Interferon-gamma (IFN-γ) Potentiates the Intracellular Activity of Rifampin (RIF) towards Intracellular Staphylococcus aureus in Human THP-1 Macrophages.

Sandrine Lemaire, Françoise Van Bambeke, Paul M. Tulkens

Cellular and Molecular Pharmacology, Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium.

Abstract (revised)

Background. Treatment of severe staphylococcal infections remains challenging, probably in relation with the ability of this bacterium to survive intracellularly. We showed previously that the intracellular activity of many antibiotics, including rifampin, is considerably lower than expected when compared to the extracellular one (CMI 2008, 14:766-77), suggesting that novel alternatives are needed to help eradicating intracellular S. aureus foci. Our aim was to assess the potential use of IFN-γ when combined with rifampin in a validated model of intracellular infection (AAC 2006, 50:841-51).

Methods. Bacteria: S. aureus strain ATCC 25923 (MIC of RIF: 0.01 mg/L [MHB; microdilution]). Intracellular activity of RIF: measured as the change in cfu after 24 h incubation of cells with increasing conc. of RIF (0.05-20 mg/L) compared to the post-phagocytosis inoculum ( = control response). Activity of increasing conc. of IFN-γ (0.01-5 µg/mL) showed previously additive effect (gain of about 2 log, cfu decrease at the highest conc. tested).

Conclusions, IFN-γ improves the activity of rifampin against intracellular S. aureus in this in vitro model, which may justify further in vivo studies.

Methods

Bacterial strains, susceptibility testing and dose-killing studies in acellular media.

We used S. aureus strain ATCC 25923 for all experiments. MICs (microdilution) and dose-killing studies in acellular media were determined in MH broth following the methods described previously 1-4.

Cells and cell infection.

THP-1 cells (ATCC TIB-202), a human myelomonocytic cell line displaying macrophage-like activity, was used in our experiments. Infection was performed as described previously 1-4. Briefly, phagocytosis of opsonized bacteria was allowed to take place during 1 h using a 4:1 bacteria-macrophage ratio. Extracellular bacteria were removed by a short term incubation with 50 mg/L gentamicin and 3 successive washings with PBS. Starting bacterial inoculum typically ranged between 1 to 2.5 x10^6 CFU/mg prot.

Assessment of antibiotic activity.

Extracellular (MH broth) and intracellular (THP-1) activity of rifampicin showed additive effect (gain of about 2 log, cfu decrease at the highest conc. tested).

We observed a decreased activity of rifampin towards the extracellular and intracellular forms of S. aureus, as compared to the extracellular ones.

When combined to rifampicin, IFN-γ (1-5 ng/mL) markedly increases the intracellular activity of the antibiotic, suggestive of an additive effect. This may need to be further explored in vivo studies.

References

1. Lowy F.D., Trends Microbiol. [2000], 8:341-343
2. Garzoni et al, Genomics [2007], 8:171

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