

Short communications

DRUG RESISTANCE OF *MYCOBACTERIUM TUBERCULOSIS* STRAINS ISOLATED FROM HIV-INFECTED ITALIAN PATIENTS: PRELIMINARY REPORT FROM A MULTICENTRIC STUDY

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SUMMARY

A multicentric prospective study started in March '93 to describe both initial and acquired resistance of *Mycobacterium Tuberculosis* in Italian HIV+ patients (pts.) to first line drugs: Rifampin (R), Isoniazid (I), Pyrazinamide (P), Ethambutol (E), Streptomycin (S). All tuberculosis (TB) cases diagnosed in HIV+ patients (pts.) were included, along with clinical-anamnestic data. Drug-susceptibility tests were performed centrally. Preliminary results indicate an overall low frequency of TB resistance to first line drugs: R=2%, P=4%, S=9%, I/E=none. However, a relevant nosocomial outbreak of multiple drug resistant (DR) TB was detected. This finding, along with some previous Italian reports of DR-TB clusters, may herald a further spread of DR-TB. Surveillance, therefore, is mandatory in Italy from now on.

KEY WORDS *HIV, tuberculosis, drug-resistance*

Italy, as well as some other European countries, is at special risk for the spread of drug-resistant tuberculosis (DR-TB). The two main reasons for this risk are the high prevalence both of TB infection among the general population and of intra-venous-drug-addicts among HIV-infected (HIV+) patients (Antonucci *et al.*, 1991). However, no study has assessed the proportions of this problem in Italy so far.

Aim of the study was to describe both initial and acquired TB resistance to first-line drugs among Italian HIV+ patients (pts.), in terms of overall frequency, geographical distribution, patterns of drug targets of resistance and related risk-factors.

The study is prospective, multicentric, with microbiological investigations centralised at the co-ordinating centre. Thirty infectious disease clinics, supported by 23 Microbiology laboratories, joined the study between February and July 1993. Expected duration of the study is 12 months from the adhesion date of each centre. At the time of writing, therefore, the study is still in progress. Each participating centre had to include all consecutive patients, observed throughout the study period, matching the following criteria: (A) confirmed HIV infection *and* (B) TB diagnosis according to the WHO case definitions. Clinical and epidemiological data

were collected along with each patient's enrolment. All *Mycobacterium tuberculosis* (MT) as well as unidentified mycobacteria strains isolated from the pts. were sent to the central laboratory, along with information about the source sample and the isolation method used. At the central laboratory, all isolates underwent identification of mycobacterium species and, those confirmed as MT, drug-susceptibility tests to first-line drugs: rifampin (RMP), streptomycin (STM), isoniazid (INH), ethambutol (EMB), pyrazinamide (PZA). All tests were performed according to CDC guide-lines and recommendations (Center for Diseases Control, 1985), along with a quality control, both internal and external to the central laboratory. Obtained data were finally analysed and related to clinical and epidemiological data, in order to investigate the DR-TB features mentioned in the aim of the study.

At the time writing (20/4/1994), enrolled pts. numbered 238. Among these pts., laboratory investigations were still in progress for 120, culture attempts failed in 18, mycobacteria other than tuberculosis (MOTT) were isolated in 21 whereas MT was isolated and confirmed at the central laboratory in 79 pts. Among these latter pts., drug-susceptibility tests were completed in 64, 7 of which

presented a relapse of TB, whereas 57 were diagnosed as new cases. These latter pts. were focused on in this preliminary report. The overall resistance found to each tested drug could appear very alarming: RMP=20/57 pts (35%), INH=20 (35%), PZA=2/52 (4%), EMB=18 (32%), STM=25 (44%). However, looking at the different drug-patterns target of resistance (see Figure 1), the occurrence of single drug resistance (SDR) was low for all tested drugs but STM (9%). Interestingly, no resistance was found to INH. In contrast, the frequency of multiple drug resistance (MDR) appeared remarkable (35% overall), most pts. showing an identical four-drugs resistance pattern. The latter findings were due to the fact that all but one MDR strain came from the same clinical centre, where a relevant nosocomial

outbreak of MDR-TB occurred, thus determining the very high frequency of DR that appeared in the raw analysis above. Importantly, most of both SDR and MDR were initial, since no pt. had previously been treated with these drugs, except for 7 pts. among those presenting the 4-drugs pattern of resistance: 3 pts. had previously taken 1 drug each (INH, STM, and EMB respectively), 1 RMP+EMB, 1 RMP+INH+EMB and 2 Rifabutin. Frequencies of DR patterns obtained after exclusion from the analysis of all pts. enrolled by the centre involved by the nosocomial outbreak of MDR-TB were: RMP=3%, PZA=3%, STM=14%, RMP+INH+EMB+STM=3%. Overall resistance to any one drug was 23%. Some conclusions can be drawn based on the preliminary data of the study. 1) To date, in Italy,

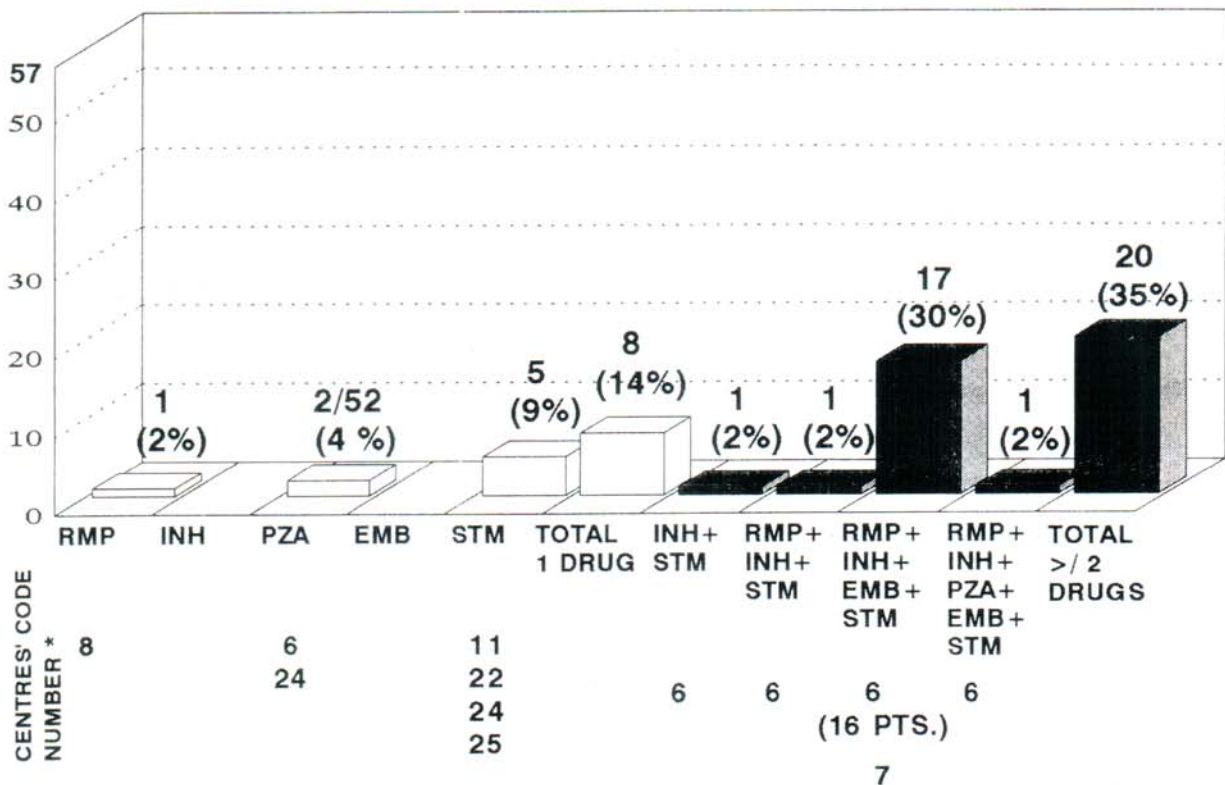


FIGURE 1 - Patterns of drug targets of resistance in 57 new cases of TB in HIV+ patients. RMP = Rifampicin, INH = Isoniazid, PZA = Pyrazinamide, EMB = Ethambutol, STM = Streptomycin. *Code numbers represent the different centres participating in the study where resistant strains were isolated.

DR-TB among HIV+pts. is low. This finding has several practical implications. For instance, first-line drugs should generally still be preferred in the treatment of new cases of TB, when drug-susceptibility tests are not available. 2) However, a relevant nosocomial outbreak of MDR-TB was observed during the study. This observation, along with other, though few, DR-TB clusters previously reported in Italy (Monno *et al.*, 1991, 1993), may herald a further spread of DR-TB, based also on the facilitating Italian epidemiological patterns. 3) Attentive surveillance of DR-TB among the HIV+Italian population, is mandatory from now on.

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