Lipid Nanoparticles for Reviving Antibiotics: Efficacy of a Gel of Daptomycin in a Methicillin-Resistant *Staphylococcus aureus* Rabbit Osteomyelitis Model

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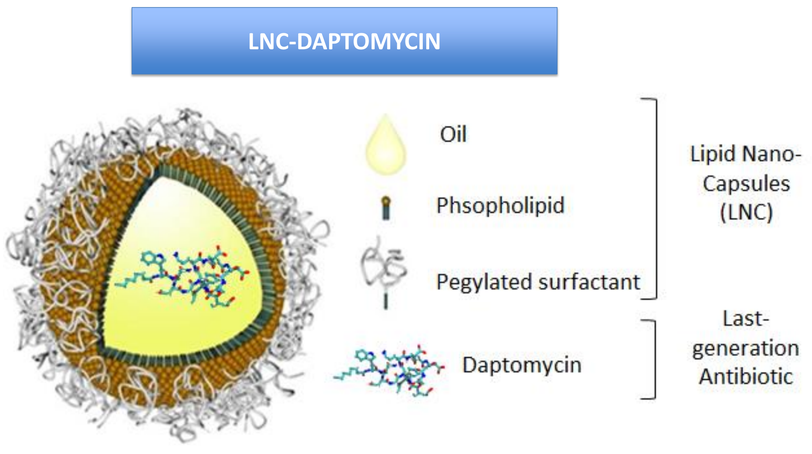
BACKGROUND

Bone and joint infections (also called osteoarticular infections, OAI) are particularly affected by the raise of multidrug-resistant bacteria. In addition, these infections are particularly difficult to treat due to local conditions (necrotic areas, bacteria sequestration in bone tissue, acidic pH, anaerobia, calcium, etc.) and biofilms production (exopolysaccharide matrix), which decrease the efficacy of antibiotics administrated through systemic delivery. Daptomycin (DAP) is a bactericidal antibiotic with activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) isolates, but its administration is exclusively by IV route. Lipid Nano-Capsules (LNCs) are known to vehicle medicines and could offer new therapeutic options.

The aim of this work was to compare the efficacy of LNC-daptomycin (LNC-DAP) formulated in a gel with that of other antistaphylococcal drugs in a MRSA osteomyelitis rabbit model.

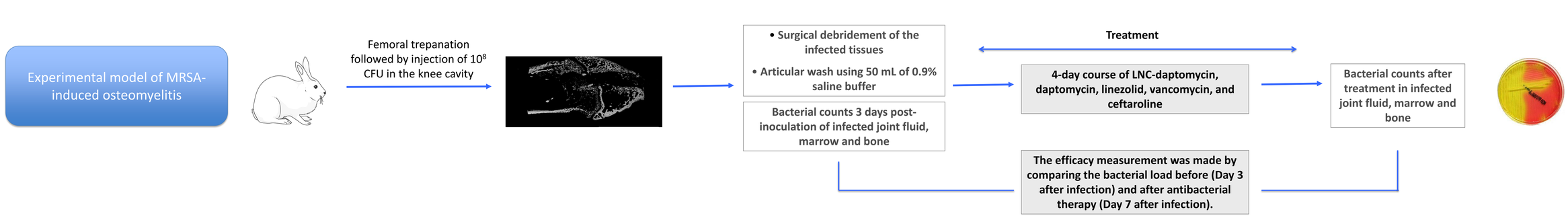


MATERIALS AND METHODS

On day 0, we used a percutaneously transarticular approach to perform a femoral trepanation of the right knee using a Jamshidi bone marrow biopsy needle (8 gauge) under general anaesthesia (ketamine, 20 mg/kg iv, and xylazine, 1 mg/kg iv). The Jamshidi needle was inserted between the two femoral condyles through the epiphysis, physis and metaphysis to reach the medullar canal. Following needle removal, the skin incision was closed. A bacterial suspension of 1 mL of *S. aureus* adjusted to 10^8 cfu/mL was injected into the knee cavity. Infection was allowed to develop for 3 days, and then a surgical debridement of the infected tissues was performed followed by an articular wash using 50 mL of 0.9% saline buffer. Samples of bone marrow and bone were removed, placed immediately on ice, weighed, homogenized in 0.5 mL of saline buffer, and then spread on agar plates using a spiral system. Treatment was started 72 h after inoculation, and antibiotics were administered for a 4 day course. At the end of the 4 day regimen, animals were euthanized, and epiphyseal bone samples and femoral bone marrow were obtained. Dilutions at 10^{-1}, 10^{-2} and 10^{-4} were performed to eliminate potential carry-over effects. Bacterial counts were determined after 48 h of incubation at 37°C. The efficacy measurement was made by comparing the bacterial load before (day 3 after infection) and after (day 7 after infection) antibacterial therapy.

Therapeutic regimens:

- Local administration of LNC-daptomycin (low (LD) and high (HD) doses).
- IV linezolid (human-equivalent dose of 600mg q12hr).
- IV vancomycin (continous infusion to reach a serum steady-state concentration of 20x the MIC (mimicking the human dose of 30 mg/kg given once daily).
- IV ceftaroline (human-equivalent dose of 600mg q12hr).
- IV daptomycin (human-equivalent dose of 6mg/kg).



RESULTS

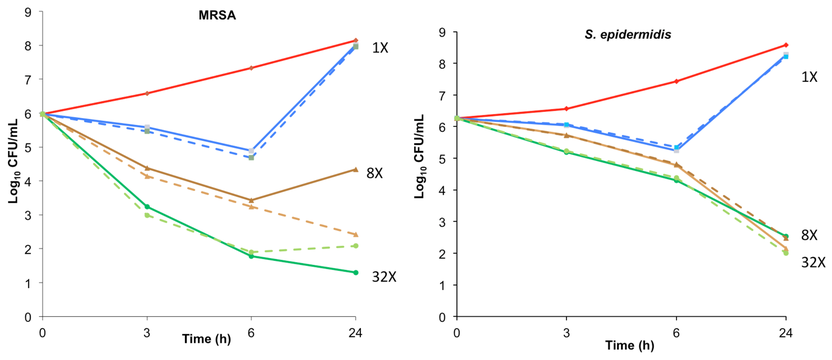


Figure 1. Time-kill curves of daptomycin and LNC-daptomycin against methicillin-resistant *S. aureus* and *S. epidermidis*. Daptomycin, solid lines; LNC-daptomycin, dashed lines.

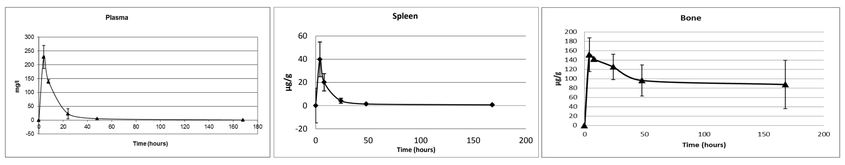


Figure 2. Pharmacokinetics of daptomycin in plasma, spleen, and bone after a local administration of LNC-daptomycin.

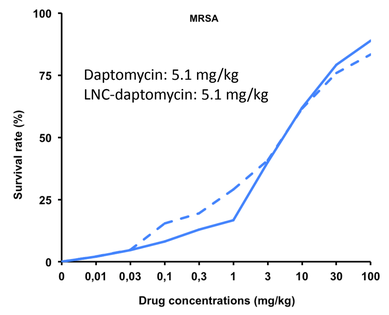


Figure 3. Mice model of MRSA-induced sepsis; determination of ED50 values. Daptomycin, solid lines; LNC-daptomycin, dashed lines.

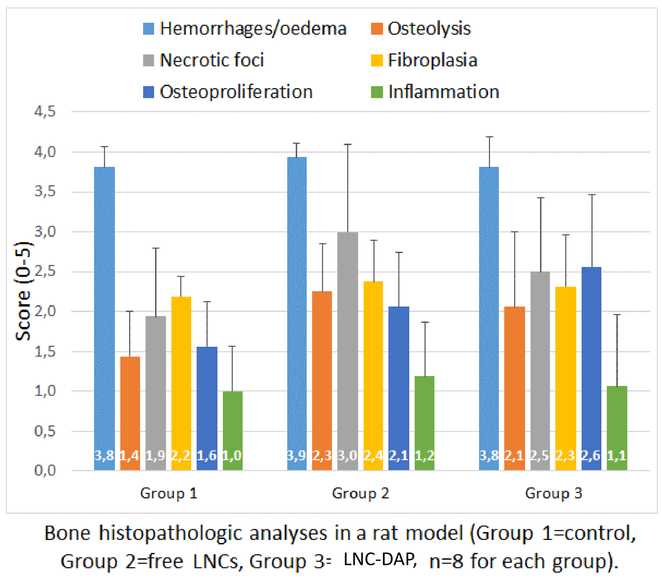


Figure 4. Histopathologic analysis of LNC-daptomycin in a rat experimental model.

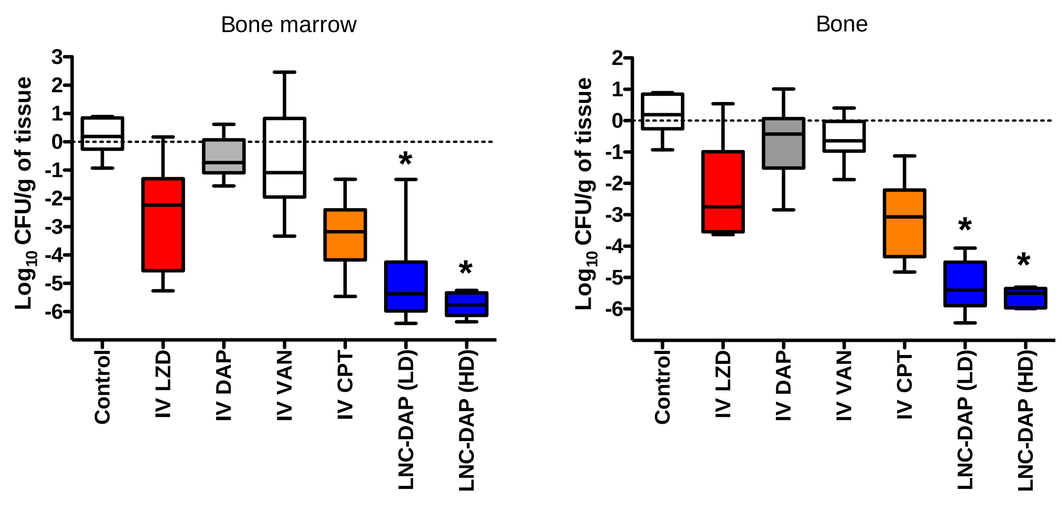


Figure 5. In vivo antibacterial efficacy of LNC-daptomycin (LD and HD) and comparators (linezolid, daptomycin, vancomycin, and ceftaroline) after 4 days of treatment for osteomyelitis due to methicillin-resistant *Staphylococcus aureus*.

CONCLUSIONS

- A gel with lipid nano-encapsulated daptomycin (LNC-DAP) showed significant *in vivo* activity after one topic application in comparison with majors anti-staphylococcal drugs administered by IV route for 4 days in a MRSA osteomyelitis rabbit model.
- The use of LNCs for local delivery of antibiotics is a promising approach to revive old antibiotics or to develop new antibacterial agents with solubility issues for example.