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Historical considerations about tuberculosis treatment

Consideraciones históricas del tratamiento médico de la tuberculosis

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ABSTRACT. Although tuberculosis is as old as humanity, its medical treatment began in the 1940's with the discovery of streptomycin. This discovery caused great expectation; However, shortly after it was noticed that patients who received it died just as well as those who did not. This gave way to treatment with multiple drugs due to the growth nature of *M. Tuberculosis*. Multiple treatments have been given since then, with various organizations worldwide participating. Due to the changing nature of the mycobacteria due to ineffective treatments or insufficient doses, the fight against this bacteria has been long, due to the appearance of monoresistance, polyresistance, evolving until today to the so-called extended resistance. All current research is aimed at better diagnostic tests and treatments that shorten its duration. This article reviews the history of medical treatment of tuberculosis.

Keywords: tuberculosis, *Mycobacterium tuberculosis*, multidrug resistant, treatment.

RESUMEN. A pesar de que la tuberculosis es tan antigua como la humanidad, su tratamiento médico inició en los años 40 con el descubrimiento de la estreptomicina. Este descubrimiento causó gran expectativa; sin embargo, poco después se notó que los pacientes que la recibían morían igual que los que no. Lo anterior dio paso al tratamiento con múltiples fármacos debido a la naturaleza de crecimiento de *M. Tuberculosis*. Múltiples tratamientos se han dado desde entonces, participando varias organizaciones a nivel mundial. Debido a la naturaleza cambiante de la micobacteria a causa de tratamientos ineficaces o dosis insuficientes, la lucha contra esta bacteria ha sido larga por la aparición de la monorresistencia, la polirresistencia, evolucionando hasta hoy a la llamada resistencia extendida. Todas las investigaciones actuales se encaminan a mejores pruebas diagnósticas y de tratamientos que acorten la duración del mismo. En este artículo se hace una revisión de la historia del tratamiento médico de la tuberculosis.

Palabras clave: tuberculosis, *Mycobacterium tuberculosis*, multidrogorresistencia, tratamiento.

INTRODUCTION

Although the tuberculosis bacillus is as old as mankind, the treatment of the disease came much later; and this, for a long time, was based on trial and error, with the selection of strains resistant to multiple drugs, as it happens nowadays. This paper only mentions some of the schemes that have been used during the history of tuberculosis treatment.

THE TREATMENTS

Effective treatment began with the introduction of streptomycin in 1946, with the first trial by the British Medical Research Council (BMRC), and immediately a very significant improvement was found in the patients clinically, bacteriologically and radiologically.[1] This created great hopes and treatments were started with this drug alone. However, five years later, patients administered streptomycin died at the same rate as those who did not receive it, due to the frequent emergence of streptomycin resistance.[2] Subsequently, the Medical Research Council (MRC) demonstrated that the combination of streptomycin with para-aminosalicylic acid (PAS) significantly reduced the incidence of streptomycin resistance.[3]

In this context, in 1952 isoniazid[4] was discovered as a wonder drug that was compared alone with the

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combination of streptomycin and PAS. The results were comparable, but the appearance of resistance to isoniazid was observed, so Crofton[5] initiated studies of combining isoniazid with streptomycin and PAS, reporting surprising results in England, Wales and Scotland; the duration of treatment lasted from one to two years. Treatment remained in-hospital. This work inspired the International Union for the Fight Against Tuberculosis to design a scheme based on streptomycin, PAS and isoniazid for three months, followed by nine months of PAS and isoniazid. The response was good, with no relapses or failures, but with many dropouts.[6] This scheme required one year of hospitalization and was very expensive, which meant that it could not be affordable in poor countries. This led to a modification of the treatment, replacing PAS with thiacetazone, which was much cheaper.[7] It was in 1960 that Wallace Fox published a study comparing outpatient versus inpatient treatment and showed that the former was much cheaper than the latter.[8] One obstacle was adherence to treatment, as one year of self-administration made it very difficult to achieve success. Thus, the World Health Organization (WHO) implemented the DOTS (Directly Observed Treatment Short course) strategy, to ensure that the patient ingested the drugs in the presence of health personnel. It was in Madras that a fully supervised intermittent regimen was established for the first time.

An important milestone in the treatment of tuberculosis during the 1950s and 1960s was the addition of pyrazinamide to isoniazid and streptomycin because of its action in killing persistent bacilli in organs after treatment with isoniazid and streptomycin.[9]

Subsequent research at the Pasteur Institute reported that rifampicin accelerated the death of bacilli in the mouse. In clinical practice, the addition of rifampicin or pyrazinamide to a six-month regimen was shown to significantly reduce the relapse rate.[10] Subsequently, several studies were conducted that adopted different conclusions to the medical treatment of tuberculosis such as: 1) the synergism of rifampicin with pyrazinamide for more rapid sterilization of lesions;[11-13] 2) the demonstration that rifampicin was an effective sterilizing agent throughout the entire treatment, while pyrazinamide was effective only during the initial phase of treatment;[14] and 3) the initial phase should last two months. The interesting thing was that, due to the cost of rifampicin at that time, in the continuation phase it was substituted by thiacetazone; however, with the appearance of the human immunodeficiency virus, there was a very significant number of toxic reactions, so it had to be substituted by ethambutol, which also made it possible to shorten the treatment time from eight to six months. The results of this treatment scheme were compelling, published by Professor Enarson of the Union for Tuberculosis and Respiratory Diseases.[15] The rifampicin regimen for the full six months proved to be much more effective than the eight months, particularly in those patients who initially had resistance to isoniazid. The WHO recommends this regimen to date.

Optimism about the treatment grew enormously and was associated with an immediate effect on fatality; patients who would have died of the disease remained alive. The trend in mortality after chemotherapy was illustrated in Norway; the greatest reduction occurred after the introduction, when multitherapy was used.[16] Subsequently, it was shown that patients did not relapse if they followed the prescribed multi treatment disciplined.[17] With the addition of rifampicin to the shortened treatment, it became possible.

After World War II, there was a major epidemic of tuberculosis and the need arose to search for the best strategies to deal with it. Styblo, from the Epidemiological Surveillance Research Unit in The Hague, The Netherlands, and the Scientific Committees of the International Union Against Tuberculosis in Paris,[18] laid the foundations for the modern epidemiology of tuberculosis, an essential element of current disease control programs. In addition, Styblo has the great merit of having been the first to demonstrate the feasibility of successfully applying modern tuberculosis control programs in some of the poorest countries in Africa. Crofton laid the foundations of modern treatment by establishing the principles universally accepted to this day.

Caneti, Rist and Grosset, from the Pasteur Institute in Paris, discovered the bacteriological principles on which the modern chemotherapy of the disease is based; and achieved the most widely used method in the world to measure the sensitivity of the bacillus to the different drugs.

Fox and Mitchinson laid the foundations of treatment by demonstrating, in their studies in Madras, that treatment within the sanatorium was not necessary, since it could be given intermittently on an outpatient basis, and the importance of directly observed treatment. This was later demonstrated in Singapore and Hong Kong.[19] The basic principles of tuberculosis treatment were tested and confirmed between 1948 and 1976.[20]

With the advent of rifampicin, initially synthesized in Italy in 1957 from *Streptomyces mediterranei*, the drug became a very important component of modern tuberculosis treatment. Rifampicin was initially introduced for drug-resistant cases. However, based on British Medical Research Council studies, it was shown that, together with isoniazid, the regimen substantially shortened treatment time, so it was included as a standard element in the late 1970s.[21]

In 1993, WHO declared tuberculosis a global emergency. In 1994, the agency launched the DOTS (Directly Observed Treatment Short course) program, or TAES (strictly observed treatment short course), with several points that made up this project; among them, supervised treatment, i.e., the

patient should take the medication in the presence of health personnel. This strategy continues to this day.[22] Directly observed treatment ensured adherence to treatment, but another important measure to prevent non-adherence was to incorporate medication in a single capsule to prevent «selective discontinuation» of treatment. Currently, a single tablet of four drugs is prescribed in an initial phase (isoniazid, rifampicin, ethambutol and pyrazinamide), followed by a continuation phase with two drugs (isoniazid and rifampicin).

DRUG RESISTANCE

Reports published by the WHO and various researchers since 1994 have warned about the increase in cases of resistance to antituberculosis drugs, especially to isoniazid and rifampicin, especially in regions of Eastern Europe, the former Soviet Union and China, as well as in Latin America, in the Dominican Republic and Argentina.[23-26] In Mexico, Granich et al.[27] published the results of surveillance of drug resistance to antituberculosis drugs, which were 2.4% for primary resistance to isoniazid and rifampicin, and 22.4% for previously treated cases. This led to the conclusion that resistance to antituberculosis drugs in Mexico was moderate to high.

Given the emergence of resistant cases, and that most of these were in low-resource countries, the International Union for Tuberculosis and Lung Disease Control[28] (UICTER) and the WHO[29] included in their guidelines standardized treatment in four categories. Category II with five drugs that included the four primary drugs plus streptomycin; and Category IV, «chronic» cases that already required expert management. Category II was indicated for failures, relapses or dropouts; it was recommended for those resource-poor countries that did not have cultures and susceptibility tests for these cases. These schemes were designed by expert opinions that did not have clinical trials to support them, which led the WHO not to recommend such schemes, as they needed to be designed based on susceptibility testing.[30] This was corroborated in a meta-analysis published by Cohen et al.[31] where treatment results varied between 11 and 85%, especially in resistance to isoniazid, rifampicin or both, in which the results were worse. The recommendation of this treatment scheme suggested by WHO was not adequate in regions where simultaneous resistance to isoniazid and rifampicin (MDR-TB) was high.

STANDARDIZED AND INDIVIDUALIZED RETREATMENTS

Due to the fact that resistant tuberculosis was prevalent in developing countries, where cultures and susceptibility tests for anti-tuberculosis drugs were difficult to access, in addition to long waiting periods for results and, added to the above, the lack of anti-tuberculosis drugs that, in addition to having been discarded previously, were toxic, expensive and difficult to acquire, and above all, the lack of experts in the field, standardized retreatment schemes were designed based on anti-tuberculosis drug profiles, In addition to this, the lack of anti-tuberculosis drugs that, in addition to having been discarded previously, were toxic, expensive and difficult to acquire, and above all the lack of experts in the field, standardized retreatment schemes were designed based on the resistance profiles in each region, and which were applicable in program conditions. Suarez et al.[32] published the results of a standardized retreatment of 18 months, based on kanamycin, three months, ciprofloxacin, ethionamide, pyrazinamide and ethambutol, with a cure success rate of 48%. As can be seen in the scheme, pyrazinamide and ethambutol were added, drugs already used previously and three never taken. In contrast, Goble et al. used an individualized regimen in 171 patients, who had a mean of six drugs taken previously, with a 56% cure rate, previously evaluated with susceptibility testing, and receiving six or more drugs for treatment.[33]

Faced with the alarming increase of resistant cases, already a global concern, with increases in cases in the so-called «red hot spots», such as some provinces in Russia, Latvia, Estonia, China, India, Argentina, attempts were made to provide treatment for resistant tuberculosis. However, this mainly affected countries with low economic resources, which did not have susceptibility tests or second-line drugs for this situation. This led organizations such as the Demian Foundation to initiate studies on standardized retreatment; Van Deun[34] published the results of a retreatment in Bangladesh in a cohort of 58 patients treated in three phases: Phase I consisted of three months with kanamycin, clofazimine, ofloxacin, prothionamide, isoniazid, pyrazinamide and ethambutol as an inpatient; Phase II consisted of the same drugs except kanamycin, this already on an outpatient basis; and a Phase III based on ethambutol and prothionamide for six months, with a cure rate of 69%. This study later gave rise to the STREAM Study (Standardized Treatment Regimens of Anti-tuberculosis drugs for Multidrug-Resistant Tuberculosis) 1 and 2.[35-37] In STREAM 2,[37] they published the results in patients with multidrug-resistant tuberculosis in several countries; the patients were assigned to four treatment groups. The study resulted in important evidence that in 76 weeks two bedaquiline regimens, a nine-month oral regimen and a six-month regimen including a second-line injectable (kanamycin), were superior in efficacy in cases resistant to rifampicin and without evidence of resistance to quinolones or aminoglycosides.

It is worth mentioning that the research carried out with new drugs (bedaquiline,[38] delamanid,[39] pretomanid[40]) and

the repositioning of other antibiotics (such as linezolid and clofazimine[41]) have made a very important contribution to the treatment of patients with resistance to rifampicin, sensitive to quinolones. For the treatment of patients with highly resistant tuberculosis: preXDR (simultaneous resistance to isoniazid, rifampicin and a quinolone and/or aminoglycoside) and XDR (simultaneous resistance to isoniazid, rifampicin, quinolone and aminoglycoside), very important studies have been published, such as the Nix study,[42] which included 109 patients, 71 XDR and 38 MDR, treated with bedaquiline, pretomanid and linezolid for 26 weeks. In this study, linezolid doses of 1,200 mg were used. Treatment success was 92% in MDR patients and 89% for XDR patients, with an average of 90%. The drawback of this scheme was the large number of adverse reactions to linezolid, so in the ZeNix[43] study the dose of linezolid was reduced to reduce the side effects, without affecting the success of the treatment.

The WHO, in its 2022 treatment guidelines,[44] makes considerations about the different drug treatments and duration. In its new classification, it only recommends the use of amikacin or streptomycin when no other drugs are available. Quinolones, bedaquiline and linezolid are prioritized, and clofazimine is already taken into account as an antituberculosis drug.

The diagnosis and treatment of the disease has advanced significantly in the last ten years. Molecular tests that include sequencing of mycobacteria make it possible to know in a timely manner its susceptibility profile, which will allow prompt action and appropriate treatment.

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