B-596

in vivo Contribution of a Filling Biomaterial Loaded with Linezolid in an Acute MRSA Osteomyelitis Model: time-dependent efficacy study about a new drug delivery system

G. Amador - *MD, PhD*[1], A. Gaudin - *MD* [1], H. Gautier - *PharmD, PhD* [2], V. Le Mabecque - *Laboratory Technician* [1], A. Miegeville - *Laboratory Technician* [1], G. Potel - *MD, PhD, Director* [1], J. Bouler - *PhD* [2], P. Weiss - *MD, PhD, Director* [2], J. Caillon - *PharmD, PhD* [1], C. Jacqueline - *Research Engeneer* [1]; [1]UPRES EA 3826, Nantes, France, [2]INSERM UMRS 791, Nantes, France.

Background: Calcium-deficient apatites (CDA) can be associated with antibiotics to form drug-delivery systems. Linezolid is considered as an alternative to vancomycin for MRSA strains with a vancomycin MIC $\geq$ 4 µg/mL. But treatment by linezolid must not be prolonged over 28 days because of hematological toxicity. The aim of this work was to assess the *in vivo* contribution of linezolid introduced by wet granulation onto CDA granules for 50 percent per gram and to compare the antimicrobial activity after 4 and 14 days, with or without systemic treatment. **Methods**: Femoral trepanation of rabbits was performed, followed by injection of 1 mL10^9 CFU MRSA (linezolid MIC 2µg/mL) into the knee cavity. A surgical debridement of the infected tissues was performed 3 days later and animals were randomly assigned to: no antibiotic treatment, $L_{(IV)}$ (computer-controlled infusion syringe pump simulating a human-equivalent [HE] dose of 10 mg/kg/12h for 4 days), $L_{(CDA50\%)}$ (100 mg CDA with linezolid 500 µg/mg) and $L_{(CDA50\%)}$ + $L_{(iv)}$ (100 mg CDA with linezolid 500 µg/mg filling in addition to a 4-day linezolid IV infusion (HE 10 mg/kg/12h)). Surviving bacteria were counted in joint fluid (JF), bone marrow (BM) and bone (BO) at days 3 (before treatment), 7 (4-day treatment) and 17 (14-day treatment). **Results:**

Treatment	n	Mean ± SD $\Delta\log_{10}$ CFU/g of tissue (day 7 - day 3)			Mean ± SD $\Delta\log_{10}$ CFU/g of tissue (day 17 - day 3)		
		JF	BM	BO	JF	BM	BO
$L_{(IV)}$	8	-0.62 ± 1.41	-2.69 ± 1.92	-2.25 ± 1.55	ND	ND	ND
$L_{(CDA50\%)}$	7	0.96 ± 1.31	-3.10 ± 0.84	-1.73 ± 0.94	-0.76 ± 1.51[a]	-2.98 ± 1.08	-1.80 ± 1.89
$L_{(CDA50\%)}$+$L_{(IV)}$	5	-0.80 ± 1.58	-3.89 ± 0.65	-3.02 ± 0.60	-2.04 ± 1.25	-4.24 ± 1.90	-3.11 ± 2.23

n : number of animals, ND : not done (major venous impairment) [a] $P<0.05$ vs JF 4-days $L_{(CDA50\%)}$ (Wilcoxon after non parametric t test)

Conclusions: (1) $L_{(IV)}$ was effective after a 4-day treatment of MRSA. (2) $L_{(CDA50\%)}$ did not exhibit a greater efficacy than $L_{(IV)}$ after 4 days (3) The antimicrobial trend of $L_{(CDA50\%)}$ seems to be boosted by the association with $L_{(IV)}$ but not in a significant way.