23	18	2	3	120	108	8	4 (3)
O3-1	103	96	5	2 (2)	12	6	2	4	115	102	7	6 (5)
O3-2	104	98	3	3 (3)	14	12	0	2	118	110	3	5 (4)
O2-2	100	96	2	2 (2)	16	15	0	1	116	111	2	3 (3)

Fav - Favourable Doubt - Doubtful Unfav - Unfavourable



**Table 5** : Adverse reactions in 512 smear positive patients admitted to the study, according to regimen

Reg.	Pts (n)	Arthralgia		Hepatitis		Gastro-intestinal		Cutaneous		Giddiness		Any	
		(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
O3	126	45	36	1	<1	9	7	4	3	0	0	52	41
O3-1	128	42	33	6	5	9	7	3	2	1	1	51	40
O3-2	131	44	34	6	5	12	9	4	3	1	1	57	44
O2-2	127	32	25	3	2	8	6	2	2	1	1	40	31
All	512	163	32	16	3	38	7	13	3	3	1	200	39

Sixteen patients developed jaundice; in 14 the drugs were temporarily withheld and then reintroduced. In the other two patients, the drugs were withheld because jaundice recurred after their reintroduction. Gastro-intestinal symptoms occurred in 6% to 9% of patients, requiring the withholding of Rifampicin in one patient. Cutaneous reactions occurred in 2% to 3%. but a modification of the regimen was necessary only for two patients.

## DISCUSSION

Previous clinical trials of 3- or 4-month regimens for the treatment of smear positive pulmonary tuberculosis had not been successful. A 3-month regimen of daily Streptomycin, Isoniazid, Rifampicin, and Pyrazinamide in the treatment of smear positive pulmonary tuberculosis in south India achieved high rates of culture conversion, but had relapse rates of 20% in the 21 months after treatment completion<sup>1</sup>. Eule et al, studying the same regimen, also reported a relapse rate of 20% among 61 patients<sup>12</sup>. Likewise, a New Delhi study of 52 patients treated with Rifampicin, Isoniazid and Pyrazinamide for 8 weeks, followed by Rifampicin and Isoniazid for 4 weeks, reported a relapse rate of 23%<sup>13</sup>. Mehrotra reported a 6% relapse rate in 53 patients with a similar regimen but the definition of relapse also required the presence of radiological deterioration, in addition to positive sputum culture and so probably underestimated the actual relapse rate<sup>14</sup>. For 4-month regimens, the reported relapse rates are 13% in an East African study<sup>15,16</sup> and 10% in Singapore<sup>17,18</sup>. These studies suggest that 3- or 4-month regimens with traditional first-line anti-tuberculosis drugs may be inadequate for the treatment of smear positive pulmonary tuberculosis.

Our study represents the first clinical trial of 3- to 5-month Ofloxacin-containing regimens for the treatment of smear positive tuberculosis. The salient feature of this study is that the cure and the relapse rates in the 4-month O3-1 regimen and 5-month O3-2 regimen are comparable to the standard 6-month regimens currently used<sup>19,20</sup>. The shorter duration of the studied regimens would hopefully improve patient adherence. Our 3-month regimen, while successful in achieving negative cultures in 99% of patients with drug susceptible tuberculosis, had a relapse rate of 8% in 24 months. Nonetheless, this rate is much lower than the 20% relapse rate reported for a 3-month regimen in an earlier study<sup>1</sup>, with the added advantage that the regimen is fully oral. We have also shown that a supplement of 1 month of Isoniazid and Rifampicin twice a week in the continuation phase could reduce the relapse rate to 4%, and a 2-month supplemental continuation phase still further to 2%. The relapse rate for the 4-month O2-2 regimen, however, was unacceptably high, at 13%, even though culture negativity at 2 months was 97%. **This strongly suggests that 2 months of intensive phase is inadequate for sterilizing the bacterial load. Thus, for ultra-short regimens, at least 3 months of four bactericidal drugs in the intensive phase appears mandatory.**

Even though we were primarily interested in establishing the efficacy of the study regimens, an intention-to-treat analysis which included patients who had inadequate chemotherapy also gave very encouraging results with only 18 (4%) of 469 patients having an unfavourable bacteriological response at the end of treatment. And, of these 18 patients, 5 had initial multi-drug resistant tuberculosis.

The proportion of patients who become culture negative at 2 months is a measure of the bactericidal activity of a regimen. In our study, culture negativity at 2 months ranged from 92% to 98%. These high rates compare favourably with the earlier studies in which a regimen of Streptomycin, Isoniazid, Rifampicin, and Pyrazinamide daily resulted in culture negativity of 91% at 2 months<sup>1</sup> and the same drugs given thrice weekly resulted in culture negativity of 89%<sup>21</sup>. These rates are also higher than the rates achieved with four-drug regimens using Ethambutol in place of Streptomycin (82%-88%<sup>22,23</sup>). The excellent rates of culture conversion in our study are important because culture conversion at 2 months has been shown to correlate well with lower relapse rate<sup>24</sup>.

As in most clinical trials of short course chemotherapy, majority of the relapses occurred in the first 6 months after the end of treatment. This observation has been widely reported<sup>1,11,22,25</sup> suggesting that a significant number of additional relapses beyond the 24-month period of follow-up would be unlikely.

Possible adverse reactions to drugs occurred in 31% to 44% of the patients, but a majority of the reactions were mild and manageable with symptomatic treatment. Arthralgia attributable to Pyrazinamide was the most common adverse reaction, reported by 25% to 36% of the patients, but this complaint required a modification of the regimen in only four patients. Similarly, of the 16 patients who developed jaundice, only 2 required a regimen change. The incidence of arthralgia and jaundice was comparable to that observed in our previous short-course studies using four drugs daily in the intensive phase<sup>1,11</sup>. We have also observed that the incidence of arthralgia and jaundice was considerably less in patients treated with four drugs thrice or twice weekly compared to those treated with the same drugs daily<sup>26</sup>. So, it is reasonable to presume that the adverse reactions in the current study could be reduced if the regimens could be given in an intermittent rhythm.

It is for note that the rates of non-adherence to treatment and patient default remained high despite the still shorter regimens used in a carefully selected patient population: more than 20% of the patients in all the

regimens did not complete the recommended number of doses. Thus, although 3- to 5-month regimens represent a significant advancement in the treatment of tuberculosis, even these regimens will require a stronger treatment discipline than currently exists in most countries where tuberculosis is endemic.

While our protocol employed Ofloxacin, a fluoroquinolone derivative which is active against *Mycobacterium tuberculosis*, other fluoroquinolone derivatives may have similar or superior qualities. Levofloxacin, the L-isomer of Ofloxacin active isomer may be more effective than Ofloxacin<sup>27</sup>. Ofloxacin is, however, widely available and is less costly than levofloxacin. Newer fluoroquinolones may offer higher efficacy with similar low toxicity.

The cost of a treatment regimen is always of great importance to a disease control programme. When we initiated this study in 1995, the cost of a single dose of 400 mg Ofloxacin was Indian Rs. 30/- (US \$ 0.66). Today, the same dose of Ofloxacin costs Rs. 6.50 as was the case with Rifampicin earlier. While the cost of a 4-month regimen containing Ofloxacin for the initial 3 months would still be higher than that of the standard 6-month treatment for smear positive tuberculosis, the savings in terms of administrative costs would be considerable. With an intermittent regimen, the cost will be further reduced.

**The success with, 4- and 5-month regimens that contain Ofloxacin and other first-line anti-tuberculosis drugs, for at least three months in the intensive phase (high cure rates in newly diagnosed patients, low relapses, and good toleration) has made us embark on a randomized clinical trial of fully intermittent 4-month regimens that include Ofloxacin. In the interim, a 4-month regimen of daily Ofloxacin, Isoniazid, Rifampicin, and Pyrazinamide for 3 months, followed by 1 month of twice-weekly Isoniazid and Rifampicin, appears so far to be equally acceptable for the treatment of drug susceptible, smear positive pulmonary tuberculosis.**

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the report and Mrs. Fathima Rahman provided statistical assistance.

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## REFERENCES

1. Tuberculosis Research Centre. Madras. and National Tuberculosis Institute. Bangalore. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in south India. *Am Rev Respir Dis* 1986; 134: 27
2. Daniel Herbert. Paramasivan C N, Venkatesan P. Kubendran G. Prabhakar R and Mitchison D A. Evaluation of bactericidal action of Ofloxacin and Sulbactam-ampicillin alone and in combination with Rifampicin and Isoniazid on *M tuberculosis in vitro*. *Anti-microb. Agents Chemother* 1996; 40: 2296
3. Holst E. Mitchison D A and Radhakrishna S. Examination of smears for tubercle bacilli by fluorescence microscopy. *Indian J Med Res* 1959; 47: 495
4. Petroff S A. A new and rapid method for the isolation and cultivation of tubercle bacilli directly from sputum and faeces. *J Exp Med* 1915: 21: 38
5. Allen B and Baker F J. *In Mycobacteria: Isolation, identification and sensitivity testing*. London. Butterworths. 1968: 17
6. Kubica S P. Differential identification of mycobacteria. VII: Key features for identification of clinically significant mycobacteria. *Am Rev Respir Dis* 1973: 107: 9
7. Tuberculosis Research Centre. Madras. Study of chemotherapy regimens of 5 and 7 months duration and the role of corticosteroids in the treatment of sputum positive patients with pulmonary tuberculosis in south India. *tubercle* 1983; 64: 73
8. Subbammal S. Nair N G K, Radhakrishna S and Tripathy S P. Comparison of various measures of sensitivity of *Mycobacterium tuberculosis* to Ethambutol. *Tubercle* 1978: 59: 185
9. Canetti G. Fox W. Khomenko A, Mahler H T, Menon N K. Mitchison D A et al. Advances in techniques of testing mycobacterial drug sensitivity and the use of the sensitivity tests in tuberculosis control programs. *Bull WHO* 1969; 41: 21
10. Sulochana S. Venkataraman P and Parmasivan C N. Evaluation of various methods of susceptibility to Ofloxacin in strains of *Mycobacterium tuberculosis*. *Indian J Med Res* 1999: 110: 186
11. Tuberculosis Research Centre. Madras. Study of chemotherapy regimens of 5 and 7 months duration and the role of corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in south India. *Tubercle* 1983; 64: 73
12. Eule H. Beck H. Evers H, et al. Daily and intermittent short-course chemotherapy using four drugs in recently detected bacillary pulmonary tuberculosis. *Bull Int Union Tuberc* 1982; 57: 63
13. Research Committee of the Tuberculosis Association of India. Short course chemotherapy of pulmonary tuberculosis. Second Tuberculosis Association of India trial. *Ind J Tub* 1984: 31: 81
14. Mehrotra M L. Gautam K D. Chaube C K. Shortest possible acceptable effective chemotherapy in ambulatory patients with pulmonary tuberculosis. Part II. Results during the 24 months after the end of chemotherapy. *Am Rev Respir Dis* 1984: 129: 1016
15. East African/ British Medical Research Council Study. Controlled clinical trial of five short-course (4-month) chemotherapy regimens in pulmonary tuberculosis. *First report. Lancet* 1978; 2: 334
16. East African/ British Medical Research Council Study. Controlled clinical trial of five short-course (4-month) chemotherapy regimens in pulmonary tuberculosis. Second report of the 4th study. *Am Rev Respir Dis* 1981: 123: 165
17. Singapore Tuberculosis Service/ British Medical Research Council. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1979; 119: 579
18. Singapore Tuberculosis Service/ British Medical Research Council. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. The results up to 30 months. *Tubercle* 1981: 62: 95
19. Treatment of Tuberculosis: Guidelines for National Programmes. 1997. WHO/TB/ 97.220
20. Bass JB Jr, Farer LS, Hopewell PC, O'Brien R, Jacobs RF, Ruben F, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. *Am J Respir Crit Care Med* 1994; 149: 1359
21. Balasubramanian R. Fully intermittent six month regimens for pulmonary tuberculosis in south India. *Ind J Tub* 1991; 38: 51
22. Tuberculosis Research Centre. A controlled clinical trial of oral short course regimens in the treatment of sputum positive pulmonary tuberculosis. *Int J Tuberc Lung Dis* 1997; 1(6): 509
23. Tuberculosis Research Centre. Madras. Interim findings on the evaluation of split drug regimens for pulmonary tuberculosis - a randomized controlled clinical trial. *Ind J Tub* 1995: 42: 201
24. Wallace Fox. Gordon A Ellard, Denis A Mitchison. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946-1986. with relevant subsequent publications. *Int J Tuberc Lung Dis* 1999; 3(10): S231
25. Singapore Tuberculosis Service/ British Medical Research Council. Long-term follow-up of a clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1986: 133: 779
26. Prabhakar R. Fully intermittent six-month regimens for pulmonary tuberculosis in south India, in Tuberculosis and Respiratory Diseases (XXVI IUAT World Conference on Tuberculosis and Respiratory Diseases), Pub. Professional Post Graduate Services. K K. 1986; 21
27. Ji B, Lounis N, Truffot-Pernot C, Grosset J. *In vitro* and *in vivo* activities of Levofloxacin against *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 1995; 39(6): 1341