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History of chemotherapy of leprosy

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Abstract Chemotherapy of leprosy over the past 70 years has passed through several phases, from sulfones, to clofazimine, and to highly bactericidal drugs like rifampicin. The use particularly of the more potent drugs in effective combinations and the development of standard multidrug therapy regimens have made a huge difference in the successful treatment of leprosy as well as in reducing tremendously the prevalence of leprosy globally. A major contributing factor to development of better drugs and drug combinations has been the introduction of the mouse footpad model to evaluate the *in vivo* activity of drugs against *Mycobacterium leprae*. The World Health Organization has recommended multidrug therapy, which has been used to treat more than 15 million patients in the last 30 years and has set an excellent record with regard to its very high rate of cure, very low occurrence of relapse, and very rare occurrence of drug resistance.
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Treatment of leprosy in the early days

For a very long time, leprosy was considered an incurable disease and a curse. The disease was shrouded in myths and mysteries; however, attempts have been made since ancient times to treat the disease empirically with traditional remedies. Among them, the treatment that stood out prominently during the last half of 19th century and the first half of the 20th century is Chaulmoogra/Hydnocarpus oil and its products. Based on folklore from Burma and Ayurvedic treatises from India, the oil was widely used due to the absence of any other alternative. The response to the oil, which was applied through inunction and injection and by mouth, was not completely satisfactory and also inconsistent.[1] Although Chaulmoogra oil treatment was based on empirical evidence, its mild bacteriostatic effect was late established in the 1970s through mouse test studies.[2]

Sulfonamides

The first attempt to treat leprosy using chemotherapy began with the discovery of sulfonamides and their possible use in treating the disease. Sulfonamide was first evaluated by Faget et al.[3] The initial results were generally unsatisfactory, but long-acting sulfonamides were tried with limited success several years later.[4]

With the success of the sulfonamides in treating various infections, other related compounds also were developed, including sulfones. This success suggested the possibility of using these drugs in the treatment of leprosy; thus came an important development in chemotherapy of leprosy, with Faget evaluating a sulfone, glucosulfone sodium (Promin), in patients in Carville, Louisiana, USA.[5] The results with Promin were found to be far superior to earlier treatments, and an historic milestone was set at Carville as a result of the use of a truly chemotherapeutic substance in the treatment of leprosy.

Although the parent sulfone, diaminodiphenyl sulfone (DDS, or Dapsone), was available before the introduction

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of Promin, it was not used due to its toxicity in doses of 1 to 2 g daily, as was generally applicable in the case of sulfonamides.

In the early days, therefore, aside from promin, several derivatives of DDS were prepared and tested in the treatment of leprosy, including sulfetrone and diasone. It was later found that all of these derivatives released the parent compound DDS, the main active substance, upon hydrolysis in the body. Because dose-related toxicity due to DDS was noted previously when DDS was given in doses similar to sulfonamides, DDS was tried in lower doses.

Trials with DDS in lower doses found the drug to be very effective, producing good clinical and bacteriologic improvement, and the first successful results with parenteral DDS were published in 1949.[6] The first successful results of oral DDS in leprosy were published.[7] Although the successful results were based on clinical and bacteriologic examination, scientific proof of the antibacterial effect of DDS came only after the development of mouse footpad studies by Shepard.[8,9]

Acedapsone (DADDS)

DADDS (DiAcetyl Diamino Diphenyl Sulphone) is a repository sulfone preparation administered once in 10 weeks that releases DDS at a fairly even rate. Shepard was the first to find it effective in preventing growth of *M leprae* in the mouse footpad. DADDS was tried among patients in Philippines, who showed clinical and bacteriologic response similar to that achieved with DDS.[10] DADDS was subsequently tried in Karimui, New Guinea[11] who found it to be an effective antileprosy drug.

Sulfone resistance

Although resistance of *M leprae* to sulfones was suspected in the 1950s and 1960s, its existence was confirmed through mouse footpad experiments only in 1966.[12] Several studies confirmed its widespread occurrence and the danger it posed for the future of leprosy control.[13]

Clofazimine (B663)

Even as dapsone in monotherapy was being used with a moderate degree of success, the long duration of treatment and slow response meant that there was an important need for better drugs. A major development in this direction was made by Vincent Barry from Dublin, who created B663. B663 was the result of a very fruitful collaboration between Barry and the Medical Research Council of Ireland (MRCI). The compound was originally synthesized in 1954 by MRCI laboratories, which collaborated with Geigy, a Swiss pharmaceutical company, to facilitate production, toxicology testing, and coordination of animal and human trials.

The clinical trials of B663 in patients with leprosy were carried out by Stanley Browne and Hogerzeil in Uzuakoli, Nigeria.[14] They reported definite clinical and bacteriologic improvement with no signs of toxicity over 12 months; however, they noted that when the drug was given over 12 months, B663 appeared to cause drug resistance, leading them to suggest that it be given in combination with DDS.

A major problem with B663 was then its high cost due to the complex nature of its production, along with Geigy's reluctance to produce the drug for mass consumption; therefore, the leprologists then concluded that B663 could be of value only as a second line of defense for use in patients unable to tolerate DDS. Clofazimine continued to be used over the years in different ways, until its use was standardized as part of the World Health Organization (WHO)-recommended multidrug therapy (MDT).

Rifampicin

Rifampicin, a semisynthetic broad-spectrum antibiotic, brought about a revolutionary change in the treatment of leprosy. Rifamycin SV, the predecessor of rifampicin, was first used by Opromolla in 1963 with successful results.[15] The *in vivo* activity of rifampicin in the mouse footpad as well as its clinical activity were later confirmed.[16] Another group also confirmed the rapid bactericidal activity of rifampicin.[17] Pattyn et al were the first to use the drug in intermittent doses in leprosy and found it to be bactericidal.[18]

Ethionamide/protionamide

Ethionamide and protionamide, which could be used interchangeably, have been used to a limited extent in leprosy after favorable results[19]; however, this treatment showed resistance after 6 months of treatment when used in monotherapy. Protionamide has been more widely used in combination with other drugs in the form of Isoprodian; however, problems of toxicity persisted. It is no longer used in the therapy of leprosy.

Other drugs

Other drugs for the treatment of leprosy have been developed and used over the years, but to very limited effect. These drugs include thiambutasine, thiacetazone, isoniazid, sulfamethoxypyrazine, Etisul, and several others. All of these drugs were rated highly by initial investigators, but their results could not be confirmed in independent controlled clinical trials.

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