Improbability of Selection for RIF Resistance in *Mycobacterium tuberculosis* by Accidental Exposure during Short-Course Therapy with Cotrifazid™

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A fixed combination of rifam-picin (RIF) + isoniazid (INH) + co-trimoxazole (SXT) (Cotrifazid™) was suggested by Freerksen et al. [1, 2] in this journal as a possible alternative for Plasmodium falci-parum-provoked malaria. In this connection, a frequently raised argument against the use of Cotrifazid on a broad scale, particularly in high TB prevalence countries, is the assumed possibility of selecting for RIF-resistant strains of tubercle bacilli, particularly in regions with possibly high INH drug resistance of Mycobacterium tuberculosis.

Indeed, this argument is not new and it was raised possibly for the first time in connection with a fixed combination of RIF + trimethoprim (TMP) (Rifaprim™). Addressing this question, Griineberg et al. [3], using an experimental in vitro design in Kirchner’ medium, made the experience that, even with a very heavy inoculum size of about 1010 organisms no RIF resistance did emerge in wild strains of M. tuberculosis, be it with RIF alone or RIF + TMP; these results were confirmed in a later publication [4]. More significantly, papers from the early years of RIF use, when RIF monotherapy was performed as a part of a trial [5, 6], showed that RIF resistance of tubercle bacilli occurred rather infrequently, but when it did it has not been observed to emerge in less than 3-4 weeks of RIF monotherapy. Also, work with staphylococci [7] showed that TMP reduced even in subinhibitory concentrations 10-to 100-fold the frequency of RIF-resistant mutants and the mutation rates to RIF alone. Finally, it was shown recently [8] that SXT inhibited in a concentration equal to or less than Cmax of SXT in man the growth of about 75% of 175 wild strains of M. tuberculosis.

To gain own experience, in vitro experiments were performed with 5 wild strains M. tuberculosis susceptible to all conventional drugs. Briefly, a liquid Dubos medium was seeded with about 1010 cfu and the organisms were exposed to either RMP alone (10 mg/l) or RMP + SXT (sulphamethoxazole 50 mg/l and TMP 2 mg/ 1). With RMP alone and after 7 weeks of incubation all 5 strains were RIF resistant (conventional tests in Lowenstein medium), whereas with RMP + SXT 2 strains did not grow at all and the 3 which grew yielded bacilli fully susceptible to RIF. It is also worth mentioning that after 2 weeks only and with RIF alone, it was not possible to select for RIF resistance under the conditions of this study.
Thus, agreeing with the findings of Griineberg and coworkers, we consider the clinical anxieties about the short-time and accidental (not recognized far advanced pulmonary tuberculosis) exposure of tubercle bacilli to RIF in Cotrifazid in the course of chemotherapy for other than mycobacterial diseases as grossly exaggerated. Because of the apparent in vitro SXT activity and of the difficulty to select for RIF resistance of tubercle bacilli in less than 3-4 weeks with RIF monotherapy, this should apply even for a situation with high INH resistance rates of tubercle bacilli.

References


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