Topical Review

The chemotherapy of tuberculosis – from the past to the future

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Introduction

Tuberculosis (TB), one of the oldest diseases known to affect humans, did not have an effective treatment until 1940–1950. The emergence of powerful anti-tuberculosis drugs in the second half of this century, and the progressive decline in the incidence of TB, suggested that eradication of the disease was possible, at least in the developed world.

The acquired immunodeficiency syndrome (AIDS) pandemic in the 1980s and the emergence of multidrug-resistant tuberculosis (MDRTB) in the last few years have shown that these expectations were too optimistic. Tuberculosis is far from being controlled and remains as much a major health problem at the end of the century as it was at the beginning (1). Today, one-third of the world population is infected with Mycobacterium tuberculosis, resulting in 8 million new cases and 2.9 million deaths from TB yearly (2).

This article provides an overview on the past, present, and future of chemotherapy for TB.

Evolution of the Chemotherapy for Tuberculosis

Table 1 shows the evolution of TB treatment in the last few decades, schematically. The modern chemotherapy era began with the introduction of streptomycin (STM) in 1943. The most important advance in the treatment of TB took place with the introduction of isoniazid (INH) in 1952 (3). This drug, combined with STM and para-aminosalicylic acid (PAS) allowed the cure of more than 90% of patients, but the treatment period was very long. In the 1960s, ethambutol (EMB) was introduced to replace the poorly tolerated PAS and the treatment period was shortened.

The reported efficacy of rifampin (RIF) in 1971 (4) was a major breakthrough because the regimens that included this drug were able to cure virtually all patients with an important shortening of the treatment period. A 6-month period of treatment adequate to cure TB was established in the 1980s in several well controlled studies after the effectiveness of pyrazinamide (PZA) on intracellular bacilli was shown (5).

Although the trend in the 1990s would have been to maintain both the number of drugs and the duration of treatment, the increasing experience with AIDS TB patients has suggested that an extended treatment (to 9 months, or 6 months after culture conversion to negative) is convenient in these patients (6,7). The emergence of MDRTR has led us to lengthen the treatment to 18 months or more, due to the lower efficacy of the drugs available for treatment of such cases (8,9). Therefore, although the situation is not as bad as it was half a century ago, we now face a problem that we believed to be overcome: the use, in some cases, of drugs of limited efficacy for prolonged periods of time.

Current Treatment Regimens (10–16)

Since the 1980s, it has been evident that short courses of therapy are as effective as longer courses in pulmonary TB. Furthermore, the costs and late toxicity of the chemotherapy were reduced, and the possibility of patient’s adherence to treatment improved with the short courses.

Today, the standard period of treatment for pulmonary TB in the absence of infection with human immunodeficiency virus (HIV) or drug resistance is 6 months. The most widely accepted regimen is the combination of INH, RIF, and PZA daily for 2 months, followed by INH and RIF daily for 4 additional months or, with appropriate dosage

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Table 1 The evolution of anti-tuberculosis treatment

<table>
<thead>
<tr>
<th>Years</th>
<th>Drugs used</th>
<th>Length of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940s</td>
<td>STM + PAS</td>
<td>24 months</td>
</tr>
<tr>
<td>1950s</td>
<td>INH + STM + PAS</td>
<td>24 months</td>
</tr>
<tr>
<td>1960s</td>
<td>INH + STM + EMB</td>
<td>18 months</td>
</tr>
<tr>
<td>1970s</td>
<td>INH + RIF + EMB</td>
<td>9-12 months</td>
</tr>
<tr>
<td>1980s</td>
<td>INH + RIF + EMB + PZA</td>
<td>6 months</td>
</tr>
<tr>
<td>1990s</td>
<td>INH + RIF + PZA + ?</td>
<td>6-7 months</td>
</tr>
</tbody>
</table>

? denotes additional drugs and time required for treatment of AIDS patients and multidrug-resistant tuberculosis. See text.

adjustments, twice- or thrice-weekly. Ethambutol or STM should be added if resistance to INH is suspected. Another regimen combines four drugs (INH, RIF, PZA, and either EMB or STM) daily for the first 2 weeks followed by the same drugs twice-weekly for 6 weeks, and INH in combination with RIF twice-weekly for 4 additional months. Finally, another regimen consists of the same four drugs thrice-weekly for 6 months.

Even shorter courses of 4 months are efficacious in cases of small mycobacterial burden as evidenced by studies carried out in Arkansas (17) and Hong Kong (18) on smear-negative pulmonary TB.

General Rules of the Anti-tuberculosis Therapy

In general, the number of drugs required should increase as the number of bacilli found in lesions increases. Consequently, the number of drugs can be reduced when the bacillary burden is reduced. Although the emergence of resistance to the anti-tuberculosis drugs is a major problem today, the main cause of failure of the therapy is the lack of adherence to the treatment. Accordingly, every effort should be made to ensure compliance.

Drug resistance should be suspected in several situations such as failure of treatment, unreliable patients, contact with patients known to have resistant strains, massive bacillary burden, homeless patients, immigrants from areas known to have resistance, and presence of positive cultures after 3 months of therapy. In the case of confirmed or suspected resistance to drugs in patients who apparently are non-responders, a single drug should never be added to the treatment because development of resistance to the new agent is the rule. In this situation, at least two, but preferably three to five drugs to which resistance is known, or thought, not to exist, should be added.

Mycobacterial Populations and Action of the Major Drugs

Mitchison suggested that there are different populations of bacilli with different rates of growth and drug susceptibilities (19). One population is in continuous growth and replication. Isoniazid is the best drug to kill these bacilli, although both RIF and STM also appear to be useful. On the opposite side of the spectrum, there is a population composed of dormant organisms to which no drug appears to be active. The remaining two populations are intracellular bacilli in an acid environment with slow growth rates susceptible to the action of PZA, and a population of mostly dormant organisms, which have intermittent spurts of metabolism. Rifampin would be the most effective drug against this population.

The rate of killing of the bacilli is not constant throughout the entire period of treatment. This rate is fastest during the first 2 days and slower during the subsequent days and weeks (20). Accordingly, the first phase is known as the early bactericidal activity and the second phase is termed the sterilizing activity.

Major anti-tuberculosis drugs can be classified according to their relative early bactericidal and sterilizing activities (21). Thus, INH is the best early bactericidal drug although its sterilizing activity is lower. Both RIF and PZA have a remarkable sterilizing activity, and in the case of RIF, a good early bactericidal activity. On the contrary, both STM and EMB have a good to intermediate early bactericidal activity and a poor sterilizing activity.

Mechanisms of Action of the Major Anti-tuberculosis Drugs (10,22,23)

The mechanism of action of INH appears to be the inhibition of an enzyme involved in the synthesis of mycolic acid, a long-chain fatty acid of the mycobacterial cell wall essential for the integrity of the bacillus. Rifampin appears to act by interfering with transcription and RNA elongation by binding of the drug to the β-subunit of the DNA-dependent RNA polymerase. Pyrazinamide is especially active against bacilli in the intracellular, acidic environment through its conversion to the active metabolite, pyrazinoic acid. Ethambutol is a bacteriostatic drug active only against actively growing bacilli. The mechanism of action is not well known but probably involves impairment of RNA synthesis. Finally, STM, like other aminoglycosides, acts in the extracellular alkaline environment through the disruption of protein synthesis by irreversible binding to the 30S subunit of the mycobacterial ribosome.
Spontaneous Resistance to Anti-tuberculosis Drugs is Genetically Determined

Theoretically all the bacilli derived from a single clone should have the same pattern of susceptibility to drugs as the original bacillus. However, the emergence of random chromosomal mutants results in organisms that are spontaneously resistant to a drug to which the original bacillus was susceptible. The mutant bacilli will give rise to a population of bacilli resistant to the same drug. These spontaneous mutations depend on the number of bacilli regardless of their localization, and their frequency is different for each drug: one mutation in $10^5$-$10^6$ bacilli for INH, $10^7$-$10^8$ for RIF, $10^2$-$10^4$ for PZA, $10^5$-$10^6$ for EMB, $10^5$-$10^6$ for STM, and $10^3$-$10^6$ for PAS (14,24-28).

The rationale for the combination of several drugs in the treatment of TB is also based on these spontaneous mutations. Thus, the probability that the progeny of a wild bacillus could become resistant to both INH and RIF is the result of the product of the individual probabilities, i.e. one mutation in $10^{12}$-$10^{14}$ bacilli. Similarly, the probability of resistance to INH, RIF, and PZA is one mutation in $10^{14}$-$10^{18}$ bacilli. Keeping in mind that the number of bacilli in patients with cavitary TB is estimated to be between $10^7$-$10^9$, the use of a single drug will certainly result in a resistant population with time. However, spontaneous resistance should not be a problem when two or three of these agents are used in combination, because the number of bacilli required to result in a spontaneously resistant bacillus is too large.

Genetic Mechanisms of Drug Resistance

Although the intimate mechanisms of resistance to the anti-tuberculosis drugs are largely unknown, recent investigations have resulted in a considerable advance in this field.

The catalase-peroxidase activity is required for the action of INH. Deletions or mutations of the catalase-peroxidase gene (katG) are associated with INH-resistance, and transfer of the wild gene to resistant organisms confers susceptibility to the drug (29-31). However, only 24% of the isolates from New York City seem to lack katG sequences (32). Consequently, other factors must also be involved in the resistance to INH.

Recently, a mis-sense mutation within the mycobacterial inhA gene has been described that confers resistance to both INH and ethionamide (33). The product of this gene, the inhA protein, differs from the original protein by a single substitution of Ser to Ala at position 94. Mutations in this gene could account for the isolates resistant to INH with normal catalase activity. However, additional studies are necessary to elucidate whether mutations in genes other than katG and inhA can also confer resistance to INH.

In the case of RIF, the molecular mechanism of resistance seems to be the substitution of a limited number of highly conserved amino acids encoded by the rpoB gene, the gene that encodes for the RNA polymerase β-subunit (34). The substitution of key amino acids would thus result in conformational changes of the β-subunit and defective binding of the drug.

Finally, resistance of M. tuberculosis to STM appears to be mediated by mutations in the gene encoding for the 16S ribosomal RNA (35) as well as in the ribosomal S12 protein gene (36).

MDRTB – Magnitude of the Problem

Multidrug-resistant TB, the third epidemic (37), has emerged as a major public health concern in the last few years. Some authors consider MDRTB an iatrogenic phenomenon. Inappropriate control of treatment, reduced funding for the fight against TB, inadequate or antiquated tools and failure to effectively apply those available, neglected or ineffective control procedures, inadequate training of healthcare workers, closure of facilities for managing TB patients, poverty, drug abuse, deterioration of the social conditions and of the public health infrastructure, patients’ access to anti-tuberculosis drugs favouring inadequate regimens, and the epidemic of HIV infection, among others, are factors that have contributed to the development of MDRTB (38,39).

Resistance to anti-tuberculosis drugs is not uniformly distributed, being more prevalent in large urban areas. Thus, New York City has more than 60% of all cases of MDRTB of the U.S. (40). In this city, the rate of drug resistance to one or more drugs has increased about 130% in 8 yr in patients not previously exposed to anti-tuberculosis drugs (41).

Previous exposure to drugs is clearly associated with drug resistance. The rate of resistance to one or more drugs in most series is 9–26% in patients without previous treatment and 13–59% in patients who have been treated before (8,26,37,40–44). Currently, resistance to INH is observed in 13–26% of patients, and MDRTB, i.e. resistance to at least INH and RIF, is found in 3–19% of all patients according to recent series (9,14,40,41).

The importance of MDRTB lies in its poor response to available treatment. In HIV-negative
Multidrug-resistant TB is also strongly associated with HIV infection (6,9,47-51). Obviously, immunosuppression is an important factor that facilitates the development of TB. Moreover, the high rates of infection with HIV in drug addict patients, a group with a high prevalence of TB, and their poor adherence to treatment leading to drug resistance, are also factors that have contributed to the propagation of MDRTB. Finally, multiple outbreaks of MDRTB have been reported in which 20-100% of patients involved were infected with HIV (8,9,14,37,52-54).

Multidrug-resistant TB carries a poor prognosis in many cases. In a study, the overall mortality rate in patients with MDRTB not infected with HIV was 37%, with a mortality directly attributable to TB of 22% (45). The prognosis in AIDS patients with MDRTB is dismal: 72-89% of patients will die with a median survival time of 4-16 weeks (8,14,41,48,55-57).

Several additional factors should be considered. Firstly, the risk for development of TB is 170 times higher in patients with AIDS, and 113 times higher in HIV-infected patients without AIDS, as compared with immunocompetent people (9). Secondly, the incidence of TB in patients with AIDS is almost 500 times the incidence in the general population (58), and 3.1 million people are co-infected with HIV and M. tuberculosis around the world (49). Thirdly, the risk for development of TB after a prolonged contact with a source case in HIV-infected patients is 37-44% in a 5-month period as compared with 2-4% in a 1-yr period in immunocompetent subjects (9,56,59); and the risk for development of active disease in tuberculin-positive patients is 7-10% in a 1-yr period in HIV-positive vs. 5-10% in a lifetime in HIV-negative subjects (8,9). Finally, HIV infection constitutes a significant risk factor for clustering in the transmission of TB as evidenced by restriction-fragment-length polymorphism (RFLP) studies (60,61).

These figures provide an idea of the magnitude of the problem, especially among HIV-infected patients, and support the urgent necessity of efficient mechanisms of control. Although additional resources are necessary, the extra cost should be compared with the enormous health and economic consequences of the dissemination of MDRTB.

Directly Observed Therapy (DOT)

Generalization of DOT programmes arises as one of the measures to undertake in order to ensure compliance with anti-tuberculosis therapy. Approximately 40% (range 20-80%) of the patients do not complete a full course of treatment (8,9,16,40,62-66). On the contrary, well designed DOT programmes have a compliance rate higher than 90% (65,66).

From an economic point of view, DOT appears to be cost-effective. It is considered cheaper than self-administered treatment, with saving rates of about $51 per patient (67). Furthermore, the cost of treatment of a patient with MDRTB at a referral hospital was estimated to be more than $200,000, the approximate cost of DOT for 700 patients (67). Also, the case of a patient with MDRTB who transmitted the disease to nine friends and relatives has been reported. The cost of hospitalization of these patients was $950,000 (68).

Despite the health and economic benefits derived from a correct treatment, only 10-15% of the TB patients in the U.S. are included in these programmes (9,67). However, all patients with MDRTB and those with intermittent regimens should be included in DOT programmes. Furthermore, DOT should be implemented if the rate of non-compliance is higher than 10% of unknown (14). Some authors even suggest that every patient with TB should receive DOT, taking into consideration the cost-effectiveness of these programmes as compared with standard regimens (67).

Future Directions

Since the introduction of RIF more than two decades ago, no other major breakthrough in the chemotherapy of TB has taken place. The use of second-line drugs such as EMB, STM, ethionamide, PAS, cycloserine, kanamycin, viomycin, amikacin, capreomycin, amithiozone, thiacetazone, rifabutin, and clofazimine, among others, can be useful in the management of patients with MDRTB while awaiting new options. In addition, in the near future the role of new drugs such as quinolones, combinations of β-lactams and β-lactamase inhibitors, and the newer macrolides in the treatment of TB needs to be established.

However, despite such an array of drugs, none has shown or is expected to show a substantially higher efficacy than INH, RIF or PZA. Accordingly, other drugs active against M. tuberculosis are urgently needed and every effort should be made to promote their investigation, development, and clinical studies directed to prove their efficacy.
The development of drug delivery systems, controlled release formulation of anti-tuberculosis drugs, liposomal encapsulated drugs, inhibitors of the aminoglycoside-modifying enzymes, the use of substances directed to increase the mycobacterial cell wall permeability, and the evaluation of non-antibiotic drugs with activity against \textit{M. tuberculosis} constitute other aspects that merit investigation.

Improvements in the knowledge of the biology of the bacillus, especially from a molecular viewpoint, and the identification of genes coding for specific enzymatic functions, should lead to the design of drugs directed to block crucial biosynthetic pathways.

The development of immunomodulators with the capacity to enhance host defence mechanisms and to promote the uptake and killing of bacilli could be a valuable weapon, especially against intracellular organisms. Cytokine therapy, particularly with substances that have anti-mycobacterial activity such as interleukin-2, granulocyte macrophage colony stimulating factor, tumour necrosis factor, interferon-gamma, and other biological response modifiers, could expand the options for treatment especially in difficult cases.

Although its role in the treatment of TB is not definitively established, immunotherapy with \textit{M. vaccae} as an adjunct to chemotherapy could be of some value particularly preventing relapses caused by growth of persisting dormant bacilli. This form of combined immunostimulant and chemotherapeutic treatment also needs to be thoroughly evaluated.

Despite these promising advances, the most important and applicable measures are a worldwide rational use of available drugs, earlier diagnosis and immediate treatment of all patients, strict control of DOT programmes. These aspects, along with measures for preventing the transmission of TB, constitute our main lines of defence against this disease. Tuberculosis, the oldest documented infectious disease which has been affecting mankind for at least 7000 yr, is not expected to be eradicated in the foreseeable future.

References


