Evaluation of the 3-drug combination, Rifater, versus 4-drug therapy in the ambulatory treatment of tuberculosis in Cape Town

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Abstract **The subjective impression among clinicians that the use of Rifater was causing delayed sputum conversion and increased drug resistance was tested in a prospective study. Adults in the Cape Town municipal area with a first episode of pulmonary tuberculosis were treated either with Rifater or a regimen consisting of isoniazid, rifampicin, pyrazinamide and ethambutol. All patients who took the treatment as prescribed (67 Rifater, 39 the 4-drug regimen) converted to a negative sputum culture by the time 90 doses had been taken. The rates of inadequate compliance and of side-effects were similar in the two groups.**

Drug sensitivity testing of bacteria cultured from pre-treatment sputum specimens revealed an overall primary resistance rate of 4,84% in the population studied, sufficiently low to preclude any necessity for routine pre-treatment drug sensitivity testing.

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The combination drug Rifater (isoniazid 80 mg, pyrazinamide 250 mg, rifampicin 120 mg) was introduced in Cape Town tuberculosis clinics in mid-1988. It was to be used as sole therapy for ambulatory patients over 7 years of age in whom tuberculosis was diagnosed for the first time. Prior to the introduction of Rifater, such patients were given 4-drug therapy with isoniazid (INH), pyrazinamide (PZA), rifampicin (RIF) and either ethambutol (EMB) or streptomycin (SMN). PZA was given for 60 doses and SMN for 90 doses. RIF and INH were administered, as is Rifater, for a total of 130 doses; treatment was given 5 days a week.

After Rifater was introduced, a subjective impression began to emerge among medical staff that it was not as effective as the old 4-drug regimens; there appeared to be more culture-positive cases at the 90-dose stage and some of these demonstrated resistance to one or more drugs. As a result, an increasing number of patients were being given EMB in addition to Rifater, and routine pre-treatment sensitivity testing was introduced. This added to the expense of treatment and placed an additional load on the laboratory.

Prompted by these observations, a literature search was conducted. This revealed that the efficacy of 3-drug regimens (INH, PZA and RIF administered as separate preparations) had been demonstrated[1,2] but that there was considerable variation in dose and duration of therapy with the individual drugs, as well as supervision and hospitalisation. Combination tablets for daily therapy had been studied in several countries[3-8] but composition of the tablets varied, as did the population and study parameters. In general, no significant difference was found between Rifater and regimens of 3 or more separate drugs. The combination tablet also appeared to be effective when pre-treatment resistance to 1 of the drugs (usually INH) existed,[4,5] but these authors recommended that treatment be augmented or adjusted in such cases.

In South Africa, Cowie and Brink[9] compared the locally available form of Rifater with 'regimen 1' (INH, PZA, RIF and SMN) and found Rifater 'effective, acceptable and free of side-effects'. However, sputum conversion was not routinely checked in this study, treatment was given for only 100 days, and the population differed from that in Cape Town. Compliance with the simpler Rifater regimen, contrary to expectations, was worse than in the regimen 1 group. The authors considered this to be due to differences in supervision of the two groups. Glatthaar *et al.*[10] compared Rifater with 'regimen 2' (INH, PZA, RIF and EMB given as separate preparations). Sputum conversion rates and 2-year relapse rates were comparable but relative compliance rates were not discussed.

An important determinant of treatment outcome, mentioned in many studies, is the drug resistance rate in the local population. No reliable rates were available for the western Cape. Nationally, primary resistance to INH was calculated at 9,5% in a survey of black adults in the Transvaal, Orange Free State, Natal and the eastern Cape.[11]

This study aimed to test subjective impressions of treatment outcomes with Rifater compared with a previous standard regimen, regarding: (*i*) primary drug resistance; (*ii*) sputum bacteriological conversion rates; (*iii*) compliance; and (*iv*) side-effects, under conditions prevailing at community-based tuberculosis clinics.

Subjects and methods

A prospective study was performed to compare Rifater with the old schedule II (INH, PZA, RIF and EMB). The purpose was to study the efficacy of the two regimens under the practical circumstances prevailing in the municipal clinics. No changes were made to normal clinic routine or to management protocols, so both patient and doctor knew which prescription each individual received. No significant bias was expected since management protocols were defined in detail and outcomes were measured by means of objective tests.

Subjects and sampling

Subjects were coloured patients over the age of 15 years, with a first episode of pulmonary tuberculosis, diagnosed by means of a chest radiograph and a positive sputum culture. Those with additional non-tuberculous pathology were excluded, as were pregnant women. Clinic numbers, issued by a clerk in order of arrival, were used to allocate treatment regimens to those who satisfied the inclusion criteria. Odd numbers received Rifater and even numbers schedule II. Thereafter the routine management plan was followed. The investigators hoped to collect 100 subjects in each treatment group in order to demonstrate any clinically significant differences.

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Treatment

Treatment regimens are detailed in Table I. No other drugs were routinely prescribed apart from an injectable contraceptive in women of child-bearing age.

TABLE I.
Treatment

Rifater		Schedule II
1 tablet/10 kg body weight to a maximum of 5 tablets	INH	400 mg
	RIF	450 mg (< 50 kg) 600 mg (≥ 50 kg)
	PZA	30 mg/kg (to nearest upper 250 mg; max. 2 g)
	EMB	20 mg/kg (to nearest upper 100 mg)

Treatment was given 5 days a week for 130 doses.

Drug-resistant cases

The pre-treatment drug sensitivity report was usually received about 6 weeks after the start of treatment. Patients who had a resistance to RIF required a major alteration in therapy and were withdrawn from the trial. Other resistant cases were to be retained in the trial without alteration in therapy but with monthly clinical and bacteriological reassessments. Adjustments would be made if further resistances emerged. (In fact, no such cases were encountered.)

Compliance

Supervisors administered and recorded treatment at work or in the clinics. Any patient not taking at least 75% of the possible dose for the month was classed as non-compliant and dropped from the study. Any other reasons for withdrawal (e.g. transfer out of area) were recorded as they occurred.

Side-effects

Side-effects were recorded and if treatment was changed, the patient was then excluded from the trial.

Investigations

The following were performed on all patients: (*i*) before commencement of therapy — chest radiography, sputum microscopy and culture, and assessment of drug sensitivities; (*ii*) after about 90 doses of treatment (within the range of 80 - 100 doses) — a radiograph, sputum culture and assessment of sensitivities; (*iii*) at 130 doses (acceptable range 125 - 135 doses) — treatment was discontinued in those patients who had a negative 90-dose culture result.

Sputum testing was performed at the South African Institute for Medical Research by means of established methods.[12] Specimens submitted for sensitivity tests were examined for sensitivity to INH, RIF, SMN, EMB and ethionamide. Radiographs were read by medical officers managing the patients.

Ethics

Both groups of patients received approved regimens. In cases where drug resistance (other than RIF) occurred, patients would have received at least two effective drugs. This was demonstrated by Brandli *et al.*[7] as adequate to achieve clinical cure. Since Rifater has been approved for use without prior investigation of drug resistance, this implies that this principle is accepted by authorities in this country.

Results

Three hundred and nineteen patients were admitted to the trial between April 1990 and August 1991. There was a high attrition rate for a variety of reasons (Table II) and the target of 200 patients successfully completing treatment as per protocol was not achieved. A premature termination of the study was necessitated when EMB became unavailable. Results of patients who did not receive EMB throughout were not included in the analysis, except for their pre-treatment sensitivities. Follow-up of those patients on Rifater who had not completed treatment by mid-November 1991 was discontinued for practical reasons.

TABLE II.
Classification of patients dropped from trial

	Rifater	Schedule II
Admitted to trial	173	146
Dropped from trial		
No pre-treatment sensitivities	4	5
Poor compliance	39	32
Admitted to hospital	4	4
Transferred out of area	4	4
Primary rifampicin resistance	1	1
Treatment changed because of complaints of 'side-effects' (before 90 doses)	10	8
No 90-dose culture result	15	8
Deviation from protocol	9	4
Became pregnant	0	3
Ethambutol unavailable	N/A	38
Follow-up not completed	20	N/A
	106	107
Suitable for analysis of 90-dose results	67	39
	173	146

Pre-treatment sputum sensitivities. Results were obtained for 310 patients. Fifteen patients (4,8%) were infected with bacteria resistant to one or more of the drugs tested (Table III). For various reasons unrelated to efficacy of treatment, none of these patients (5 on Rifater, 10 on schedule II) reached 90 doses on the original regimen.

TABLE III.
Primary resistance rates

Resistant to	No.	%
INH alone	10	3,23
INH + RIF	1	0,32
INH + RIF + EMB	1*	0,32
Streptomycin alone	3	0,97
Total	15	4,84
Total patients with INH resistance	12	3,87
Total patients with rifampicin resistance	2	0,65

Total specimens analysed = 310.
* This patient was a nurse working in a general hospital.

Number of patients with a positive sputum culture after 90 doses. In both treatment groups, all patients who had taken their medication according to protocol had a negative sputum culture by 90 doses.

Non-compliance rate. Most cases of inadequate compliance had already occurred by 90 doses. Four patients on Rifater and 2 on schedule II defaulted after the 90-dose stage. Although the percentage of non-compliance on schedule II (43,0%) appeared considerably higher than the percentage on Rifater (35,5%), the difference was not statistically significant (χ^2 = 0,84, P = 0,36; OR = 1,37, CI 0,74 - 2,55) (Table IV).

TABLE IV.
Non-compliance rates

	No. of patients*	Poor compliers	
		No.	%
Rifater	121	43	35,5
Schedule II	79	34	43,0

* This denominator consists of all patients with known outcome and who were managed according to protocol, viz. non-compliant patients, those with no 90-dose culture result and those suitable for analysis (Table II).

Side-effects. A total of 147 patients (92 Rifater, 55 schedule II) were observed for the full period of therapy. Eighteen (10 Rifater, 8 schedule II) complained of symptoms which could have been due to treatment (Table V). A direct relationship was demonstrated between drugs and 'side-effects' in only 3 cases. Two patients on Rifater reacted to INH when re-challenged with the drugs separately (1 rash, 1 jaundice) and one on schedule II developed a rash due to EMB. There was no significant difference between the two treatment groups in respect of incidence of complaints ($\chi^2 = 0,16$, $P = 0,69$) or side-effects (Fisher's exact test, $P = 0,69$).

TABLE V.
Side-effects

	Patients*	Reported side-effects		Proven side-effects	
		No.	%	No.	%
Rifater	92	10	10,9	2	2,2
Schedule II	55	8	14,5	1	1,8

* This denominator consists of those whose treatment was changed because of side-effects, those with no 90-dose culture result, and those suitable for analysis (Table II).

Discussion

In spite of not achieving the target of 100 patients completing each treatment regimen, numbers were sufficient to reflect any clinically important differences. No patient failed to achieve sputum conversion by 90 doses provided medication was taken regularly. Assessment of chest radiographs performed at 90 doses showed either improvement or occasionally (those with minimal lesions) no change, for all these cases. In spite of this, a considerable number of patients received treatment for longer than the standard 130 doses. Review of these patients' records led to the conclusion that the labelling of a patient's progress as unsatisfactory (one of the original reasons for the study) was a reflection of individual prescribing habits and not based upon documented unsatisfactory progress.

The primary drug resistance rate was low, indicating that in adult coloureds in the western Cape who have not previously suffered from tuberculosis, there should be no hesitation in prescribing standard regimens without performing pre-treatment bacterial sensitivity tests.

The non-compliance rate was high in both groups. There appeared to be poorer compliance on schedule II but this was not statistically significant. Although larger sample sizes might have demonstrated a small difference between the two, this finding was in keeping with previous subjective observations that no noticeable improvement had occurred when Rifater was introduced. It is most important to note that few of these non-compliant patients 'dropped out' altogether. Although they were excluded from further follow-up in the trial, the majority did eventually complete a course of therapy. The non-compliance rate of the study is therefore not an index of 'case holding' in these clinics.

The incidence of proven side-effects was very low in both groups. The incidence might have been higher as there were many more complaints. However, these were not proven, as the prescribed system of management (re-challenging with separate drugs) was not followed in all cases. In addition, in several patients, other confusing factors such as excess alcohol intake were present. These could not be discounted as the cause of the symptoms.

Conclusions

The broad conclusions therefore are that the combination drug, Rifater, is as effective as a regimen consisting of INH, RIF, PZA and EMB, but that under local conditions it does not offer any striking clinical or management advantages. As a consequence of the low primary bacterial resistance rate in this community, no additional investigations are considered necessary when prescribing Rifater for patients who have not previously been treated for tuberculosis. However, even if expensive additional investigations are no longer performed, the cost of a 130-dose course of Rifater for a patient over 50 kg in weight is R471. The equivalent course of schedule II ranges from R214 (50 kg) to R263 for the maximum doses of the four drugs. Since variation in efficacy of currently available drug regimens is a very minor determinant of cure rates, interventions which address the inadequate compliance rate could be expected to have a greater and more cost-effective impact on the epidemic of tuberculosis.

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