29th ECCMID Amsterdam, Netherlands 13 – 16 April 2019

The congress of ESCMID

O0920 The *in vitro* interplay between dalbavancin and human phagocytes against staphylococci causing skin and skin-structure infections

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Background: The skin and soft tissue infections (SSTIs) increase represents a major concern in both community and hospital setting, carrying a significant economic burden, as well as morbidity and mortality, especially when caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Dalbavancin (DAL), a lipoglycopeptide, is indicated for the treatment of SSTIs, and has a broad spectrum of action against most microorganisms, including those resistant to other antimicrobials. The aim of this study was to determine the straightforward performance of DAL upon the binomial antibiotic resistant staphylococci and host defenses, to establish its potential immunomodulating activity.

Materials/methods: DAL effect (at 1xMIC or 2xMIC) on human polymorphonuclear cells (PMNs) functional activities (microbicidal activity and cytokine release profile) was investigated by incubating MRSA and phagocytes for different incubation times. To differentiate between any separate effect of DAL on the bacteria and PMNs, *in vitro* DAL pretreatment assays were also performed by the exposure of each of them to DAL (at 1xMIC) for 1 h, before they were incubated together.

Results: Our results evidenced in DAL presence an enhanced MRSA killing activity by PMNs in comparison with DAL-free controls, within 90 minutes of incubation. In fact, in control condition PMNs were able to scanty kill ingested MRSA, whereas with the addition of DAL at 1xMIC or 2XMIC, significantly ($p<0.01$) enhanced their staphylococcal killing (Figure 1A). The assays with DAL pre-treated MRSA or PMNs highlighted a similar trend: an improved staphylococcal killing due to DAL direct effect on both staphylococci and PMNs within 90 minutes of incubation (Figure 1 B). In parallel a decreased level of TNF-α was observed in DAL-treated PMNs in presence of MRSA.

Conclusions: Neutrophil-mediated killing is a crucial defense system against *S. aureus*, however the pathogen has evolved many strategies to resist killing. In the present study, we highlighted that DAL acts in synergism with neutrophils by modulating both staphylococcal killing and cytokine release. A role of TNF in apoptosis regulation has been observed that could indirectly influence the killing capacity. These preliminary results draw attention to the need of a deeper understanding of the mechanisms exerted by DAL on neutrophil functional activities.

Figure 1A. *In vitro* MRSA killing by human PMNs with DAL (1xMIC or 2xMIC)

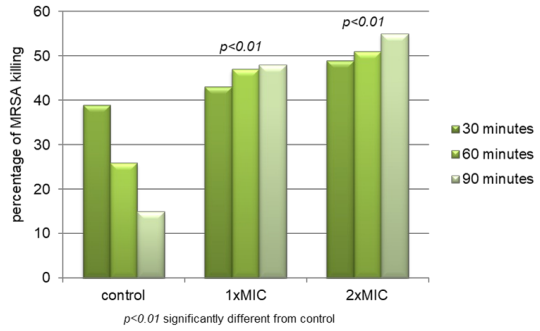

Figure 1B. *In vitro* pre-treatment assays with DAL (1xMIC)