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Combined chemotherapy including rifabutin for rifampicin and isoniazid resistant pulmonary tuberculosis

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ABSTRACT: A prospective multicentre open study has been conducted in France in order to assess the efficacy and tolerability of an antimycobacterial regimen including rifabutin in the treatment of patients with pulmonary tuberculosis due to rifampicin and isoniazid resistant bacilli.

Patients were treated with daily rifabutin (450–600 mg), associated with companion drugs to which the organisms remained susceptible; in most cases the regimen included a fluoroquinolone. The duration of treatment was initially scheduled for a minimum period of 12 months after sputum culture conversion.

Thirty nine patients were enrolled, 23 of whom were treated for at least 12 months. Culture conversion was obtained at the end of the twelfth month in 14 out of 23 patients. Twenty one out of 39 patients experienced adverse events. These were, however, serious enough to discontinue treatment in only four patients.

These results suggest that an antimycobacterial combination including rifabutin might contribute to the treatment of multi-resistant pulmonary tuberculosis.

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It is, to date, difficult to treat patients with pulmonary tuberculosis caused by *Mycobacterium tuberculosis* resistant to rifampicin and isoniazid. This stems from the fact that treatment often relies upon the administration of antimicrobials demonstrating either weak activity or poor tolerability. Fortunately, in developed countries, primary rifampicin resistance rate of *M. tuberculosis* is low: 0.1–1% of tested strains [1, 2]. The frequency of acquired rifampicin resistance is probably higher, because of inadequate treatment or poor compliance by patients [3].

Rifabutin is a rifamycin SV derivative. Its minimal inhibitory concentrations against rifampicin susceptible *M. tuberculosis* are 20 times lower than those of rifampicin [4]. Moreover, 30–40% of rifampicin resistant strains show susceptibility to rifabutin. As a result, it was proposed to use rifabutin in the treatment of rifampicin resistant tuberculosis patients [5, 6].

The aim of our study was to evaluate, in pulmonary tuberculosis patients resistant to both rifampicin and isoniazid, the efficacy and tolerability of rifabutin containing combined regimens. These consisted of one or several other drugs to which the bacilli had remained susceptible.

Patients and methods

Patients

Criteria for eligibility included: age over 18 yrs, pulmonary tuberculosis bacteriologically confirmed with bacilli resistant to at least rifampicin and isoniazid, acceptance of hospitalization for the first three months of therapy for better assessment of compliance and, finally, acceptance of regular follow-up during two years after treatment initiation.

Patients with malignancy, positive human immunodeficiency virus (HIV) serology, pregnancy, known hypersensitivity to rifampicin or serious illness, contraindicating administration of prescribed drugs, were excluded.

The study was approved by an institutional review board and all subjects gave written informed consent.

Methods

Patients were treated daily with a single dose of 600 mg rifabutin (450 mg for patients with body

weight ≤50 kg) combined with remaining active antituberculosis drugs. Duration of treatment was initially scheduled for at least 12 months after sputum conversion. In the case of resistance or intolerance to all available drugs, a fluoroquinolone (pefloxacin or ofloxacin) was added to avoid monotherapy.

Results

From June 1986 to December 1988, a total of 46 patients from 24 different hospitals in France (1–5 patients per centre) were proposed for enrolment. Only 39 patients, 11 females (mean age 33 yrs) and 28 males (mean age 40 yrs) fulfilled the criteria of inclusion and were, therefore, enrolled in the study. Most had bilateral cavitary disease and all had previously been unsuccessfully treated with regimens containing rifampicin and isoniazid. The mean duration of tuberculosis was 12 yrs (range 1–45 yrs); mean number of previous relapses was 2.5 (range 0–11). Clinical status was poor in most patients. The following symptoms: fever, cough, dyspnoea, sputum, and asthenia were present in 22 out of 39 patients. Mean body weight loss during the preceding year was 6 kg (range 0–16 kg).

Table 1. – Results of drug susceptibility testing before the initiation of rifabutin treatment (n=39)

Drugs to which the organisms were resistant before treatment				
R + H only n=4	R + H + other drugs n=35			
S (3)	S+E (3)	S+C+E (2)	S+E+P+C (1)	S+E+Q+T+C (1)
T (2)	S+P (2)	S+P+Z (1)	S+E+Z+Tb (1)	C+Z+E+T+P (1)
E (1)	E+P (2)	S+E+Cp (1)	S+E+C+Cp (1)	S+E+Z+T+Cp (1)
Z (1)	S+K (1)	E+Z+T (1)	S+E+C+Tb (2)	S+E+Z+C+Tb (1)
	E+T (1)	S+Z+Tb (1)	S+E+Q+Tb (1)	S+K+Z+T+Cp (1)
			S+E+Z+P (1)	
			S+E+K+Cp (1)	

R: rifampicin; H: isoniazid; S: streptomycin; T: thioamide; E: ethambutol; K: kanamycin; Z: pyrazinamide; Tb: thiosemicarbazone; C: cycloserine; Cp: capreomycin; Q: fluoroquinolone. Numbers in brackets indicate number of patients who were resistant to a given combination of drugs.

Acid-fast bacilli were detected by direct microscopic examination of sputum smears of 33 out of the 39 patients. The organisms of all but 4 of the 39 patients were also resistant to at least one antituberculosis drug other than rifampicin and isoniazid (table 1): 26 strains were resistant to streptomycin, 3 to kanamycin, 18 to ethambutol and 8 to pyrazinamide. Resistance to streptomycin was associated with resistance to ethambutol in 13 cases, to pyrazinamide in 3 cases, and to both in 4 cases. Resistance to thioamide was demonstrated in 8 cases. All strains were susceptible to at least one minor antituberculosis drug, cycloserine, capreomycin or *p*-aminosalicylic acid (PAS). MICs of rifampicin (fig. 1) were high (median concentration 256 $mg \cdot l^{-1}$) with, however, a wide range (16–512 $mg \cdot l^{-1}$). MICs of rifabutin were lower than those of rifampicin in all cases (median concentration 8 $mg \cdot l^{-1}$), but also with a wide range (0.12–32 $mg \cdot l^{-1}$). MICs of ofloxacin were 4 $mg \cdot l^{-1}$ for all but two strains, which were isolated from patients previously treated with a quinolone.

Patient compliance was carefully surveyed by nursing staff during the first three months under investigator's supervision. Thereafter, it was only monitored by questioning the patients.

All subjects were assessed before enrolment, on day 15 and at the end of month 1, 2, 3, 4, 6, 9, 12, 15, 18, 24 and 36 after initiation of therapy. Assessment included medical history, physical examination and laboratory tests including haematological, biochemical, bacteriological tests, and chest X-rays. Furthermore, all patients were monitored for adverse reactions.

The last isolate of *M. tuberculosis* obtained before enrolment, and each isolate at the end of months 2, 6 and 12, were sent to the reference laboratory (J. Grosset) for identification and susceptibility tests (Isolator lysis - centrifugation system; see list of tested drugs - table 1) according to the proportion method [7] as well as for measurement of the minimal inhibitory concentrations (MICs) of rifabutin and rifampicin, using a 7H11 medium.

The main evaluation criterion for treatment efficacy was sputum culture conversion. Treatment failure was judged either on the absence of culture conversion after 12 months, or on the reappearance of at least two successive positive cultures one month apart following temporary conversion. Relapse was defined as the reappearance of at least two successive positive cultures one month apart during the 12 months following discontinuation of treatment, when conversion had been reached.

Success was defined as the persistence of negative cultures 12 months after initial conversion.

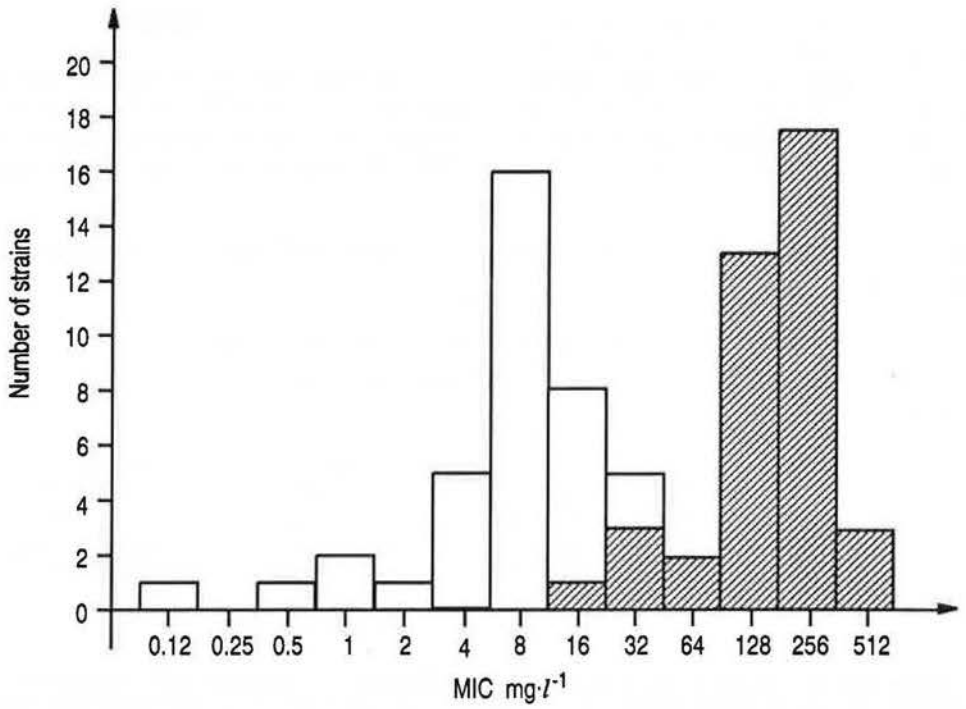

Fig. 1. – Minimal inhibitory concentrations (MICs) of rifabutin (▭) and rifampicin (▨) against *M. tuberculosis* strains isolated before treatment with rifabutin.

Table 2. – Treatment with first line and second line drugs combined with rifabutin in the 39 patients with rifampicin and isoniazid resistant *M. tuberculosis*

	Second line drugs												
	None	K	T	Q	K+T	K+Q	T+Q	Q+Cs	K+T+Q	T+C+K	Q+C+K	Q+T+C+K	Q+Cp+P+Clof
First line drugs													
None				4		1	1		1		1	1	1
S													1
Z	1	2		2			2	1	2	1			
E	1			3			2		3				
S+Z			1				1						
E+Z					1				2				
S+E+Z				2			1						

The treatment was prescribed according to results of drug susceptibility tests. Rifabutin was associated with 1 to 5 other drugs made up by a combination of first and second line drugs. Number indicates the number of patients treated by a given combination of drugs. S: streptomycin; Z: pyrazinamide; E: ethambutol; K: kanamycin; T: thioamide; Q: quinolone; P: *p*-amino salicylic acid (PAS); Cs: cycloserine; Cp: capreomycin; Clof: clofazimine.

Antituberculosis regimens

The choice of companion drugs to be combined with rifabutin was determined by results of initial susceptibility tests. Table 2 shows the regimen administered.

Companion drugs were classified according to their own activity into two groups:

1. First line drugs, such as streptomycin (1,000 mg *q.d.*), ethambutol (20 mg·kg^{-1} *q.d.*) and pyrazinamide (1,200–1,500 mg *q.d.*).
2. Second line drugs including kanamycin (1,000 mg *q.d.*), thioamide (500 mg *q.d.*), quinolone (ofloxacin 400 mg *q.d.* or pefloxacin 800 mg *q.d.*), cycloserine, (1,000 mg *q.d.*), PAS (12 g *q.d.*), capreomycin (1,000 mg *q.d.*) and clofazimine (100 mg *q.d.*). It is of interest to note that 10 patients did not receive any first line antibiotic in combination with rifabutin.

Response to therapy

Safety assessment. Tolerability was satisfactory in 18 patients, whereas adverse events were seen in 21 patients. These were, however, serious enough to discontinue treatment in four patients only. Nausea and vomiting, most frequently attributed to thioamide, were

observed in 13 patients and resulted in discontinuation of treatment in two patients, who were treated with rifabutin and ethionamide, respectively. Three patients receiving streptomycin or kanamycin reported hearing loss and vertigo but did not discontinue the treatment. One out of four patients with joint pain, possibly related to pyrazinamide and/or fluoroquinolone, stopped treatment on the tenth month. Finally, one patient discontinued treatment after developing leucopenia possibly related to rifabutin on day 15.

Duration of therapy. Twenty three out of 39 patients completed the trial. Reasons for early drop out in the remaining 16 patients were adverse events in four, death related to tuberculosis in two after 9 and 11 months of treatment, patient's own decision in five (due to lack of improvement between months 3 and 5 for four of them, and during month 6 for the other), loss in follow-up in five (between months 3 and 7). Of these five patients, sputum conversion had been observed in three.

Laboratory results. No significantly abnormal laboratory results were recorded during the course of treatment, (according to erythrocyte sedimentation rate, blood urea, complete blood count, serum creatinine, glucose and transaminases when assessed at months 3, 6, 9 and 12), except for one case of increased serum bilirubin and the other of leucopenia (white blood cells (WBC): 1,700·mm^{-3}), which led to discontinuation of treatment.

Changes in bacteriological status. Table 3 summarizes the changes in bacteriological status for the 39 patients. At the end of the first month of treatment, 14 out of the 39 patients (36%) already exhibited negative cultures. The sputum conversion number remained stable at month 6 and month 12.

Table 3. – Changes in bacteriological status

	Month of treatment						
	0	1/2	1	3	6	9	12
Number of patients	39	39	37	35	29	26	23
Culture not available	0	0	2	4	2	2	0
Culture done	39	39	35	31	27	24	23
Culture negative	0	0	14	13*	14†	14†	14†

*: At 3 months one patient dropped out; †: a new patient had negative conversion at 6 months, making the final number of 14 patients completing the 12 month study.

Bacteriological efficacy was still obtained in 14 of the 23 patients who completed the twelve months course of therapy. This represents 36% of the patients overall. Among these 14 patients, 6 permanently stopped their treatment after 12 months. Follow-up data could be obtained for only four of them. They all had persistent negative cultures at 16, 17, 18 and 24 months after discontinuation of treatment, respectively. Eight patients continued their treatment over 12 months (mean duration 16 months; range 13–22 months). Of these, one was lost at follow-up at month 15 whereas the remaining seven had persistent negative cultures at 7, 10, 12, 17, 21, 22 and 24 months after discontinuation of treatment, respectively.

Susceptibility tests

In accordance with the protocol, susceptibility tests were performed with isolates obtained during treatment. Among the strains isolated in the nine patients whose cultures remained positive at month 12, eight exhibited an acquired resistance to fluoroquinolone (7 cases), thioamide (3 cases), kanamycin (2 cases), and pyrazinamide (2 cases).

No change in rifabutin susceptibility was recorded either for cultures which were positive prior to conversion by month 12, or for cultures which remained positive after month 12.

Comparison between patients exhibiting conversion of cultures at month 12 and patients with persistent positive cultures

Factors likely to contribute to the success or failure of treatment in the 23 patients who underwent at least 12 months of treatment were studied. This led to the following observations:

1. the nine patients whose cultures remained positive had a longer history of pulmonary tuberculosis (16 *versus* 8 yrs) and a more extensive radiological finding as compared with the 14 patients who converted;
2. compliance to treatment (defined as failure to keep consecutive follow-up appointments or to take study medication as directed), as admitted by the patients, was poor in 7 out of 9 patients who failed to convert. Conversely, compliance was good in patients whose culture showed conversion;
3. the number of active drugs administered in combination with rifabutin was similar in the two groups. This suggests that individual factors played a major role in determining successful or unsuccessful outcome.

Discussion

This study demonstrated that a 12 month period of treatment with a combined chemotherapy including rifabutin could induce sputum conversion in 14 out of 39 patients who had bacilli resistant to at least rifampicin and isoniazid, which represents a success rate of only 36%. This figure could reasonably have been higher if more than 23 out of the 39 patients had been able to complete the 12 month treatment course. Alternatively, if some of the early drop-out patients did not convert, this would lower the success rate. As this is difficult to predict we suggest a figure of 61%, *i.e.* 14 of the 23 patients, as a conversion rate for those who went through the 12 months treatment period. This does not, by any means, prejudge the overall conversion rate.

Primary rifampicin resistance rate of *M. tuberculosis*

is low in developed countries. Unfortunately, multi-resistant tuberculosis often emerges, as the result of acquired resistance. One could expect to circumvent this difficulty with the recent *in vitro* finding of low MICs of rifabutin against rifampicin-resistant *M. tuberculosis* strains.

The number of patients from this category in France is estimated to range from 20–50 cases per year. It would have been unrealistic to perform a randomized trial comparing rifampicin to rifabutin with such a low number of potentially eligible patients. This is why we have deliberately chosen a prospective open study, which was agreed by the local Ethics Committee. However, the conduct of such a study is difficult. Firstly, the bacilli are resistant to the most active anti-tuberculosis drugs, including rifampicin and isoniazid, and the remaining potentially active drugs display poor efficacy. Secondly, the so-called "second line drugs" are getting scarce, which further limits the choice of companion drugs for rifabutin. Thirdly, the patients are quite difficult to manage, resulting in a significant number of drop-outs in our study. This could probably be explained by both the relatively poor tolerability of the second line drugs and poor compliance of patients. This is a well-known phenomenon among tuberculous patients who have multi-resistant bacilli, being previously treated but experiencing recurrence of disease [8]. Finally, it is impossible for ethical reason to prescribe a "gold standard" drug regimen to multi-resistant tuberculosis, since the companion drugs combined with rifabutin have to be chosen according to remaining susceptibility.

It is, therefore, rather difficult to assess the respective role of rifabutin and companion drugs in cases of successful treatment. Our encouraging results are compatible with other published data on the outcome of patients with multi-resistant pulmonary tuberculosis treated with a regimen including rifabutin. Indeed, FELTEN [9] observed four conversions out of seven in a series of 21 patients after seven months. MADSEN and GOBLE [10] observed five conversions before 6 months out of nine patients who were managed on chemotherapy in a series of 16 patients. O'BRIEN *et al.* [11], when comparing regimens containing three different daily doses of rifabutin (150, 300 and 450 mg), obtained a 43% conversion rate with the 450 mg dosage, which is close to the dosage used in our study. These authors concluded that a better success rate was more likely with the addition of at least four active drugs to rifabutin.

Likewise, we conclude that an anti-mycobacterial re-gimen which includes rifabutin combined with at least one second line active drug, to which the bacilli had remained susceptible, might be successfully used to treat multi-resistant pulmonary tuberculosis. As sputum conversion could occur as early as the first month of treatment, it is imperative to systematically hospitalize patients for at least two months after starting treatment. This allows better monitoring of treatment efficacy and/or side-effects as well as compliance of patients.

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