

RIFAMPICIN: present status and perspectives*

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Rifampicin was discovered in 1965 in our laboratories in the frame of an extensive program of chemical modifications of rifamycin B, a natural metabolite of *Nocardia mediterranea*^{1,2}. In the 18 years since the synthesis and the first biological evaluation of rifampicin in our laboratories a large amount of information has been accumulated on the biological and clinical properties of this antibiotic. More than 8.000 scientific papers concerning rifampicin have been published until now. The available data can be summarized indicating that rifampicin possesses the following general biologic profile:

1. A broad antibacterial spectrum with very high activity against Mycobacteria, gram-positive and gram-negative cocci, many gram-negative bacilli, most anaerobes and cellular prokaryotic parasites (e.g. Chlamydia, Brucella). Table I reports the minimal inhibitory concentrations of rifampicin against a variety of pathogenic bacteria.

2. A rapid bactericidal action on the sensitive strains.

3. A mechanism of action, unique among the chemotherapeutic agents, consisting in the irreversible inhibition of bacterial DNA-dependent RNA polymerase, without effect on the corresponding mammalian enzyme.

4. Frequency of resistant mutants in many bacterial species of the order of 10^{-8} .

5. Bacterial resistance determined genetically in the chromosome: no extrachromosomal factor found.

6. Bactericidal action against microorganisms inside leukocytes and macrophages.

7. Very good oral absorption with a half-life of 2-3 hours and excellent distribution in body tissues and fluids.

8. Low toxicity as a consequence of its specific mechanism of action.

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Table 1 - IN VITRO ANTIBACTERIAL ACTIVITY OF RIFAMPICIN

MICROORGANISMS	M.I.C. $\mu\text{g/ml}$	MICROORGANISMS	M.I.C. $\mu\text{g/ml}$
Staphylococcus aureus	0.001 - 0.1	Pseudomonas aeruginosa	1 - 20
Staphylococcus epidermidis	0.001 - 0.1	Escherichia coli	0 - 10
Streptococcus pneumoniae	0.001 - 0.1	Klebsiella pneumoniae	5 - 50
Streptococcus pyogenes	0.001 - 0.1	Proteus vulgaris	1 - 10
Corynebacterium diphtheriae	0.001 - 0.1	Salmonella typhi	1 - 10
Clostridium perfringens	0.001 - 0.1	Shigella spp.	5 - 50
Mycobacterium tuberculosis	0.1 - 1.0	Brucella melitensis	0.1 - 5
Mycobacterium leprae	0.1 - 0.5	Haemophilus influenzae	0.1 - 1.0
Atypical mycobacteria		Neisseria gonorrhoeae	0.001 - 1.0
- group I	0.1 - 1.0(90%)	Neisseria meningitidis	0.001 - 1.0
- group II	0.1 - 1.0(80%)	Bacteroides fragilis	0.1 - 1.0
- group III	0.1 - 1.0(40%)	Legionella pneumophila	< 0.1
- group IV	0.1 - 1.0(30%)		
PLT Agents (Chlamydia trachomatis)	0.007		

The development of clinical uses of rifampicin had a very peculiar pathway. Since the first clinical trials rifampicin appeared to be a very powerful antituberculosis agent. In the course of many years of clinical trials and experience, rifampicin has proved very valuable in the therapy of tuberculosis, especially in permitting the introduction of short course chemotherapy. In fact, with the use of rifampicin plus isoniazid for 6-9 months with the addition of a third drug in the first 2-3 months of therapy it is possible to reduce the duration of therapy to one half or even one third of that previously required to achieve similar results with other drug combinations.³ The very good activity of rifampicin in tuberculosis has strongly conditioned its use in other infections.

In an Editorial of Lancet⁴ entitled "Rifampicin : for tuberculosis only?" the nature of the problem has been clearly discussed. The Editorial emphasized the fact that "rifampicin has an amazingly broad antimicrobial spectrum being effective against virtually all pathogenic bacteria" and that is "remarkably free of side-effects". The exclusion of the use of rifampicin from the treatment of non-tuberculous serious diseases could be justified only if the widespread use of rifampicin would lead to emergence of rifampicin-resistant strains of *M. tuberculosis*. This risk is practically non-existent.

Firstly, it has been ascertained that monotherapy with rifampicin of chronic cavitating tuberculous (a condition highly favourable to the emergence of resistance)

led to the selection of resistant mutants in 2 out of 11 patients only after 1 month of monotherapy.⁵

Secondly, recent in vitro experiments demonstrate the improbability of selection of rifampicin resistance in *M. tuberculosis* by exposure during treatments of short duration (up to 14 days).⁶

Thirdly, the convincing evidence that rifampicin can be used in non-tuberculous infections without risk of development of wide-spread rifampicin-resistant *M. tuberculosis* derives from epidemiological data. In fact, two surveys on primary resistance of *M. tuberculosis* to rifampicin comparatively in countries where the use of the antibiotic is restricted to tuberculosis and in those where it is available also for non-tuberculous infections indicated that *M. tuberculosis* had remained uniformly sensitive to rifampicin after several years of use in both groups of the countries.^{7,8}

The evidence of the non-emergence of resistant strains of *M. tuberculosis* and of the efficacy of rifampicin in the treatment of severe infections has renewed the interest of the medical community for this antibiotic. The number of clinical reports concerning the use of rifampicin in non-tuberculous infections has increased significantly during the last years.⁹

PERSPECTIVES OF RESEARCH ON RIFAMPICIN

As above mentioned, there is a huge amount of information in the scientific literature on the activity of

rifampicin in a variety of infectious diseases. I will try here to summarize the available information in specific areas with an attempt to indicate some aspects open to further investigation.

Tuberculosis The therapeutic role of rifampicin in tuberculosis has been extensively investigated and there are now a number of short course regimens of 6-9 months duration that are very highly effective, of low toxicity and well accepted. Effective short course regimens should be available for all countries, whether technically advanced or developing. It will be necessary to evaluate the various proposed short course regimens taking into account the socioeconomic and epidemiological situation and the health care system of each country. Therefore, research on the development of short course chemotherapy is highly important as well as investigation of the advantages to be gained by the use of short course chemotherapy under field conditions.¹⁰ Also the economic efficiency of the chemotherapeutic treatments of tuberculosis must be evaluated taking into account, together with the cost of drugs, all the parameters related to the various regimens : failures and relapses rates, cost of diagnosis and supervision, number of newly infected people due to the time for sputum conversion etc. Where this evaluation has been carefully performed the overall results have been in favour of the short course chemotherapy of tuberculosis with the rifampicin/isoniazid combination. Research into the economics of tuberculosis control programmes and their integration into primary health care is necessary.¹¹

Leprosy Rifampicin is very active against *Mycobacterium leprae*. In animal models and in humans rifampicin shows higher and quicker bactericidal effect against *M. leprae* than any other antileprosy drug.¹²⁻¹⁴ A single high dose of rifampicin accomplishes as much bacterial killing in a few days as dapsone monotherapy for several months. The role of rifampicin on leprosy is particularly important in reducing the period of infectivity and in view of the increasing incidence of dapsone-resistant leprosy. Very good results have been obtained by several investigators in the treatment of leprosy with rifampicin alone or in combination with other drugs. All the regimens presently under study contain rifampicin in various regimens in combination with other drugs. At present, a regimen recommended by WHO multibacillary leprosy contains rifampicin in combination with dapsone, clofazimine and possibly ethionamide. In case of paucibacillary leprose a short course chemotherapy with rifampicin and dapsone has been recommended.¹⁵ However, the best regimens and schedules of treatment are still to be defined. Since the process of defining an optimal regimen for the various form of leprosy is still going on, there is also uncertainty about the most appropriate duration of chemotherapy.

Staphylococcal infections Studies performed in many laboratories indicate that rifampicin has a very powerful antistaphylococcal activity. According to Sabath et al,¹⁶ rifampicin is the most

active of 65 antibiotics tested against 36 clinical isolates of *S. aureus* and 35 of *S. epidermidis*, with M.I.C. of 0.001 and 0.002 $\mu\text{g/ml}$ against the two species respectively. Particularly important is the activity of rifampicin on multiresistant strains of *S. aureus*. Nosocomial infections caused by methicillin-resistant strains of *S. aureus* are becoming rather common in developed countries.¹⁷⁻¹⁹ The medical literature reports numerous cases of successful treatment with rifampicin (in combination with drugs) of severe, often multiresistant, staphylococcal infections including : endocarditis, arthritis, osteomyelitis, infection of heart and CSF-shunt prosthesis. Many cases of infections were reported to be refractory to antibiotic therapy until the addition of rifampicin.²⁰⁻²³ The good penetration of rifampicin into the tissue and its killing effect on the intracellular microorganisms are the main reasons for the efficacy of rifampicin in staphylococcal infections in chronic granulomatous disease, in abscesses and in other deep seated infections.²⁴ (osteomyelitis, arthritis, infected prosthesis). In case of infection with a large population of pathogens rifampicin should be used in combination with another drug active against the infecting organism in order to prevent the development of resistance to rifampicin. Rifampicin alone, or in combination with cloxacillin, eradicates nasal carriage of staphylococci and it has been considered useful in interrupting staphylococcal outbreaks involving hemodialysis patients.²⁶

Legionellosis The Legionellaceae are a recently discovered family of gram-negative bacilli, including various species, all considered potential agents of pneumonia in man. The best studied species is *Legionella pneumophila*, which was responsible of the outbreak of pneumonia in a convention of veterans in Philadelphia in 1976. It has been estimated that presently from 1 to 4.5% of all pneumonia in USA are probably legionellosis.

Rifampicin is the most active antibiotic against *L. pneumophila* (and related organisms) in vitro. In experimental infections in guinea pigs, rifampicin was very effective and comparable to or slightly better than erythromycin. The Center for Disease Control, Atlanta suggested that if a patient with Legionnaires disease is responding poorly to erythromycin alone, consideration be given to adding rifampicin.²⁷ There are until now a limited number of clinical reports on the use of rifampicin in legionellosis, for the most part in combination with and, for the rest, in continuation to erythromycin. The results have been in general favourable.

In consideration of the high activity of rifampicin against *L. pneumophila* in vitro and in experimental infections, and of the capacity of this drug to penetrate into the macrophages where the pathogen is frequently located, rifampicin deserves a more careful investigation for the evaluation of its therapeutic role in the treatment of legionellosis.

Gonococcal urethritis Rifampicin is active against *Neisseria gonorrhoeae* at the concentrations much lower than those achievable in body tissues and fluids after oral administration of 900-1200 mg.

There are many reported cases of treatment of gonorrhea with rifampicin. The cure rate is generally slightly higher than 90%.^{28,29} *N. gonorrhoeae* is an evolving species, subjected to the selective effects of penicillins and other antibiotics since the last 40 years. Differences in susceptibility of the gonococcus to antibiotics require that each area determines its own ideal treatment schedules. Rifampicin shows characteristics appropriate for the treatment of gonococcal infections: it has an efficacy around 90%, it can be administered in a single dose to both sexes, it has no cross resistance with other antgonococcal drugs and it is not active against *Treponema pallidum*, so it does not mask the presence of syphilis. Laboratory studies show that the combination of rifampicin plus erythromycin could be beneficial in preventing the emergence of bacterial resistance.³⁰ Treatment of gonococcal urethritis in men with a single oral dose of rifampicin and erythromycin gave 96% of cure rate. The single-dose rifampicin-erythromycin is a promising treatment for gonococcal urethritis and deserves further study.³¹

Chlamydial infections *Chlamydia trachomatis* is a human intracellular pathogen causing severe diseases, like trachoma and most of the non-gonococcal

urethritis (NGU). Rifampicin is the most active antibiotic against *C. trachomatis* in vitro, followed by tetracycline and erythromycin.^{32, 33} Various clinical trials indicated the efficacy of rifampicin eye ointment in the treatment of trachoma. In a recent double blind comparison of topical therapy of chlamydial ocular infection with rifampicin or chlortetracycline the beneficial effects of therapy with the two antibiotics were statistically significant, but there was no difference in the efficacy of the two drugs.³⁴ There are few clinical reports on the effect of rifampicin in the treatment of NGU. A study indicated that Chlamydia could not be recovered from the urethra of patients initially chlamydia-positive, following a rifampicin treatment for six days.³⁵ Also lymphogranuloma venereum has been treated successfully with rifampicin.³⁶ The role of *C. trachomatis* in sexually transmitted infections of the genital tract represents a problem of current epidemiological research.³⁷ and the recent development of improved cell culture methods for *C. trachomatis* has greatly simplified the diagnostics and the in vitro testing of drugs against these organisms.³⁸ It would be important to perform etiological studies of NGU in different areas and controlled clinical trials on the NGU sustained by Chlamydia in order to assess the role of rifampicin in the chemotherapy of this disease.

Anaerobes. The *Bacteroides fragilis* group is clinically the most important among the anaerobic bacteria. It is the most frequently found in clinical samples

and it is the most resistant to antibiotics. Comparison of in vitro susceptibility of *B. fragilis* to other antimicrobial agents indicated that rifampicin is one of the most active drug.^{39, 40} In a localized mouse abscess infection caused by *B. fragilis* the therapeutic efficacy of rifampicin compared favorably with metronidazole and was clearly superior to clindamycin, two drugs currently used for the treatment of infections due to anaerobes.⁴¹

The therapeutic potential of rifampicin in clinical infections due to anaerobes has yet to be defined. The ability of rifampicin to penetrate into the tissues and abscesses, coupled with its high activity against the anaerobic pathogens, constitutes a rational basis for proper clinical investigations in anaerobic infections.

Brucellosis. Rifampicin shows a very good in vitro activity against various *Brucella* species. In vivo it has been shown to be superior to tetracycline in the therapy of experimental brucellosis in mice and guinea pigs.⁴² There are several reports on the efficacy of the treatment of human brucellosis. On the basis of the obtained results there is evidence the rifampicin could be one of the most effective therapeutic tools in the treatment of brucellosis in the future, also in combination with tetracycline. Further clinical studies are needed for establishing the optimal regimen or combination of regimens.

Cutaneous Leishmaniasis. Some reports on the effectiveness of rifampicin

therapy in cutaneous leishmaniasis.⁴³⁻⁴⁶ resulted quite surprising in view of the fact that rifampicin is not generally active on eukaryotic cells. The clinical effectiveness of rifampicin has been judged always taking into account that cutaneous leishmaniasis has a tendency to spontaneous remission. The direct effect of rifampicin on *Leishmania* organisms has not yet been sufficiently studied, but there is an indication that rifampicin inhibits the transcription of kinetoplast RNA in one species of *Leishmania*.⁴⁷ A recent trial gave very favorable clinical results confirmed by protozoological examination.⁴⁸ Further studies are needed with rifampicin in cutaneous leishmaniasis, a disease for which the parenteral administration of an organic antimonial drug is practically the only accepted, although not satisfactory, systemic treatment.

Meningococcal meningitis. Since many years rifampicin is recommended as the drug of choice for prophylaxis in case of meningococcal meningitis because it is about 90% effective in carriage eradication and associated with very few side effects in controlled studies.⁴⁹ Minocycline has practically the same effectiveness but more side effects and sulfadiazine is ineffective in the frequent cases of meningococci resistant to sulpha. A recent study on the in vitro effect of rifampicin plus erythromycin against *Neisseria meningitidis* indicates that this combination could avoid the reported emergence of rifampicin resistant strains and seems to justify a trial of

this combination in eradicating the meningococcal carriers.⁵⁰

The low minimal inhibitory concentrations of rifampicin against *N. meningitidis* (0.001-0.1 $\mu\text{g}/\text{ml}$) and of the good diffusion of the antibiotic into the body tissues and fluids including the CSF through the inflamed meninges justify the use of rifampicin in the treatment of meningococcal meningitis. The recent introduction of an intravenous formulation of rifampicin has permitted a better use of this antibiotic for the treatment of bacterial meningitis with good results.^{51, 52}

Infections due to *Haemophilus*. *Haemophilus influenzae* type B is responsible of a variety of severe diseases (meningitis, pneumonia, epiglottitis etc.) especially in children. The pathogen is inhibited in vitro by rifampicin at concentrations of the order of 0.1-1.0 $\mu\text{g}/\text{ml}$. Administration of rifampicin gives levels of the antibiotics in body fluids, including saliva and CSF, that exceed the M.I.C. Several studies have shown that rifampicin effectively decreases nasopharyngeal carriage of *H. influenzae* type B. On the basis of these data the Center for Disease Control, Atlanta, has recently recommended chemoprophylaxis with rifampicin (20 mg/kg for 4 days) for prevention of secondary cases of *H. influenzae* type B diseases.⁵³ There was some disagreement on this recommendation, mainly for practical reasons.⁵⁴

Haemophilus ducreyi is the etiological agent of chancroid, a sexually transmitted disease. The pathogen is highly sensitive to rifampicin (M.I.C. =

0,0001–1.0 μ /ml).⁵⁵ Until now only few cases of chancroid have been treated with rifampicin, with very encouraging results.

Urinary tract infections (UTI).

Rifampicin is a potentially useful drug for the treatment of UTI. In fact, it has a large antimicrobial spectrum, covering the most common urinary tract pathogens, it is bactericidal and it reaches high concentrations in the urines. Furthermore, it shows a good penetration into the urinary tract tissues, including the prostate gland. One of the disadvantages of the use of rifampicin in infections sustained by a large population of pathogens (a situation frequently found in severe UTI) is the selection of one-step mutants with a high level of resistance. In order to exploit the high bactericidal effect of rifampicin and eliminate the resistant mutants, it has been frequently used with success in combination with other chemotherapeutic agents.⁵⁶ The combination of rifampicin and trimethoprim has been extensively studied for the treatment of the UTI, in consideration of the pharmacokinetic and microbiological characteristics of trimethoprim as a companion drug for rifampicin.⁵⁷ Rifampicin and trimethoprim are synergistic against a wide range of microorganisms in vitro and in experimental infections,⁵⁸ but the most relevant advantage of the combination resides in the mutual effect on the prevention of bacterial resistance especially in the concentrations that they reach in the urines.^{59, 60} Controlled Clinical trials have

clearly shown the high efficacy of the rifampicin/trimethoprim combination in the treatment of severe UTI.

Conclusions

The present status and the perspectives of the clinical uses of rifampicin, as above summarized, are far from being complete. For example, the synergistic effect of rifampicin with amphotericin B in the treatment of severe fungal infections,⁶¹ and the recently reported clinical efficacy on *Pneumocystis carinii* pneumonia⁶² indicate other interesting areas of this antibiotic in the treatment of severe infections. As mentioned in the introduction, there is an increasing interest in the medical community for the therapeutic applications of rifampicin also in non-tuberculous infections.

Among the biological properties of rifampicin, those which are more responsible for the chemotherapeutic effectiveness are the bactericidal effect at low concentrations and the good penetration into the phagocytic cells. Concerning the last property, it is known that microorganisms of some genera, when ingested by phagocytic cells, can remain alive, multiply inside them and remain protected from the action of most antibiotics. The intracellular bacterial location plays a relevant role in diseases due to *Mycobacteria*, *Brucella*, *Legionella*, *Clamidia*, *Listeria*, *Shigella*, *Mycoplasma*, *Salmonella*, *Escherichia* and also to *Staphylococcus*, *Streptococcus* and *Neisseria*. With the exception of *Mycoplasma*, representatives of the other microorganisms are sensitive to

rifampicin at very low concentrations. Rifampicin, due to its ability to penetrate the phagocytic inside the cells. The effect of rifampicin on intracellular bacteria is certainly one of the major factors of its efficacy in diseases like tuberculosis, leprosy, brucellosis, straphylococcal infections in chronic granulomatous disease, in abscesses and in other deep seated

infections.

Eighteen years after the discovery of rifampicin, there is a sound scientific evidence of its great usefulness in the treatment of certain infections, but, in some other diseases caused by susceptible organisms, the definition of its chemotherapeutic role is still an exciting area of medical research.

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