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From the past to the future: Clofazimine in the treatment of MDR-TB

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Abstract

Clofazimine (CFZ), *B.*663 or Lamprene, is a fat-soluble rimino-phenazine dye developed in the 1950s by Vincent Barry as an antituberculosis drug. CFZ has a MIC for *Mycobacterium tuberculosis (M.tb)* in the range of 0.6-1.2 µg/ml, and estimated half-life of 70 days in humans, thus accumulating in tissues. CFZ was not advanced for the treatment of human tuberculosis (TB), but was used for the treatment of leprosy and later, unsuccessfully, for the treatment of *Mycobacterium avium* complex infection in AIDS patients. The development of multidrug (MDR)- and extensively drug-resistant (XDR)-TB has kindled a renewed interest in CFZ despite never having been evaluated for this purpose.

We assessed the contribution of CFZ to a second-line regimen in mice infected with a KatG W149R mutation INH-resistant *M.tb* strain. During treatment of 9 months duration, the decline in lung colony-forming units was assessed monthly using selective 7H11 agar supplemented with 0.4% charcoal to overcome clofazimine carry over. Culture-positive relapse was assessed 6 months after treatment cessation.

The addition of CFZ resulted in culture-negative lungs after 5 months of treatment, while mice receiving the non-CFZ-containing regimen remained positive after 9 months. The proportion of relapses was 3/15, 3/15, 5/15, 1/14 and 1/15 among mice treated with clofazimine for 5, 6, 7, 8 and 9 months, respectively ($p>0.1$). On average, the rate of relapse-free cure among clofazimine-treated mice was 82.4%. Extensive pharmacokinetic study was performed to assess accumulation and clearance in mouse tissues.

In conclusion, the clofazimine contribution was very positive in these experimental conditions.

Biography

Jacques H. Grosset completed his MD at age 25 from Paris University (France). He had a leading role as student and Professor in mycobacterial research and clinical laboratories in Algeria and Paris, from 1956-2002. Since 2002, he has been a Professor at the Center for Tuberculosis Research, Johns Hopkins University. Since 2011, he is also Visiting Scientist, KwaZulu-Natal Research Institute for TB and HIV.

He served as Chairman of the WHO/THELEP (Chemotherapy of leprosy) Steering Committee, Geneva, 1983-1992, and Chairman of the WHO THEMYC (Chemotherapy of mycobacterial diseases) Steering Committee, 1993-1995. He has published over 300 papers in peer-reviewed journals.