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O0228 High-dose isoniazid in short-course MDR-TB treatment

Lorenzo Guglielmetti*[1 2], Jérôme Robert[1 2], Florence Brossier[1 2], Vincent Jarlier[1 2], Wladimir Sougakoff[1 2], Nicolas Veziris[1 2 3], Alexandra Aubry[1 2]

[1]APHP, Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux (CNR-MyRMA), Bactériologie-Hygiène, Hôpitaux Universitaires Pitié Salpêtrière-Charles Foix, Paris, France, *[2]Sorbonne Université, Université Pierre et Marie Curie 06, Unité 1135, Team E13 (Bactériologie), CR7 INSERM, Centre d'Immunologie et des Maladies Infectieuses, Paris, France*, *[3]APHP, Hôpitaux Universitaires de l'Est Parisien, Paris, France*

Background: The use of a standardized shortcourse MDR-TB regimen (SCR), including high-dose isoniazid (HdH), is recommended by WHO for rifampicin-resistant patients with no resistance-conferring mutation for fluoroquinolones and injectables. However, the high frequency of high-level isoniazid resistance is likely to limit the interest of HdH. In addition, patients may already have enough (≥4) effective drugs in the SCR without relying on HdH.
The objective of this study was to assess the efficacy of HdH in eligible patients for the SCR.

Materials/methods: The database of the French National Reference Center for Mycobacteria, including all rifampicin-resistant tuberculosis cases diagnosed in France from 01/01/2010 to 31/12/2016, was searched for patients harbouring isolates with: 1) Phenotypic drug susceptibility testing (DST) results available for a second-line injectable, a fluoroquinolone, ethionamide, ethambutol; 2) DST or *pncA* sequencing results for pyrazinamide; 3) molecular testing results for *gyrA* and *rrs* (GenoType MTBDRsl). Eligibility for the SCR was defined as absence of *gyrA*/*rrs* mutations. High-level isoniazid resistance was defined as resistance to 1.0 mg/L in Lowenstein-Jensen medium.

Results: Out of 497 rifampicin-resistant cases, 322 (65%) were eligible for the SCR. Overall, 298 (93%) had isolates with high-level resistance to isoniazid. This proportion is consistent regardless of the geographical origin of the patients (e.g. 94% among patients born in WHO region Europe, 90% in Africa). The number of effective drugs in SCR are shown in the Table.

Conclusions: The administration of HdH in SCR may have limited benefit because of the high frequency of resistance to 1.0 mg/L isoniazid in patients eligible for the SCR according to WHO recommendations. In addition, patients with susceptibility or low-level resistance to isoniazid appear to have isolates susceptible to ≥4 drugs besides HdH. Therefore, the use of HdH should be carefully evaluated taking into account its potential toxicity.

Table:

	Effective drugs, median (IQR)	Patients with ≥4 effective drugs (counting HdH), N (%)	Patients with ≥4 effective drugs (not counting HdH), N (%)
All (n=322)	4 (3-6)	233 (72%)	233 (72%)
High-level isoniazid resistance (n=298)	4 (3-5)	209 (70%)	209 (70%)

Low-level resistance or susceptibility to isoniazid (n=24)	6 (6-7)	24 (100%)	24 (100%)