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The Effectiveness Of Short-Term Treatment Regimens In The Treatment Of Drug-Resistant Forms Of Tuberculosis

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ABSTRACT

The discovery of rifampicin was the turning point away from the standard long term treatment for tuberculosis of 18 to 24 months and towards a 6-month curative programme. Rifampicin has proven to be highly effective and vital to short-course tuberculosis therapy, but its disadvantage is its cost.

This makes it relatively unavailable where it is most needed, i.e. in countries where tuberculosis is still rampant, but which are economically underdeveloped. In such areas other needs take precedence over a chronic and non-spectacular medical condition like tuberculosis. During the past 10 years pyrazinamide has been 'rediscovered' and restudied, and when used in combination with rifampicin has been shown to play an important role in short-course chemotherapy. Its contribution to efficacy does not appear to extend beyond the first 2 months of therapy, and it should be discontinued after 2 months. This relatively short administration period helps to minimise adverse reactions to the drug. The main measure of success in short-course chemotherapy is the relapse rate, and this has been higher, sometimes unacceptably so, in regimens where bacteriostatic drugs were substituted for bactericidal ones. In conclusion, isoniazid, rifampicin and pyrazinamide in combination may be deemed essential to an effective short-course regimen of 6 months' duration.

1. OBJECTIVE:

This article reviews the role that existing drugs and new compounds could have in shortening or improving treatment for TB. The key to treatment shortening seems to be sterilizing activity, or the ability of drugs to kill mycobacteria that persist after the initial days of multi-drug treatment.

Curtailing the duration of treatment to less than 6 months in smear-positive tuberculosis results in high relapse rates and thus is not acceptable. Several studies have been undertaken varying the drug combinations, the dosages and the drug administration routines (i.e. whether daily followed by intermittent or intermittent throughout), in an effort to arrive at the simplest, most effective, least toxic and most economical all-round treatment programme. Such studies are still in progress. When recommended dosage regiments are followed, the incidence of adverse reactions is low with short-course therapy, and in only 5% or less of patients is it necessary to withdraw one or more drugs.

2. RESULTS:

Among existing anti-TB drugs, the rifamycins hold the greatest potential for shortening treatment and improving outcomes, in both HIV-infected and HIV-uninfected populations, without dramatic increases in toxicity. Clinical studies underway or being planned, are supported by in vitro , animal and human evidence of increased sterilizing activity--without significant increases in toxicity--at elevated daily doses. Fluoroquinolones also seem to have significant sterilizing activity. At present, at least two class members are being evaluated for treatment shortening with different combinations of first-line drugs. However, in light of apparent rapid selection for fluoroquinolone-resistant mutants, relative frequency of serious adverse events and a perceived need to 'reserve' fluoroquinolones for the treatment of drug-resistant TB, their exact role in TB treatment remains to be determined. Other possible improvements may come from inhaled delivery or split dosing (linezolid) of anti-TB drugs for which toxicity (ethionamide) or lack of absorption (aminoglycosides and polypeptides) precludes delivery of maximally effective, oral doses, once daily.

New classes of drugs with novel mechanisms of action, nitroimidazopyrans and a diary lquinoline, among others, may soon provide opportunities for improving treatment of drug-resistant TB or shortening treatment of drug-susceptible TB.

Given the global burden of tuberculosis, shortened treatment regimens with existing or repurposed drugs are needed to contribute to tuberculosis control. The long duration of treatment of drug-susceptible tuberculosis (DS-TB) is associated with nonadherence and loss to follow up, and the treatment success rate of multidrug-resistant tuberculosis (MDR-TB) is low (approximately 50%) with longer regimens. In this review article, we report recent advances and ongoing clinical trials aimed at shortening regimens for DS-TB and MDR-TB.

We discuss the role of high-dose rifampin, as well as that of clofazimine and linezolid in regimens for DS-TB. There are at least 5 ongoing clinical trials and 17 observational studies and clinical trials evaluating shorter regimens for DS-TB and MDR-TB, respectively.

We also report the results of observational studies and clinical trials evaluating a standardized nine-month moxifloxacin-based regimen for MDR-TB. Further studies, especially randomized clinical trials, are needed to evaluate regimens including newer drugs, drugs proven to be or highly likely to be efficacious, and all-oral drugs in an effort to eliminate the need for injectable drugs. Given the global burden of tuberculosis, shortened regimens with existing or repurposed drugs are needed to contribute to tuberculosis control.

The current standard antituberculosis chemotherapy treatment regimen currently recommended by the World Health Organization (WHO) consists of a 2-month intensive phase with isoniazid, rifampin, pyrazinamide, and ethambutol, followed by a 4-month continuation phase with isoniazid and rifampin. Isoniazid and rifampin are the drugs with the greatest early bactericidal activity, and rifampin and pyrazinamide are the drugs with the greatest sterilizing power.

Ethambutol is bacteriostatic and is strategically associated with the more potent drugs to prevent the emergence of resistant bacilli. The major justification for using this longer treatment regimen is to reduce recurrence.[1] In addition, previously published data do not support the use of shortened treatment regimens in adults with newly diagnosed pulmonary drug-susceptible tuberculosis (DS-TB).

However, the long duration of DS-TB treatment is associated with nonadherence and loss to follow-up. Four-month treatment regimens that replace ethambutol with moxifloxacin or gatifloxacin, or those that replace isoniazid with moxifloxacin, increase relapse substantially when compared with standard 6-month treatment regimens.

However, the treatment success rate of multidrug-resistant tuberculosis (MDR-TB) is low (approximately 50%) with longer regimens, although recent studies involving new drugs have suggested that better results are possible also at the programmatic level. The development of efficacious, safe, and shorter treatment regimens for both DS-TB and MDR-TB could significantly improve tuberculosis management and treatment success rates.

Johnson & Johnson Pharmaceuticals Company (J&J) holds a patent for bedaquiline and is therefore the only pharmaceutical company to participate in a collective effort to develop a drug and demonstrate its therapeutic value.

Financial support comes from civil society and charities, as well as the TB patient community, who are desperate to improve the effectiveness of treatment for DR-TB patients. Bedaquiline was approved in 2012 and became the first drug for the treatment of DR-TB in more than 40 years. But by the end of 2018, only 28,700 people globally received the drug - less than 20% of all those who could benefit from it.

The clinical effectiveness of anti-tuberculosis drugs is determined by many factors, among which the main ones are:

- the massiveness of the mycobacterial population itself;
- sensitivity or resistance of the mycobacteria in it to the drugs used;
- the ability of individual individuals to reproduce quickly;
- the level of the created bacteriostatic concentration;
- the degree of penetration of drugs into the affected areas and activity in them;
- the ability of drugs to act on extra- and intracellular (phagocytosed) microbes;

Amid this alarmingly unmet medical need and J&J's unauthorized monopoly on drug availability and pricing in 2018, MSF openly called on the company to lower the cost of the drug and give it access to those who need it. We highlighted J&J's collaborative efforts that established the clinical value of bedaquiline, as well as analysis that showed the drug could be manufactured and sold profitably at 25 US cents per daily dose. We urged the company to allow the production of cheaper generics of the drug and reduce the price of bedaquiline to one US dollar per day.

With progressive and acutely progressive tuberculosis (infiltrative, miliary, disseminated fibro-cavernous and caseous pneumonia), there is an intensive multiplication of mycobacteria in the patient's body, their release into the tissue of the affected organ, spread by hematogenous, lymphogenous and bronchogenic pathways, resulting in the appearance of areas of inflammation, caseous necrosis develops.

Most of mycobacteria during this period are extracellular, and that part of the mycobacterial population, which turned out to be phagocytosed by macrophages, due to the intense destruction of phagocytes, again appears to be located extracellularly. Consequently, the intracellular localization of mycobacteria at this stage is a relatively short period in the process of vital activity of the multiplying mycobacterial population.

In terms of effective chemotherapy, drug resistance of Mycobacterium tuberculosis is of great clinical importance. In a large and actively multiplying bacterial population, there is always a small number of wild mutants resistant to anti-TB drugs in a ratio of 1 mutant resistant to isoniazid or streptomycin per million, 1 to rifampicin per 100 million and 1 to ethambutol per 100 thousand susceptible mycobacterium tuberculosis (MBT). Taking into account the fact that there are 100 million MBT in a cavity with a diameter of 2 cm, there are mutants for all anti-tuberculosis drugs.

With proper and adequate chemotherapy, these mutants have no practical value. But as a result of improper treatment, when inadequate regimens of chemotherapy and a combination of anti-tuberculosis drugs are prescribed, suboptimal doses calculated in mg per 1 kg of the patient's body weight and dividing the daily dose of drugs into 2-3 doses, the ratio between the number of resistant and resistant mycobacteria changes. Under these conditions, the multiplication of mainly drug-resistant microbes occurs - this part of the bacterial population increases.

As the tuberculous inflammation subsides, during chemotherapy, the size of the mycobacterial population decreases due to the destruction of mycobacteria. In clinical conditions, this population dynamics is manifested in a decrease in the number of excreted Mycobacterium tuberculosis in the sputum, and then in the termination of bacterial excretion.

In the conditions of ongoing chemotherapy, leading to a decrease in the mycobacterial population and suppression of the reproduction of mycobacterium tuberculosis, a part of the mycobacteria that are in a state of persistence remains in the patient's body. Persistent mycobacteria are often detected only by microscopic examination, because when sown on nutrient media, they do not give growth. These mycobacteria are called "sleeping" or "dormant", sometimes - "killed". As one of the variants of persistence of mycobacteria, their transformation into L-forms, ultra-small and filterable forms is possible. At this stage, when the intensive reproduction of the mycobacterial population is replaced by the state of persistence of the rest of it, mycobacteria are often found mainly intracellularly (inside phagocytes).

Isoniazid, rifampicin, ethionamide, ethambutol, cycloserine and fluoroquinolones have more or less the same activity against intra- and extracellular Mycobacterium tuberculosis. Aminoglycosides and capreomycin have significantly less bacteriostatic activity on intracellularly located mycobacteria. Pyrazinamide, with a relatively low bacteriostatic activity, enhances the effect of isoniazid, rifampicin, ethambutol and other drugs, penetrates very well into cells and has a pronounced activity in the acidic environment of caseosis.

The simultaneous appointment of several anti-tuberculosis drugs (at least 4) allows you to complete the course of treatment before the appearance of drug resistance of mycobacteria, or to overcome their initial resistance to one or two drugs.

In connection with the different state of the mycobacterial population at different stages of the disease, it is scientifically grounded to divide the chemotherapy of tuberculosis into 2 periods or phases of treatment .

In October, Médecins Sans Frontières, along with other civic organizations, reiterated these calls at the opening ceremony of the 49th World Conference on Lung Health in The Hague. In addition, ahead of the first ever UN High-Level Meeting on Tuberculosis in September 2018, we called on world leaders to translate their ambitious promises into bold and real life-

saving actions, including increasing the availability of existing drugs and diagnostic tests, and developing and releasing faster, safer and easier tools in the future.

We continue to strive to ensure that our patients receive the most effective treatment for tuberculosis. We also continue to put pressure on governments and pharmaceutical companies to fulfill their commitments to reduce suffering and reduce deaths from this terrible disease. In 2018, 19,400 MSF patients received TB treatment, including 2,840 MDR-TB patients.

The MSF Campaign for Access to Essential Medicines was launched in 1999 with the aim of increasing the availability and acceleration of the development of essential medicines, diagnostic tests and vaccines for patients in MSF programs and beyond.

One problem is that multiple drugs are required to effectively treat drug-resistant tuberculosis. However, pharmaceutical companies have developed bedaquiline and delamanid separately and have not studied their safety and effectiveness in combination with pre-existing drugs.

This generally accepted research and development model does not exploit all possibilities and only leads to delays in the creation of effective treatments. In partnership with other organizations, MSF is conducting critical research to develop an evidence base for the therapeutic value of new DR-TB treatment options and can improve our patients' chances of survival. These studies will not be completed until 2022; however, based on data from drug safety monitoring and operational research in clinical trials, in 2018 the World Health Organization updated its DR-TB treatment guidelines to include the new drug bedaquiline.

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