MADRAS STUDY OF SHORT-COURSE CHEMOTHERAPY IN PULMONARY TUBERCULOSIS

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This article presents the results of a controlled clinical study of 3 shortcourse regimens conducted at the Tuberculosis Research Centre, Madras, in collaboration with the British Medical Research Council and the World Health Organization.

The patients came from the poorest sections of the population of Madras City. They were all aged 12 years or more, and had newly diagnosed previously untreated pulmonary tuberculosis with sputum cultures positive for *M. tuberculosis.* All the patients were treated on an ambulatory basis and received every dose under full supervision in the clinic.

Patients were randomly allocated to three regimens. In all there was an initial intensive daily phase of 2 months, and this was followed by a twice-weekly intermittent phase of 3 or 5 months.

In the first regimen (regimen $RSHZ/S_2H_2Z_2$ - 5), the patients were treated with 4 drugs: rifampicine, streptomycin, isoniazid and pyrazinamide, daily for 2 months. Rifampicin was discontinued thereafter, and the treatment was continued with the remaining 3 drugs given twice-weekly for 3 months, ie. a total of 5 months.

The second regimen (regimen $RSHZ/S_2H_2Z_2$ - 7) was similar to the first regimen in the daily phase, but the twice-weekly phase was longer by 2 months so that the total duration was 7 months

Rifampicin was excluded from the third regimen, regimen $SHZ/S_2H_2Z_2$ - 7. This was identical to the second regimen in all other respects.

The dosages in the daily phase were: *streptomycin,* 0.75 g; *isoniazid,* 400 mg; *rifampicin,* 10 mg/kg body-weight and *pyrazinamide,* 40 mg/kg. In the twice-weekly phase the dosages were *streptomycin,* 0.75 g; *isoniazid,* 15 mg/kg and *pyrazinamide,* 70 mg/kg. *Pyridoxine,* 6 mg, was administered with each dose of isoniazid in both the daily and intermittent phases.

In the past, steroids have been used by several workers in standard chemotherapy with equivocal results. They have not been so far used in short-course chemotherapy. It was thought that the immunosuppressive effect of steroids on the host might lead to multiplication of dormant bacilli, thus rendering them susceptible to the bactericidal effect of the antituberculosis drugs.

In order to investigate this possibility, half the patients in each regimen, selected at random were prescribed a steroid - prednisolone - as adjuvant during the initial phase. The dosage of prednisolone was 20 mg, three times a day, in the first week and was tapered off gradually.

In all, there were 558 eligible patients with pretreatment drug-sensitive cultures in the study. Of these, 4 patients died within the first week. Four others died of non-tuberculous causes, having negative sputum cultures at the time or death. Chemotherapy was changed on account of drug toxicity in 4 cases, and 16 patients were grossly irregular.

The main comparisons of therapeutic efficacy are based on the remaining 530 patients, namely 129 $SHRZ/S_2H_2Z_2$ - 5,132 $SHRZ/S_2H_2Z^2$ - 7 and 269 $SHZ/S_2H_2Z_2$ - 7 patients.

The degree of regularity was high in all three series. Thus in each series, more than 90% of the patients had received more than 80% of their scheduled chemotherapy.

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The proportion of patients with all cultures negative at each month of treatment was higher with the rifampicin regimens combined than with the non-rifampicin regimen during the first 2 months (at 1 month, 50% compared with 31%; at 2 months 92% and 74%). The differences at both these months namely 1% in the first and 18% in the second, are statistically significant. There was no difference in the subsequent months. It is also worthy of note that at the end of the rifampicin phase (i.e. 2 months), 92% of the patients had all cultures negative.

The proportion of patients with favourable response at the end of treatment was 100% with each of the regimens.

There did not appear to be any difference between the steroid and non-steroid groups treated with the rifampicin regimens. In the non-rifampicin regimen, however, there was a suggestion that the proportion culture-negative was higher in the steroid group during the first month. The difference, however, is not significant.

The patients who completed their chemotherapy are all being followed up to a period of 60 months. Results of follow-up for 18 months are now available.

Five per cent (5%) of 129 patients on regimen SHRZ/$S_2H_2Z_2$ - 5 had a bacteriological relapse. Sane of 104 patients on regimen SHRZ/$S_2H_2Z_2$ - 7 had a relapse within this period. This regimen would therefore appear to be a sterilizing one. Among patients on regimen SHZ/$S_2H_2Z_2$ - 7, 4% had a bacteriological relapse. None of the relapse rates are high and the results of the non-rifampicin regimen may be considered as particularly encouraging.

We are reasonably confident, based on experience with shortcourse regimens elsewhere, that these relapse rates are unlikely to increase during the latter period of follow-up. All patients who had a relapse did so with cultures sensitive to streptomycin and isoniazid and could therefore be retreated with standard drugs.

There were, in all, 115 patients who had drug-resistant cultures at the time they were admitted to the study.

Considering the non-rifampicin regimen, all the 12 patients with streptomycin resistance had a favourable response, compared with 12 to 18 with resistance to isoniazid alone and 4 of 25 with resistance to both streptomycin and isoniazid. Thus, resistance to streptomycin alone was of no consequence but resistance to isoniazid either alone or with resistance to streptomycin was associated with an unfavourable prognosis. Correspondingly, in patients treated with the rifampicin regimens, 17 of 19 patients with resistance to isoniazid alone and 18 of 26 patients with resistance to both drugs had a favourable response. Thus, the fourth drug, rifampicin, has been largely successful in compensating for streptomycin and isoniazid. In all, 78 patients had a favourable response at the end of chemotherapy and relapse occurred in 3 of them, i.e., 4%. Thus, the relapse rates were no higher than in patients who had drug-sensitive cultures initially.

In the present study, it had been planned to admit patients with a history of previous chemotherapy up to 3 months. The 530 patients with drug-sensitive cultures reported so far had no chemotherapy or had at best received chemotherapy up to 2 weeks. There were, in addition, 22 patients with pretreatment drug-sensitive cultures who had had up to 3 months of specific chemotherapy. Thus, there were 667 patients in all. Of these, 115 (17%) had resistance to at least one drug. Despite the high level of drug resistance, the two rifampicin regimens were highly effective - 96%-98% - and the efficacy of the non-rifampicin regimen was only slightly lower, namely, 92%.

Considering adverse reactions to drugs, jaundice occurred in 15 (3%) of 530 patients; the incidence was similar in the rifampicin and the non-rifamicin regimen, either with or without prednisolone, and could not be attributed to any drug. Fourteen per cent (14%) of patients in the rifampicin series complained of arthralgia. Correspondingly, 34% in the non-rifampicin series had similar complaints. This difference is highly significant, suggesting that the concurrent administration of rifampicin may have had an ameliorating effect on arthralgia due to pyrazinamide.

Prednisolone did not appear to have influenced the incidence of arthralgia.

In total, serious toxicity requiring either reduction in dosage or termination occurred in 29 (6% patients, including 23 (5%) due to streptomycin, 3 due to isoniazid and 3 due to pyrazinamide.

In summary:

1. The three regimens investigated were all 100% effective at the end of chemotherapy and were associated with low relapse rates, namely 0-5%, in about a year of follow-up.
2. The SHRZ/$S_2H_2Z_2$ - 7 was the most effective regimen with no relapses so far. Reducing the duration of chemotherapy with the rifampicin regimen or dropping off rifampicin carried only small penalty of up to 5% relapses.
3. The non-rifampicin regimen has the vital advantage of a lower cost and is therefore particularly suitable for application in developing countries.
4. The administration of prednisolone for 2 months did not effect the speed of sputum conversion in any regimen.

The present study has shown that a 5-month regimen containing rifampicin and a 7-month regmen without rifampicin are both highly effective. We are. however, greatly encouraged by the findings and are planning to undertake studies to shorten the duration further.

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