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Assessment of a combined preparation of isoniazid, rifampicin and pyrazinamide (Rifater®) in the initial phase of chemotherapy in three 6-month regimens for smear-positive pulmonary tuberculosis: a five-year follow-up report

S. K. Teo

Department of Medicine, Alexandra Hospital, Singapore

SUMMARY

SETTING: Singapore Tuberculosis Service.

OBJECTIVE: To assess the acceptability, efficacy and relapse rate of a combined formulation of three drugs—isoniazid, rifampicin and pyrazinamide (Rifater®)—given in the initial phase of chemotherapy in three 6-month regimens ($2SHRZ/4H_3R_3$, $1SHRZ/5H_3R_3$ and $2HRZ/4H_3R_3$) under direct observation for all patients.

DESIGN: A randomised, controlled, unblinded study comparing a group of patients treated with Rifater® and another given the three component drugs as separate formulations.

RESULTS: The 310 patients admitted to the study were divided into two groups of 155 patients. The frequency of side effects was similar in both groups. Of 271 patients with drug-sensitive strains who had completed treatment without interruption, sputum cultures converted in all patients. At the end of 5 years, there were 15 relapses: three (2.2%) in the separate drugs group and 12 (9.3%) in the Rifater® group. Exclusion of two cases in the Rifater® group, one with silicotuberculosis and another with no bacteriological confirmation of diagnosis, gave a relapse rate of 7.9% ($P = 0.03$ for the comparison of relapse rates in the two groups).

CONCLUSION: A combined formulation of three drugs given daily in the initial phase of 6-month short-course therapy, followed by intermittent treatment with isoniazid and rifampicin given three times a week under direct observation for all patients, appears to be less effective than treatment with the component drugs given as separate formulations.

KEY WORDS: Rifater®; combined formulations; short-course chemotherapy; fixed-dose combinations

A PREVIOUS STUDY in Singapore has shown that a 6-month regimen of rifampicin and isoniazid given three times weekly after an initial daily phase of isoniazid, rifampicin and pyrazinamide is highly effective in the treatment of smear-positive pulmonary tuberculosis.[1] However, patients have to take three different medications and contend with two formulations of isoniazid (100 mg and 300 mg) and rifampicin (150 mg and 300 mg). This can lead to errors in prescribing, patients taking the wrong dosages, non-compliance with the prescribed treatment, and monotherapy.

The aim of the present study was to investigate the acceptability and efficacy of a combined formulation (Rifater®) of three drugs—isoniazid (H), rifampicin (R) and pyrazinamide (Z)—which could simplify treatment and improve compliance. Rifater® was given during the initial phase of treatment in three different 6-month regimens. The results at 24 months showed Rifater® to be less effective for the prevention of relapse compared with treatment in which the component drugs were given as separate formulations, with a borderline level of statistical significance.[2] To assess the relapse rate over a longer period, the patients were followed for 5 years after initiation of treatment; the results are reported here.

METHODS

Patients of Chinese, Malay and Indian ethnic origin, aged 15 years or more with smear-positive pulmonary tuberculosis confirmed to be due to *Mycobacterium tuberculosis* by sputum culture, and with no history of previous antituberculosis treatment, were eligible for the study. The patients were assessed consecutively and randomly allocated to one of three 6-month regimens as follows:

Initial phase: 1) HRZ plus streptomycin (S) daily for 2 months (2SHRZ, or 2SF for the combined formulation); 2) the same drugs as regimen 1 but given for a duration of 1 month (1SHRZ, or 1SF); 3) the

Correspondence to: Dr Seng-Kee Teo, 378 Alexandra Road, Singapore 159964. Fax: (+65) 479 3183.
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same drugs as regimen 1 excluding streptomycin, given for 2 months (2HRZ, or 2F).

Continuation phase: H and R were given three times a week in all three regimens for a total duration of 6 months.

In the initial daily phase, H, R and Z were allocated at random to be given as a combined drug formulation (Rifater®) or as separate formulations. Rifater® was formulated to contain H 50 mg, R 120 mg and Z 300 mg in each tablet. The dosages of Rifater® were based on body weight: 1) ⩽42 kg, four tablets (H 200 mg, R 480 mg, Z 1200 mg); 2) 43–57 kg, five tablets (H 250 mg, R 600 mg, Z 1500 mg); 3) ⩾58 kg, six tablets (H 300 mg, R 720 mg, Z 1800 mg).

The corresponding dosages for the regimens using separate drugs are as follows: 1) H 300 mg, R 450 mg, Z 1500 mg; 2) H 300 mg, R 600 mg, Z 1500 mg; 3) H 300 mg, R 600 mg, Z 2000 mg.

Streptomycin was given in a fixed-dose injection of 0.75 g daily for the 2SHRZ (or 2SF) and 1SHRZ (or 1F) regimens, regardless of body weight.

During the continuation phase, the dosages of isoniazid and rifampicin given intermittently were identical in both treatment groups; body weight ⩽42 kg, isoniazid six tablets (600 mg); 43–57 kg, isoniazid eight tablets (800 mg); ⩾58 kg, isoniazid 10 tablets (1000 mg). All were given two capsules of rifampicin 600 mg.

Chemotherapy was given to all patients under direct observation during the initial and continuation phase at the community health clinic nearest to their home or place of work, or at the Department of Tuberculosis Control Clinic when they attended for assessment.

Assessment of therapeutic progress

Patients were admitted to the study between October 1983 and August 1987. They were assessed on admission by a clinician and monthly up to 18 months, then once every 3 months up to 30 months, and once every 6 months up to 5 years from the date of admission to the study. Five sputum specimens were examined bacteriologically (smear and culture) before treatment; thereafter one specimen was examined monthly in London and one in Singapore at months 1 to 6, then in Singapore two specimens were examined once every month up to 18 months, and at each follow-up visit up to 60 months.

If there was a positive result either on smear or culture examination, additional sputum specimens were collected each month for 3 months; positive cultures were identified and tested for susceptibility to isoniazid, streptomycin and rifampicin. The laboratory methods and definitions of drug resistance have been reported previously.[3,4] A posterior-anterior chest radiograph was performed on admission to the study and at 3, 6, 30 and 60 months or at any time when there was suspicion of relapse.

To ensure that all relapses were identified, especially among patients who had defaulted, records of all new smear- or culture-positive cases from the Central Tuberculosis Laboratory and new cases of tuberculosis notified to the Department of Tuberculosis Control were reviewed. The Central Tuberculosis Laboratory is the only laboratory in Singapore to provide drug sensitivity testing for doctors working in the public and the private health sectors. The cause of death was ascertained for patients who had died and additional information from the attending physician was obtained if necessary. After the end of the 5-year follow-up period, further attempts were made to contact all those patients who had defaulted.

Statistical analysis

Analysis of treatment response was based on all patients who were given treatment (intention-to-treat principle), and also on patients who completed the full course of treatment without interruption. Assessment of relapse was based on patients who completed 6 months of treatment without interruption. Relapse rates were calculated using the Kaplan-Meier method and compared using the log rank method. A P value of <0.05 was considered statistically significant.

RESULTS

Population studied

A total of 310 patients (Table 1) were admitted to the study; 155 were allocated to the combined and 155 the separate formulations.[2] Three patients were excluded from bacteriological analysis pretreatment because of negative sputum cultures. A total of 307 patients were treated, 290 with drug-sensitive strains pretreatment and 17 with drug-resistant strains. Of the 290 patients, 146 were in the separate drugs group and 144 in the combined formulation group.

The patient characteristics were similar to those reported previously.[2] Treatment was interrupted or

Table 1 Patients assessed

Patients	Separate drugs formulation	Combined formulation
No. at randomization	155	155
Pretreatment exclusion	2	1
No. on treatment	153	154
No. with drug resistance	7	10
No. with sensitive strains	146	144
No. with missed treatment	7	9
No. defaulted during therapy	0	3
No. completing therapy	139	132
After end of therapy		
Defaulted	4	4
Emigrated	0	2
Died	6	8
No. remaining at 5 years	129	118
No. included in analysis*	130	121

*Included four defaulters who were assessed at the end of the study (one on $2HRZ/4H_3R_3$; two on $2F/4H_3R_3$; one on $2SF/4H_3R_3$).

Table 2 Relapses in patients with drug susceptible strains pretreatment

Formulation regimen	No. of patients assessed		Relapses in 5 years *n* (%)	Bacteriological confirmation	Month of relapse after end of chemotherapy
	At end of therapy	At 5 years			
Separate					
$2SHRZ/4H_3R_3$	46	42	0 (0)	0	—
$1SHRZ/5H_3R_3$	46	43	2 (4.5)	2	6, 42
$2HRZ/4H_3R_3$	47	42	1 (2.2)	1	8
Total	139	130	3 (2.2)	3	
Combined					
$2SF/4H_3R_3$	48	42	3 (6.4)	3	3, 3, 5
$1SF/5H_3R_3$	41	41	4 (9.8)	4	3, 7, 21, 48
$2F/4H_3R_3$	43	38	5 (12.2)	4	3, 6, 7, 30, 44
Total	132	121	12 (9.3)	11	

modified in 19 patients because of adverse drug reactions or default, and the remaining 271 completed the full course of treatment. Of the 271 patients with drug susceptible bacilli who completed the full course of therapy (Table 2), 24 were not assessable at 5 years (or 54 months after the end of chemotherapy): 10 were in the separate drugs group and 14 in the combined formulation group.

Patients with drug sensitive strains

Separate drugs group

Of the 146 patients in the separate drugs group, 139 completed the full course of treatment, and seven had their treatment interrupted or modified because of drug reactions. There were 27 diabetic patients in this group. Of the 139 patients, 10 were not assessable at 5 years (six died of causes unrelated to TB and four had defaulted), leaving a total of 129. One patient who had defaulted one year after completion of therapy was contacted at the end of the study and included in the relapse analysis. He was in good health but declined to attend for reassessment. Of the seven patients with modified treatment, four continued to be given a 6-month regimen, one was treated for 9 months and two for 18 months.

Combined formulation group

There were 144 patients in this group, including 21 with diabetes mellitus. A full course of therapy was given to 132 patients, and treatment was interrupted or changed in another 12. Of the 132 patients, 14 were not assessable at the end of 5 years: eight had died of causes unrelated to tuberculosis, four had defaulted and two had emigrated, giving a balance of 118 patients. Three patients who had defaulted after completion of treatment (at months 8, 9 and 36) were contacted at the end of the study. They were in good health but declined to have further investigations. Of the 12 patients who interrupted treatment, six were treated with a 6-month regimen, two were treated for 9 months, and one for 12 months. Two defaulted at 30 days and 38 days, respectively, after starting treatment, and one died of non-tuberculous pneumonia after receiving a total of 4 months of treatment. His sputum culture had converted at 1 month and chest X-ray showed good radiological improvement when he was last reviewed. He was earlier treated for dysphagia and muscle weakness. This patient was not considered to have failed treatment.

Patient acceptance and adverse reactions

Complaints by patients and adverse reactions related to medication were reported mainly during the first 2 months of treatment. These are described in greater detail in the earlier report.[2] Rifater® appears to be well accepted by patients; the incidence of adverse reactions was similar in both treatment groups.

Assessment of relapse

Bacteriological relapse after chemotherapy was defined as a positive culture with a growth of 10 or more colonies in 2 different months during any 3-month period up to 30 months, and during any 6-month period up to 60 months.

Response during chemotherapy

Of the 307 patients who were given treatment, failure occurred in three (one on the separate and two on the combined formulations). The patient on the separate drugs formulation ($2SHRZ/4H_3R_3$) had diabetes mellitus and resistance to both isoniazid and streptomycin pretreatment. The two patients in the combined formulation group, who defaulted at 30 and 38 days, respectively, and remained culture positive, were considered to have failed treatment in the 'intention-to-treat' analysis. Overall, there was one failure (0.65%) in the separate drugs group ($n = 153$) and two failures (1.3%) in the combined formulation group ($n = 154$). The corresponding failure rates for only those patients with drug-sensitive strains ($n = 290$) were 0% (0/146) and 1.4% (2/144); if the two defaulters with positive sputum cultures were excluded, there were no failures in either group.

Sputum conversion

Of the 271 patients with drug-sensitive strains who were treated according to the treatment protocol, sputum conversion was seen in 98%, 92% and 97% of cases on regimens 1, 2 and 3, respectively, at 2 months; at 3 months all except one patient had negative cultures. Of the 17 patients whose treatment did not follow the treatment protocol, 16 had sputum conversion within 2 months and 1 converted at 3 months.

Bacteriologic results after chemotherapy

Overall there were 15 relapses over a period of 5 years among those who had continuous treatment for 6 months. None of the 16 patients with treatment modifications (excluding two defaulters and one who died during therapy) relapsed during follow-up over a period of 40 to 60 months.

Separate drugs group

Of the 139 patients on the separate drugs regimens who completed treatment, 130 could be assessed at 60 months (Table 1): there were three relapses, two of which occurred within 1 year of completion of therapy and one at 42 months. The relapse rate was 2.2% (95% confidence interval [CI] 0.7–6.4).

Combined formulation group

Of the 132 patients on the Rifater® regimen treated according to the protocol, 121 were assessable at 60 months. There were 12 relapses, of which one (2F/$4H_3R_3$) was based on radiologic deterioration confirmed by an independent assessor, giving a rate of 9.3% (95%CI 5.3–15.9). Eight of the relapses occurred within 1 year of chemotherapy, and four occurred at 21, 30, 44 and 48 months after chemotherapy. One patient who relapsed ($2SF/4H_3R_3$) was diagnosed to have silicosis after chemotherapy was started, when radiological improvement revealed background nodulation suggestive of pneumoconiosis. This was supported by a past history of working in a granite quarry. Two patients (one on $2SF/4H_3R_3$ and the other on $2F/4H_3R_3$) had diabetes mellitus which was not well controlled. Exclusion of the patient without bacteriological confirmation and silicotuberculosis gives a relapse rate of 7.9% (95%CI 4.1–14.7).

Outcome of treatment for relapsed cases

Fourteen patients (in both treatment groups) relapsed with drug susceptible strains. In the fifteenth patient there was no bacteriological confirmation, and thus no possibility for sensitivity testing. All the other patients except one responded favourably to a second course of chemotherapy. This patient (on $1SF/5H_3R_3$) spent some time in prison and most likely did not take the medication regularly. He developed resistance to isoniazid and rifampicin during follow up, but was tested negative for human immunodeficiency virus (HIV) infection.

Therapeutic results in patients with drug-resistant bacilli pretreatment

There were 17 patients with drug-resistant strains prior to treatment. One patient (on $2SHRZ/4H_3R_3$) with initial resistance to streptomycin and isoniazid had an unfavourable response during chemotherapy; another (on $1SF/5H_3R_3$) was a diabetic who relapsed 22 months after completion of treatment. The diagnosis of relapse was based on clinical findings and radiological deterioration. He responded to a second course of treatment.

DISCUSSION

A combined drug formulation, Rifater®, given in the initial treatment phase of a 6-month regimen, was found to be highly effective during chemotherapy for patients with drug-susceptible bacilli who completed 6 months of chemotherapy.[2] There were no bacteriologic failures during therapy, and all patients except one had negative sputum cultures by the end of 3 months. However, at the end of 24 months of follow up (18 months after the end of chemotherapy), patients treated with the Rifater® regimen had a higher relapse rate (6.3%) than those treated with the same drugs given as separate formulations (1%); the difference was statistically significant ($P = 0.04$).

The number of relapses had increased to 15 at the end of 5 years of follow up, 12 in the combined formulation group and three in the separate drugs group. The corresponding relapse rates were 9.3% and 2.2%; the difference is statistically significant ($P = 0.01$). One patient in the Rifater® group (on $2SF/4H_3R_3$), who was diagnosed with silicotuberculosis, relapsed within 3 months after stopping treatment. The result is not surprising, as 6 months of chemotherapy is known to be inadequate for this condition.[5] The diagnosis of tuberculosis in another patient was based on clinical and radiological evidence of deterioration without bacteriological confirmation. He responded to antituberculosis chemotherapy. Exclusion of these two cases in the relapse analysis give a rate of 7.9% (95% CI 4.3–14.2, Figure) which is significantly higher than the rate of 2.2% in the separate formulation group ($P = 0.03$).

There is no obvious reason to account for the difference in these relapse rates. The bioavailability of the three drugs was shown to be similar in both formulations,[6] and the dosages of the component drugs given to the two groups of patients were similar on a mg/kg basis.

The possibility of exogenous reinfection as a cause of relapse cannot be excluded without DNA fingerprinting. However, this is considered to be an unlikely cause of the higher relapse rate of patients in the com-

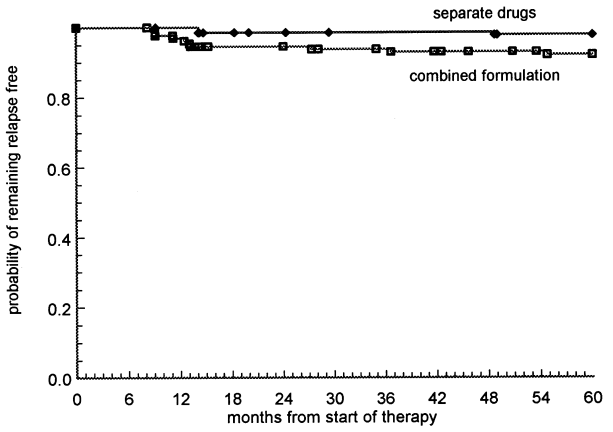

Figure Kaplan-Meier estimate of freedom from relapse.

bined formulation group. A previous study in Singapore,[1] using the same regimens, gave relapse rates of 2–3% over a period of 5 years which included patients with late relapses at 45 and 54 months. A similar relapse rate (2.2%) was also seen among patients treated with a separate drugs formulation in the present study.

The presence of risk factors such as HIV infection and diabetes mellitus may affect the treatment results. However, there is no evidence to suggest that both conditions may have contributed to the significantly higher number of relapses among patients in the combined formulation group. All the relapsed cases had rapid sputum conversion within 2–3 months of treatment. One patient on whom HIV testing was done because of an unfavourable response to therapy for relapse had a negative result. The incidence of HIV infection was low in Singapore during the period of the study, with morbidity rates of 0.8 to 19.5 per million population from 1985 to 1992. No cases of HIV infection were reported before 1985.[7]

Diabetes mellitus was present in two of 12 relapse cases in the group treated with a combined formulation. Although diabetes has been reported to cause reactivation of healed tuberculous lesions,[8] previous studies have not reported a higher relapse rate among diabetic patients treated with 6-month regimens. In the present study, none of the 27 diabetic patients treated with a separate drugs regimen relapsed during follow up. The two diabetic patients who relapsed did not have gastrointestinal symptoms to suggest the possibility of impaired drug absorption. However, there is no information on the bioavailability of Rifater® in diabetic patients.

Studies on Rifater® in other countries have reported good results. Chaulet and Boulahbal,[9] in Algeria, investigated the efficacy of a daily 6-month regimen with Rifater® given during the first 2 months. The combined failure and relapse rate for the Rifater® regimen was 2% compared with a rate of 1% in the control group. A slightly different dosage was used, with five tablets given for patients weighing between 44–55 kg and six tablets for patients ⩾56 kg, instead of 43–57 kg and ⩾58 kg, respectively, for patients in the present study. A study from Thailand reported a low relapse rate of 3% among 65 patients who were treated with a daily 6-month regimen and followed up for 36 months after completion of treatment.[10] The Rifater® was given during the initial 2 months followed by Rifinah® (a combination of isoniazid and rifampicin) in the continuation phase. However, the formulation used is slightly different from that in the present study: each tablet contained more isoniazid (80 mg), less pyrazinamide (250 mg), and an equal amount of rifampicin (120 mg).

In the US Public Health Service Study 21,[11] a daily 6-month regimen was investigated and a relapse rate of 3.4% was reported over a period of 24 months. Again, a different preparation was used, containing more isoniazid (75 mg) and rifampicin (150 mg) and less pyrazinamide (400 mg) in each tablet. In two of the three studies mentioned, the preparation of Rifater® is different from that used in the present study.

In the Hong Kong study,[12] a special preparation of Rifater® was investigated and found to be highly effective. However, this preparation was designed for use in 6-month regimens in which chemotherapy was given three times weekly throughout the course of therapy, with the addition of 4 months of streptomycin in three of the four regimens investigated. When streptomycin was omitted in the combined formulation group, three bacteriological failures occurred during therapy, and the relapse rate (9%) was higher than in the group on separate formulations (4%). However, the difference was not statistically significant. Bioavailability studies in the relapsed patients did not indicate impaired absorption of rifampicin or isoniazid. It is also interesting that in the present study patients treated with the two regimens containing both streptomycin and Rifater® appear to have lower relapse rates compared with those treated with a nonstreptomycin-containing regimen. The numbers are too small, however, for a valid comparison.

The present study has shown that in Singapore, treatment with Rifater® is somewhat less effective than chemotherapy using a separate drugs formulation. This assessment is based on the combined results of therapy with three different regimens which have been shown to be equally effective in a previous study.[1] However, the level of significance ($P = 0.03$) for the difference between the relapse rates (7.9% vs 2.2%) is not high. With the comparatively small numbers of patients studied, the results cannot be accepted as firm evidence that Rifater® is therapeutically inferior. However, when direct supervision of drug therapy is deficient, the increased adherence that can be expected with Rifater® could probably compensate for the limited difference of efficacy between both formulations. The International Union Against Tuberculosis and Lung Disease (IUATLD),[13] the World

Health Organization (WHO)[14] and the American Thoracic Society (ATS)[15] have all recommended wider use of combined formulations in tuberculosis treatment.

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RÉSUMÉ

CADRE : Les services de tuberculose de Singapour.
OBJECTIF : Apprécier l'acceptabilité, l'efficacité et le taux de rechute d'une formulation combinée de 3 médicaments, l'isoniazide, la rifampicine et le pyrazinamide (Rifater®) donnée dans la phase initiale de la chimiothérapie dans trois régimes de 6 mois (2SHRZ/4H_3R_3, 1SHRZ/5H_3R_3, 2HRZ/4H_3R_3) sous supervision directe pour l'ensemble des patients.
SCHÉMA : Etude non aveugle, randomisée et contrôlée comparant des patients traités par le Rifater® et ceux recevant en formulations séparées les 3 médicaments qui le composent.
RÉSULTATS : L'étude a admis 310 patients dont 155 dans chaque groupe. La fréquence des effets collatéraux a été similaire dans les deux groupes. Les cultures d'expectorations se sont négativées chez les 271 patients dont les souches étaient sensibles aux médicaments et qui ont terminé le traitement sans interruption. A la fin des 5 ans, on a noté 15 rechutes, dont trois (2,2%) dans le groupe à médicaments séparés et 12 (9,3%) dans le groupe Rifater®. L'exclusion de deux cas dans le groupe Rifater®, l'un atteint de silico-tuberculose et l'autre sans confirmation bactériologique du diagnostic, donne un taux de rechute de 7,9% (P = 0,03 pour la comparaison des taux de rechute dans les deux groupes).
CONCLUSION : La formulation combinée des trois médicaments administrée quotidiennement dans la phase initiale d'une chimiothérapie de courte durée de 6 mois, suivie par une thérapeutique intermittente à base d'isoniazide et de rifampicine trois fois par semaine, sous observation directe pour tous les patients, s'avère moins efficace que le traitement comportant les trois mêmes drogues quand elles sont données en formulations séparées.

RESUMEN

MARCO DE REFERENCIA: Servicio de Tuberculosis de Singapur.

OBJETIVO: Evaluar la aceptación, la eficacia y el índice de recaídas de una combinación fija de drogas, isoniacida, rifampicina y pirazinamida (Rifater®) suministrada en la fase inicial de la quimioterapia en tres esquemas de seis meses ($2SHRZ/4H_3R_3$, $1SHRZ/5H_3R_3$, $2HRZ/4H_3R_3$) con supervisión directa de todos los pacientes.

MÉTODO: Un estudio controlado aleatorio no ciego que comparó los pacientes tratados con Rifater® con otros que recibieron las tres drogas aisladamente.

RESULTADOS: Se incorporaron al estudio 310 pacientes, 155 en cada grupo. La frecuencia de los efectos colaterales fueron similares en ambos grupos. Sobre los 271 pacientes con cepas sensibles que completaron el tratamiento sin interrupciones, los esputos se convirtieron en todos los casos. Al cabo de cinco años hubo 15 recaídas, tres (2,2%) entre quienes recibían las drogas aisladas y 12 (9,3%) en el grupo que recibía Rifater®, uno con silicotuberculosis y otro sin confirmación bacteriológica, con lo que el índice de recaídas fue del 7,9% ($P = 0,03$ para la comparación del índice de recaídas en los dos grupos).

CONCLUSIÓN: Un esquema de combinación fija de drogas suministrado diariamente en la fase inicial de un esquema de seis meses, seguido de un esquema intermitente con isoniacida y rifampicina tres veces por semana, con supervisión directa de todos los pacientes, parece ser menos efectivo que un tratamiento con las tres drogas dadas aisladamente.