Rifampicin

Proceedings of a Symposium

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Chairmen: G. Daddi, C. Grassi and J. Grosset

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Foreword

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The extraordinary regression of tuberculosis in recent years has led to official and unofficial optimism; careful evaluation, however, shows that this does not appear to be fully justified. In fact, it must be stated that unfortunately tuberculosis is still among us.

The mathematical processing of Dr Aldo Giobbi's data, obtained in Milan, has made it possible to predict that 15 to 20 years from now the tuberculinic index (i.e., the limit established by the WHO as that at which tuberculosis is no longer considered a social disease in a particular country) will fall to 1% at 14 years of age. This is an epidemiological forecast made on the basis of the supposition that everything goes well. However, when the unforeseeable tubercular endemics in countries with a high level of well-being and excellent health services are taken into consideration, it is clear that the moment to relax our guard in the fight against tuberculosis has not yet arrived.

It must therefore be considered that this symposium took place at a highly opportune time. Among other things, it indicated rifampicin's contribution to the most modern trends in tuberculosis chemotherapy — i.e., that the inclusion of this antibiotic, which is extremely effective and well tolerated if administered correctly, in suitable treatment regimens permits great reductions in the duration of treatment with absolutely favourable results even after several years have elapsed.

Introduction

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The introduction of this symposium was a task which I very willingly undertook because its subject — rifampicin and the treatment of tuberculosis — is an important topic of current interest.

What were the reasons for subtitling the symposium 'TB Today: from prevention of resistance to prevention of relapse'? Firstly, it was thought to be appropriate, ten years after rifampicin's introduction into the treatment of tuberculosis and on the basis of its value as a therapeutically active and well tolerated drug (proven by the results of approximately 4,500 published papers and a series of national and international scientific meetings), to focus on two points in particular which substantially comprise and identify the current problems arising in the treatment of tuberculosis — the prevention of resistance and the prevention of relapses. These two objectives can be ensured precisely by those therapeutic regimens which include rifampicin. The microbiological and clinical therapeutic papers presented at this symposium by famous, experienced phthisiologists deal with these problems and provide an opportunity to compare their opinions. These papers re-affirm what has been reported in the most recent literature: namely, the absolute validity of these therapeutic regimens that constitute a decisive step forward in the treatment of tuberculosis as far as the prevention of resistance and relapse is concerned.

It is to be hoped that these papers and the subsequent discussion will lead to an eventually unambiguous trend in the treatment of tuberculosis and that they will suggest a line of conduct which, while providing for variations necessitated by particular pathological situations, will avoid the excessive multiplication of therapeutic regimens and thus decisively contribute to solving the problems posed by the treatment of tuberculosis today. We did not come to this symposium for further confirmation of rifampicin's therapeutic efficacy; it would also be superfluous to list the numerous previous symposia which have already sanctioned this antibiotic's leading role in the treatment of tuberculosis. However, I must, in a personal recollection, mention the VI International Congress of Chemotherapy held in Tokyo in 1970 when, following the interdisciplinary meeting between clinicians, pharmacologists, toxicologists, physiologists and chemists, the scientific world paid tribute to this drug, a product of Italian research, and to its discoverer, Professor Piero Sensi of Milan. Rather, we came to this symposium to discuss and emphasize the validity of modern therapeutic regimens for treating tuberculosis and to suggest their practical application. This is a problem which is currently very pressing; in this regard I feel that it is very important to

mention that this symposium was organized under the joint patronage of three scientific associations — the Italian Federation for the Fight against Tuberculosis and Social Pulmonary Diseases, the International Chemotherapy Society, and the International Forlanini Association.

Contents

New microbial aspects of the treatment of tuberculosis

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Summary

The rational use of drugs for tuberculosis treatment requires that both the intracellular and the extracellular populations of bacilli are controlled. For practical purposes, isoniazid and rifampicin are bactericidal to both populations, but streptomycin and kanamycin are bactericidal only to extracellular bacilli. Pyrazinamide acts only on intracellular bacilli. Ethionamide, ethambutol and cycloserine are mainly bacteriostatic for both populations. Isoniazid/streptomycin treatment gives rapid sputum conversion, but intracellular bacilli are eliminated only by long periods of isoniazid treatment (18 months). The addition of pyrazinamide gives a relapse rate of around 3% after 9 months' treatment with this regimen. The isoniazid/rifampicin combination gives practically no relapses after 9 months; this combination must be given for at least 6 months, but the addition of streptomycin or pyrazinamide may allow further reduction of treatment times. If isoniazid and rifampicin cannot be given together, effective alternatives are isoniazid/aminosalicylic acid, isoniazid/ethambutol or rifampicin/ethambutol, perhaps with the initial addition of streptomycin or kanamycin.

Since the discovery of rifampicin the effectiveness of antitubercular chemotherapy has increased considerably. By combining the two major bactericidal drugs — isoniazid and rifampicin — it has become possible to avoid failures and relapses in almost 100% of cases and even to shorten greatly the total duration of treatment [1-3]. However, in order to achieve this, the available drugs must be used rationally and it is consequently necessary to evaluate their activities on the different populations of bacilli present in tuberculous disease. This is what we shall attempt to do in this paper, using pulmonary tuberculosis as an example of tuberculous disease.

Bacillary populations in pulmonary tuberculosis

Tuberculosis is a model of an infectious disease with intracellular bacterial multiplication. However, it would be erroneous to believe that all bacilli remain intracellular during the course of the disease. Bacilli phagocytosed by macrophages

are, in effect, released by caseous necrosis. Bacilli can even multiply intensively outside the cells when liquefaction of the caseum and the state of local conditions (especially bronchial permeability) lead to the formation of a cavity. It is therefore necessary to distinguish at least two bacillary populations in pulmonary tuberculosis.

The first is represented by extracellular bacilli. These are located in caseous lesions, nodules and cavities. Their numbers may reach 100 million in a cavity [4]. Since the cavity and the bronchial 'tree' are linked via the bronchus draining the cavity, the bacilli originating in the cavity are found in the sputum of tuberculous patients. Thus, in chemotherapy, the disappearance of bacilli from the sputum is proof of activity on the extracellular bacilli. However, drug-resistant mutants always exist among these bacilli and there is a danger that they will multiply selectively during treatment if two bactericidal drugs are not associated in the regimen. Extracellular bacilli are, therefore, responsible for early therapeutic failures. They are accessible to the action of streptomycin, a drug which acts only on extracellular bacilli, and inaccessible to that of pyrazinamide, a drug which acts only on intracellular bacilli.

The second bacillary population is represented by intracellular bacilli. These bacilli are present within macrophages and thus have reduced potential for multiplication. Their numbers quite probably do not exceed 10,000 to 100,000 bacilli. Since they are captive, they are not found in the sputum as are the extracellular bacilli. Sputum conversion during chemotherapy is therefore no proof of action on the intracellular bacilli. Rather, action on these bacilli is measured by the percentage of relapses occurring after withdrawal of treatment. In fact, one of the characteristics of intracellular bacilli is their prolonged persistence within macrophages despite chemotherapy. Unlike extracellular bacilli, they are inaccessible to the action of streptomycin but are accessible to that of pyrazinamide.

Respective effectiveness of the main antitubercular drugs

The effectiveness of a drug during an infectious process is the result of the drug's own antibacterial activity on the one hand and of its pharmacokinetic properties on the other. The antibacterial activity of antitubercular drugs depends on the minimum inhibitory concentration (MIC) of each drug for the tubercle bacillus and on the proportion of mutants resistant to each drug existing in wild strains of tubercle bacilli. These two properties define the theoretical antibacterial activity *in vitro*. The pharmacokinetic properties govern the diffusion of the drug in the extracellular medium and into the cells. They therefore govern the bioavailability of the drug, i.e., its true effectiveness on extracellular and intracellular bacilli.

Taking these different properties into account (Tables I and II), a classification of the major drugs can be established. Generally speaking, it can be considered that those drugs reaching the bacilli at concentrations at least ten times the MIC are bactericidal antibiotics. Using this criterion, isoniazid and rifampicin are drugs which can be classified as being highly bactericidal to both extracellular and intracellular bacilli. However, a reservation must be made with regard to isoniazid, which becomes non-bactericidal after six hours in rapid inactivators. Streptomycin and kanamycin are bactericidal only to extracellular bacilli; they

Table I: MIC factors (or number of times by which the drug serum levels surpass the MIC) for major drugs acting on intracellular bacilli.

Drug	Oral dose (mg)	MIC factor	
		third hour	sixth hour
Isoniazid			
rapid inactivator	450	50	8
slow inactivator	450	90	45
Rifampicin	600	60	30
Ethionamide	500	5	7
Ethambutol	1200	3	2
Cycloserine	500	4.5	3.5

Table II: MIC factors developed in the serum and within macrophages by aminosides and pyrazinamide.

Drug	Dose (g)	MIC factors			
		serum		macrophages	
		third hour	sixth hour	third hour	sixth hour
Streptomycin	1	60	20	3-5	0
Kanamycin	1	60	20	3-5	0
Viomycin	1	5	3	0	0
Capreomycin	1	5	3	0	0
Pyrazinamide	2	0	0	10-15	8-10

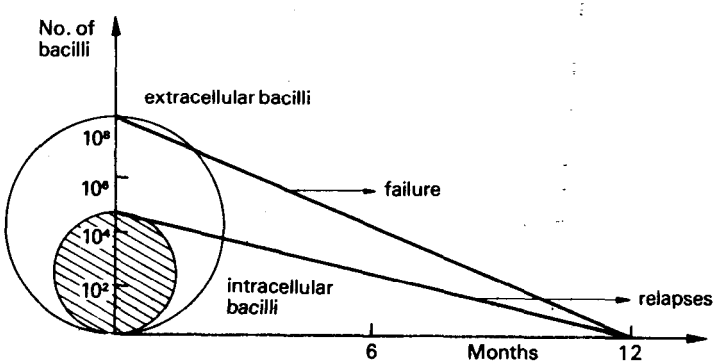

Fig. 1: Diagram of the two populations of tubercle bacilli and their evolution during chemotherapy.

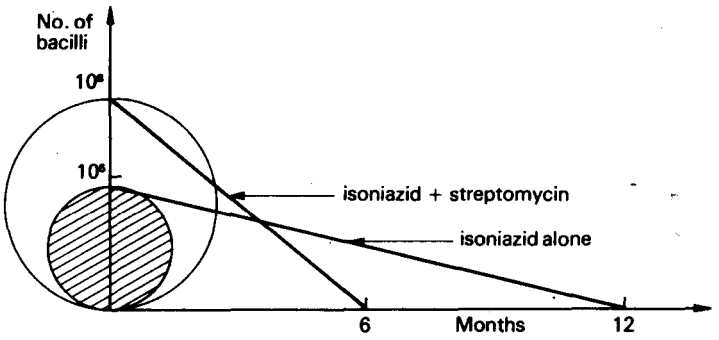

Fig. 2: Effects on bacterial populations of combinations using isoniazid and streptomycin.

have no action on intracellular bacilli. Pyrazinamide, on the contrary, is bactericidal to intracellular bacilli while it has no effect on the extracellular bacilli. The other drugs — ethionamide, ethambutol and cycloserine — are mainly bacteriostatic, but their effect is exerted on both extra- and intracellular bacilli.

Effectiveness of various drug regimens on bacillary populations

As figure 1 shows, the objective of antitubercular therapy is to eliminate the intracellular and extracellular bacillary populations. The efficacy of the major drug associations available can be determined if the specific characteristics of the two bacillary populations are taken into account together with the obstacles (failures, relapses) each of them present to the success of treatment.

Isoniazid/streptomycin

In patients with pulmonary tuberculosis treated with isoniazid and streptomycin, it can be assumed that the extracellular bacilli are reached by both drugs at bactericidal concentrations. Sputum conversion should therefore be obtained rapidly and regularly, provided that the two drugs are given daily during the initial treatment period. By contrast, as figure 2 shows, the intracellular bacilli are reached only by isoniazid. Thus, the disappearance of these bacilli can only be obtained through extremely long treatment regimens using isoniazid.

Clinical experience fully confirms these theoretical assumptions. In the East African/British Medical Research Council investigation of 1972 [5], summarized in table III, six months of daily treatment with isoniazid/streptomycin led to sputum conversion in nearly 100% of cases (with a very small percentage of therapeutic failures); however, this was followed by nearly 30% of relapses. If administration of isoniazid is continued for up to 18 months, as was done in the

Table III: Efficacy of short-term and long-term treatment regimens using isoniazid plus streptomycin.

Regimen	Duration of treatment	Total No. of patients	Failures at six months	Relapses during the following two years (%)
Isoniazid/streptomycin	6 months	112	2	29
Isoniazid/streptomycin/ thioacetazone followed by isoniazid/thioacetazone	2 months 16 months	102	4	4

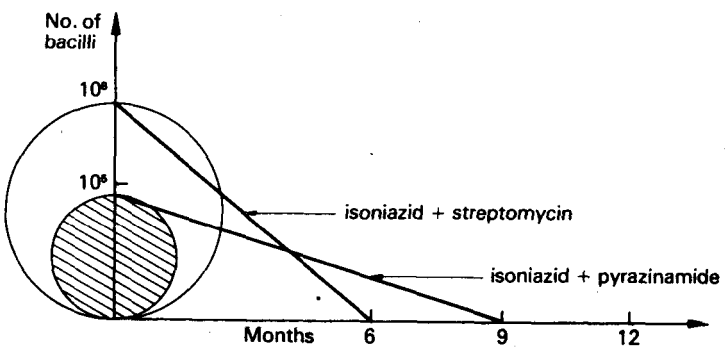

Fig. 3: Effects on bacterial populations of isoniazid combinations with streptomycin and pyrazinamide.

regimen consisting of streptomycin/isoniazid/thioacetazone for two months followed by isoniazid/thioacetazone for 16 months, the percentage of relapses falls to 4%.

Isoniazid/streptomycin/pyrazinamide

The weakness of the isoniazid/streptomycin combination lies mainly in streptomycin's ineffectiveness on intracellular bacilli. The addition of pyrazinamide, which acts only on these bacilli, should thus accelerate their destruction and consequently permit a shortening of the total treatment time (Fig. 3).

Clinical experience [5, 6] confirms this hypothesis. The relapse rate after six months' treatment with this triple combination is only 11-13%, and a mere 3% after nine months' therapy. The latter percentage is the same as that produced by the double combination, isoniazid/streptomycin, administered for 18 months. Thus, the addition of pyrazinamide can shorten the duration of treatment by half (Table IV).

Table IV: Comparative efficacies of the isoniazid/streptomycin and the isoniazid/streptomycin/pyrazinamide regimens.

Study	Regimen	Duration	Failures at end of treatment (%)	Relapses (%)
East African/ British Medical Research Council (1972)	Isoniazid/streptomycin/	6 months	2	29
	Isoniazid/streptomycin/ pyrazinamide	6 months	0	11
Hong Kong/ British Medical Research Council (1975)	Isoniazid/streptomycin/ pyrazinamide	6 months	0	13
	Isoniazid/streptomycin/ pyrazinamide	9 months	0	3

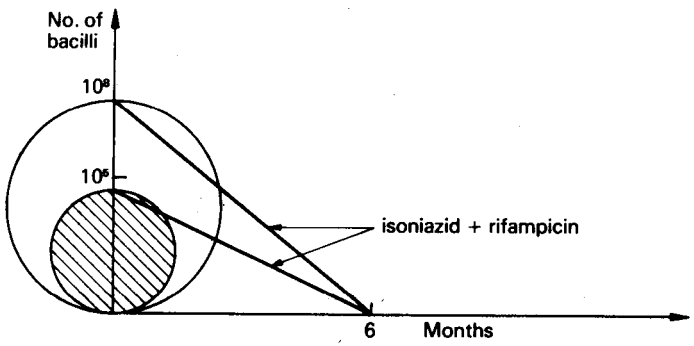

Fig. 4: Effects on bacterial populations of the isoniazid/rifampicin combination.

Isoniazid/rifampicin

Isoniazid and rifampicin are both bactericidal to extracellular and intracellular bacilli. Thus, under double chemotherapy with isoniazid plus rifampicin, the two bacillary populations are destroyed in a shorter time than is the case for the other drug combinations (Fig. 4). Table V summarizes the results of controlled studies carried out in France [7], East Africa [8] and Great Britain [9] and shows that the isoniazid/rifampicin combination leads to elimination of the extra- and intracellular bacillary populations within six months, without therapeutic failures and with a 5% relapse rate. This percentage becomes practically nil if treatment with the isoniazid/rifampicin combination is continued for nine months.

In brief, six months' treatment with isoniazid/rifampicin has much the same

*Table V: Efficacy of the isoniazid/rifampicin regimen; * = a single isolated culture being found.*

Study	Total No. of patients	Duration	Failures at end of treatment	Relapses during the following two years (%)
France (1977)	55	6 months	0	5
	62	9 months	0	0
	60	12 months	0	0
East Africa (1974)	170	6 months	0	5
Great Britain (1976)				
cavities < 2 cm	160	6 months	0	5
	155	12 months	0	1
cavities > 2 cm	135	9 months	0	0 (2*)
	127	18 months	0	0 (1*)

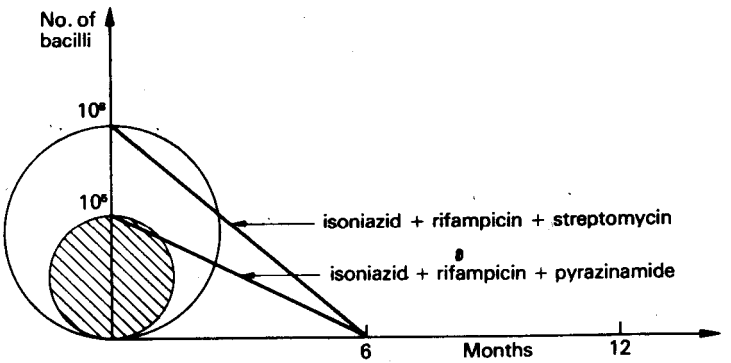

Fig. 5: Improvement of modern chemotherapy: Current studies of new cases (with sensitive bacilli).

effectiveness (measured in terms of sputum conversion, failure and relapse percentages) as nine months' treatment with the triple combination of isoniazid/streptomycin/pyrazinamide and 18 months' treatment with the standard streptomycin (for two months), isoniazid and thioacetazone combination.

Can we hope to improve the effectiveness of the isoniazid/rifampicin regimen? Although this regimen is currently the most effective, it must be administered for at least six months in order to obtain excellent therapeutic effectiveness. The question which thus arises is whether it would not be possible to shorten treatment even further by the simultaneous administration of other drugs. As figure 5 shows, two drugs could possibly increase the effectiveness of this regimen and

*Table VI: Comparative efficacies of isoniazid/rifampicin, isoniazid/rifampicin/streptomycin and isoniazid/rifampicin/streptomycin/pyrazinamide; * = significant (P = 0.006) and ** = significant (P = 0.06).*

Regimens	Duration	Total No. of patients	Negative at 2 months (%)	Failures	Relapses (%)
Isoniazid/rifampicin, daily	6 months	164	64	1	7
Isoniazid/rifampicin/ streptomycin, daily	6 months	171	70	0	2**
Isoniazid/rifampicin/ streptomycin/pyrazinamide, daily, followed by isoniazid/streptomycin/pyrazinamide, twice weekly	2 months 4 months	159	82*	2	4

thus permit further shortening of the total treatment period. These two drugs are streptomycin, bactericidal for extracellular bacilli, and pyrazinamide, which is bactericidal for intracellular bacilli. Clinical trials carried out in East Africa in 1976 [10, 11] appear to confirm the efficacy of these quadruple regimens. In fact, table VI shows that the addition of streptomycin and pyrazinamide significantly increases the sputum conversion percentage after two months of treatment and reduces that of relapses on withdrawal of treatment.

Isoniazid/aminosalicylic acid, isoniazid/ethambutol, and rifampicin/ethambutol combinations

In some cases, due to bacterial resistance or expense, isoniazid and rifampicin cannot be administered simultaneously. In these cases, the drug associated with isoniazid or rifampicin is aminosalicylic acid (para-aminosalicylic acid) or, more often, ethambutol. In the case of the isoniazid/aminosalicylic acid combination, the extracellular bacilli are reached by a bactericidal drug (isoniazid) and a bacteriostatic one (aminosalicylic acid); the intracellular bacilli are reached by isoniazid alone since aminosalicylic acid does not penetrate into the cells. With the isoniazid/ethambutol or rifampicin/ethambutol combination, the extracellular and intracellular bacilli will be reached by a bactericidal drug and a bacteriostatic one (ethambutol) since the latter penetrates well into the cells. The elimination of the two bacillary populations will thus be obtained slowly, but less slowly if ethambutol is used rather than aminosalicylic acid (Fig. 6). Treatment should therefore be of long duration. It does not, in all cases, prevent the selection of mutants resistant to the bactericidal drugs among the population of extracellular bacilli, which leads to a high percentage of therapeutic failures. Moreover, it cannot totally sterilize the intracellular population, so that a certain percentage of relapses occurs. In fact, table VII shows that the percentage of failures (with acquired resistance to isoniazid or to rifampicin) is 4 to 13% after a year of treat-

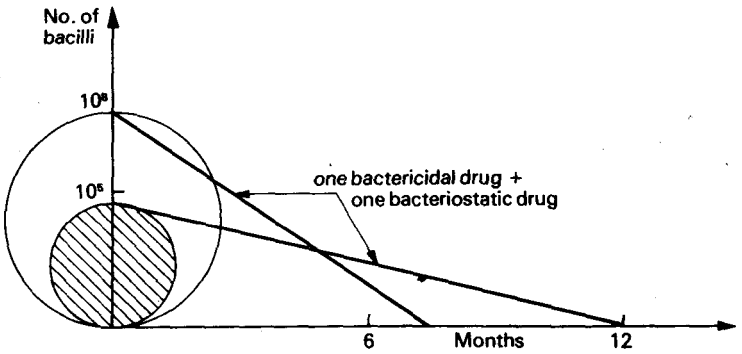

Fig. 6: Effects on bacterial populations of isoniazid/aminosalicylic acid; isoniazid/ethambutol and rifampicin/ethambutol combinations (a bactericidal plus a bacteriostatic drug).

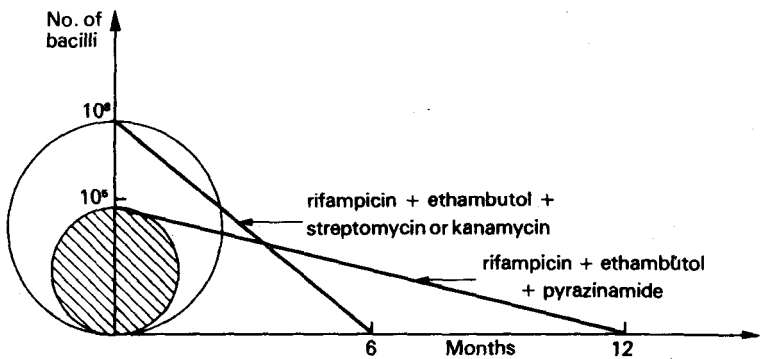

Fig. 7: Possible studies of the treatment of cases with isoniazid-resistant bacilli.

ment, while the percentage of relapses is 1 to 9% [12-17]. It is interesting to note that the percentage of relapses appears to be smaller with the rifampicin/ethambutol combination than with the isoniazid/ethambutol one, which confirms the remarkable activity of rifampicin on intracellular bacilli [18, 19].

How can the effectiveness of the rifampicin/ethambutol combination be increased? A priori, it is easy to increase the effectiveness of the rifampicin/ethambutol combination. To speed up the destruction of extracellular bacilli and lessen the risk of selection of resistant mutants, it is sufficient to add streptomycin (or

Table VII: Efficacies of isoniazid/aminosalicylic acid, isoniazid/ethambutol and rifampicin/ethambutol combinations.

Study	Regimens	Total No. of patients	Failures (%)	Relapses (%)
Madras (1960)	Isoniazid/aminosalicylic acid, daily	86	9	7
Madras (1971)	Isoniazid/aminosalicylic acid, daily	83	13	0
Madras (1973)	Isoniazid/ethambutol, daily with 15 days' streptomycin administration	105	4	9
Hong Kong (1975)	Rifampicin/ethambutol, daily	91	13	3
Algiers (1975)	Rifampicin/ethambutol, daily for 3 months, then twice weekly	113	4.4*	1
Poland (1976)	Rifampicin/ethambutol, daily for 3 months, then twice weekly	329	5	3

kanamycin if streptomycin had been given previously) during the first months or even the first weeks of treatment. In fact, it is well known that the administration of streptomycin during the first weeks of treatment considerably improves the overall effectiveness of isoniazid/aminosalicylic acid and isoniazid/thioacetazone regimens. These observations, although dated, are perfectly applicable to the rifampicin/ethambutol regimen (Fig. 7). In addition, the simultaneous administration of pyrazinamide should make it possible to increase the activity of the rifampicin/ethambutol combination on intracellular bacilli, which should in turn lead to a drop in the relapse rate. Although no clinical trial has, up to now, afforded any precise information on this matter, it is probable that the increase in effectiveness contributed by pyrazinamide to this combination will be in the same order as that which it affords to the isoniazid/streptomycin regimen. In any event, further studies are necessary in order to achieve more rational utilization of the available drugs.

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