In vitro evaluation of novel bi- or tri-antibiotic combinations against clinical isolates of Mycobacterium abscessus

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Introduction

➢ Mycobacterium abscessus (Mab) is an emerging pathogen, intrinsically resistant to many antmycobacterial drugs (1).
➢ Current treatment is limited to combination of intravenous amikacin (AMK), and cefoxitin (FOX) with oral clarithromycin (CLR). In most cases, it is associated with treatment failure (2).
➢ FOX is known to degrade in vitro with the degradation half-life of 1.5 days which may lead to misinterpretation of time-kill results (article under revision with AAC).
➢ Recent reports demonstrate intrinsic resistance to CLR in Mab clinical isolates. Fluoroquinolones, rifamycines, linezolid or clofazimine can be added when standard therapy is ineffective (3,4).

Purpose

➢ To evaluate the in vitro efficacy of several combinations against clinical isolates of Mab including FOX and AMK and replacing CLR to avoid the induced resistance.

Materials/Methods

➢ Materials/Methods included: (1) Reference strains: CIP104536 (A), CLR resistant isolate Ma1611 (B), and FOX (C). 
(2) T28 (pulmonary abscessus isolate from Lariboisier Hospital, Paris).

Fig. 1: Experimental protocol

Table I: Antibiotics used for combination time-kill assay, containing cefoxitin and antibiotic combined with 3rd antibiotic

Table II: Susceptibility data for different Mab isolates tested by broth microdilution

Fig. 3: In vitro activity of reference tri-combinations against Mab (A) CIP104536 (B) Ma1611 and (C) T28. Log change was calculated using respective positive control data. For Comparisons purposes results are compared at day 4 and day 8.

Results

➢ Comparison of the effect of several tri-combination against reference strain CIP104536 and clinical isolates at day 4 and day 8

➢ Tri-combinations including CLO or CIP were also active against CIP104536 but inactive against Ma1611.
➢ Almost all tested triple combinations were inactive against T28 except for tri-combination with LZD & MXF.

➢ Clinical isolate T28 was resistant to all antibiotics
➢ CIP104536 and Ma1611 were susceptible to intermediate against all tested antibiotics.

Effect of several antibiotics alone and in bi- and combination against MDR clinical isolate T28

➢ T28 was highly resistant to AMK because of A1408G mutation of the rrs gene encoding rRNA 16S. FOX alone was not much efficient, so it was used in bi-combinations. FOX with RFB was the most active bi-combination against T28.

Conclusion & perspective

➢ Tri-combinations were highly efficient against Mab CIP104536 and intermediate to susceptible clinical isolate Ma1611 but not against MDR isolate T28.
➢ The synergy between FOX and rifamycines suggests a potent role of this combinations that may warrant further optimization of treatment regimen for the treatment of M. abscessus pulmonary infections.

References

1) Nessar et al., JAC, 2012
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