SHORT REVIEW

ANTI-TUBERCULOUS CHEMOTHERAPY: 120 YEARS ON

C. N. Ekweani

Department of Medicine, Ahmadu Bello University Teaching Hospital, Kaduna, Nigeria
Reprint requests to: Dr. C. N. Ekweani, Department of Medicine, A. B. U. Teaching Hospital, Kaduna, Nigeria

Abstract
The last 120 years have witnessed the discovery of very effective drugs for the treatment of tuberculosis and the evolution of anti-tuberculous drug regimens to the present state where the disease can be cured with the use of 4 or more drugs given for 6 - 12 months provided the drugs are taken regularly and for long enough. The DOTS strategy makes this possible. With this development the outlook for the TB patient has markedly improved and the prospect for the worldwide control of this rampant and dreadful disease is bright. However certain obstacles have to be overcome before this prospect can be fully realised. These include poverty and poor living conditions, the scourge of HIV/AIDS and the inefficient use of anti-tuberculous drugs.

Key words: Tuberculosis, chemotherapy, poverty, HIV/AIDS

Introduction
It is about 120 years since Robert Koch discovered the tubercle, bacillus, the organism that causes tuberculosis (TB). That important discovery raised the possibility of a cure for this dreadful disease and aroused an intense interest in chemotherapy. This led to many animal studies and clinical trials. As a result of these studies and trials, the first effective anti-tuberculous drug, streptomycin, was discovered in 1944 by Schatz, Bugie and Waksman. Thereafter, other effective drugs were discovered and chemotherapy has now become the mainstay of management of tuberculosis. Yet the goal of relieving all suffering from tuberculosis in the world, let alone eradicating it, remains as elusive as it must have been in 1882. The disease is still rampant in developing countries due to poor living conditions, overcrowding and inefficient use of effective chemotherapy. Another major factor contributing to the high prevalence in these countries is the human immunodeficiency virus (HIV), which impairs the immune defenses of affected persons, predisposing them to opportunistic infections such as tuberculosis.

Non-pharmacological measures
The development of modern effective anti-tuberculosis chemotherapy was preceded by numerous non-pharmacological measures such as hygienic measures, sanatorium treatment, the practice of artificial pneumothorax, thoracoplasty and immunotherapy by the injection of tuberculin. The efficacy of these measures was however difficult to prove in the absence of controlled trials. Gold therapy followed from 1925 to 1935 but, like previous attempts, its efficacy could not be proven.

Sulphonamides, Streptomyacin, PAS, INH
The first effective anti-tuberculous chemotherapeutic agents were the sulphonamides, followed by streptomycin, para-aminosalicylic (PAS) acid and isoniazid (INH). Their efficacy was demonstrated by numerous clinical trials.

These trials highlighted the efficacy of streptomycin and the sulphonamides in the treatment of tuberculosis, the problem of bacterial resistance when these agents were used alone, and the value of combining streptomycin and/or PAS with INH as a solution to the problem of resistance. Another trial showed that the optimal duration of therapy with these drugs was 2 years.

The Madras study proved that ambulatory treatment was as effective as in-patient treatment while another Madras study showed that intermittent treatment was first as effective as continuous treatment and had the advantage of improving patient compliance and reducing cost.

Short course therapy
The next major development was short course therapy. The introduction of rifampicin and pyrazinamide in the early 1970’s made possible...
regimens of 9 months as in the so-called ‘short-course’ therapy. This form of therapy is based on the observations both in vivo and in vitro from several studies showing that rifampicin and pyrazinamide eliminate special bacterial populations. Rifampicin acts mainly against rapidly dividing bacilli. Pyrazinamide on the other hand, acts against the so-called “persisters” organisms that are metabolizing or dividing very slowly. 24-30

Short-course regimes consist of an initial intensive phase that includes combinations of bacterial drugs namely rifampicin, pyrazinamide, INH and streptomycin followed by a continuation phase of either twice-weekly or daily drugs. A review by Fox 31 of selected short course regimes has shown that bacteriostatic drugs play little or no role in such regimens.

The implications and benefits of short course therapy include:
1. Total quality of drugs used is less, which means less chronic toxicity and less cost.
2. Total delivery of health services is less
3. More efforts can be concentrated on ensuring patient compliance.
4. Patients who abscond early are less likely to relapse.
5. Routine follow-up after the end of treatment can be abandoned.

Short-course therapy is currently the most effective treatment for most patients with tuberculosis and has been recommended by World Health Organisation (WHO) as part of the directly observed treatment short course (DOTS) strategy for the worldwide control of tuberculosis. With this strategy, WHO envisages that in those countries where the incidence of tuberculosis is stable and HIV I absent, given a 70% case detection rate and 85% cure rate, the annual incidence of the disease will reduce by 11% per year. 32

Current recommendations for the treatment of pulmonary and extra-pulmonary tuberculosis are given below. 33 With regards to the notations used for anti-tuberculous treatment regimes outlined hereunder, the drugs are represented by the letters of the alphabets e.g. R (Rifampicin); H (INH); Z (Pyrazinamide); E (Ethambutol); S (streptomycin) while the durations of therapy in months is represented by Arabic numerals e.g. 2, 4, 6.

Section 1: Pulmonary tuberculosis

Category A: Uncomplicated tuberculosis

Category A1: Primary treatment (no treatment within the previous 5 years): 2HRZ + (E or S). 4HR.

The drugs may be given daily or intermittently (thrice weekly) in both the initial and continuation phases. For patients with extensive disease or evidence of drug resistant TB the initial phase may be extended to 3 or 4 months while the total duration of treatment may remain at 6 months.

Category A2: Re-treatment: (for those who have received treatment within the previous 5 years): 3(4) HRZES. 6(5) HR + or – E.

Category B: Drug resistant tuberculosis

There are no documented regimes for these types of tuberculosis. It is important to avoid the “addition phenomenon”-namely adding a single drug to a failing regimes. Otherwise acquired resistance to the newly added drug will develop. Instead add at least 2, 3 or more drugs to which the organisms ARE sensitive or which had not already been administered to the patient. Treatment duration should not be less than 12 months in this case.

Category C: Multi-drug-resistant TB (MDR-TB)

For MDR-TB, that is TB that is resistant to at least isoniazid and rifampicin. A combination of drugs to which the organism is likely to be sensitive should be used, namely, a regimes that includes 5 or 6 drugs for the initial 6 months and then 3 or 4 drugs subsequently. Apart from the first-line drugs other drugs available include the quinolones (e.g. ofloxacin, levofloxacin, ciprofloxacin), prothionamide, ethionamide, cycloserine, para- amino salicylic acid, clofazimine and the aminoglycosides kanamycin, amikacin. The optimal duration of treatment for MDR-TB has not been clearly established but some authorities recommend a total duration of 18 to 24 months or 24 months after negative culture. With the inclusion of quinolones duration may be shortened to 12 to 18 months. The longer duration may be required for patients with diabetes mellitus, silicosis, slow sputum conversion or extensive disease.

Section 2: Extrapulmonary tuberculosis

Due to lack of a sufficient number of larger-scale studies consensus is lacking especially on the optima duration of treatment. The following regimes are recommended based on limited current evidence and local experience. Adjunctive steroid treatment can be useful in tuberculous pericarditis, tuberculous meningitis, tuberculous lymphadenitis, tuberculous pleural effusion, fulminant pulmonary tuberculosis and genitourinary tuberculosis.

Category A: TB Meningitis including central nervous system TB

3HRZE. 9HRZ.

Streptomycin may be added for the initial 2 months and duration may be extended to 18 or 24 months for CNS tuberculosis.

Category B: Miliary TB

3HRZ + (E or S). 9HR

Category C: TB of bone and joint

2HRZE/1OH.

Duration if treatment may be reduced to 6 or 9 months in the case of TB spine or other cases of mild disease.
Category D: TB lymphadenitis
Where lymph node affection in the neck is solitary or few, limited to the upper cervical chain or posterior triangle and the chest X-ray is clear, the same treatment as outlined in section 1 Category A is recommended and should be given for 6 months.

For other situations the duration of therapy should be 9 months. It has to be noted that the clinical response of TB of the lymph nodes during treatment may be quite unpredictable sometimes with paradoxical increases in size probably due to immunological reactions. Furthermore residual nodes may still be palpable after completing the full course of treatment.

Category E: TB pericarditis, TB peritonitis and genitourinary TB
The recommendation is as in section 1 Category A1 but the continuation phase is extended such that total duration of treatment is 9 months.

Section 3: Pulmonary tuberculosis associated with medical disease or special settings

Category A: Diabetes mellitus
The recommendation is as in section 1 category A1 but the continuation phase is extended such that the total duration is 9 months.

Category B: Immunodeficient patients
Recommendation is same as for section 1 category A1 but total duration should be 9 months.

For re-treatment and drug resistant cases the recommendations are the same for seronegative patients except that a longer duration of treatment is necessary. Universal precaution and infection control measures should be strictly enforced, if drugs are to be given by injection.

Category C: Pregnancy
All the first line drugs can be used with the exception of streptomycin because of foetal ototoxicity. The safety of the second line drugs and ofloxacin have not been established and these drugs should be avoided. The taking of anti-tuberculous drugs is itself not a contraindication to breast-feeding.

Category D: Children
The regimens are similar to the adult regimens except that ethambutol should be avoided in children until they are at least 6 years old and able to report visual changes accurately. The drug dosages should be based on body weight.

Category E: Liver dysfunction
Transient bilirubin and alanine transaminase level changes are common and do not indicate true hepatotoxicity. Drug-induced hepatitis however necessitates the withholding of all drugs until liver function normalizes. During extensive disease and pending full recovery of liver function, ofloxacin can be used together with streptomycin and ethambutol as an interim measure. Experience has shown that the optimal dose for ofloxacin is between 400-600mg once daily. Inclusion of ofloxacin as a component of a definitive regimen should only be considered when the patient is intolerant of rifampicin and INH given concomitantly. Optimal duration of ofloxacin-containing regimens should be at least 1 year.

Category F: Renal impairment
The development of drug induced renal impairment is an indication for the withdrawal of streptomycin or rifampicin. If there is pre-existing renal impairment, rifampicin, INH and pyrazinamide can be given in the usual doses. However in severe renal impairment INH should be given at 200mg once daily with pyridoxine to avoid peripheral neuropathy.

Streptomycin and ethambutol require the renal route for elimination and should be used with caution in patients with renal impairment.

References