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Temocillin 6g daily in critically ill patients : continuous infusion *vs*. conventional administration

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TEMOCILLIN

- 6-α-methoxy-ticarcillin
- Spectrum directed only against Gram negative bacteria without non-fermenters (*Pseudomonas aeruginosa*, *Acinetobacter* spp.)
- active against all producers of β-lactamase(s) including ESBL and AmpC
- Indications
  - urinary tract infections
  - Gram negative nosocomial infections (LRTI, IAI, bacteremia, …)

6g vs 4g

- Usual posology is 4g per day
- PK/PD parameters have been determined for 2g q12h and 4g/24h (De Jongh et al., JAC 2008) : 4g seems sufficient on average but might be not enough for some patients with large Vd
- Since Vd can be highly variable in critically ill patients, we have explored the possibility to increase the dose up to 6g per day

Aim of the study

- Pharmacokinetics and safety of 6g daily of Temocillin
- Comparison of conventional administration (2g q8h – TID) vs. 6g/24h in continuous infusion (CI)
- PK/PD analysis

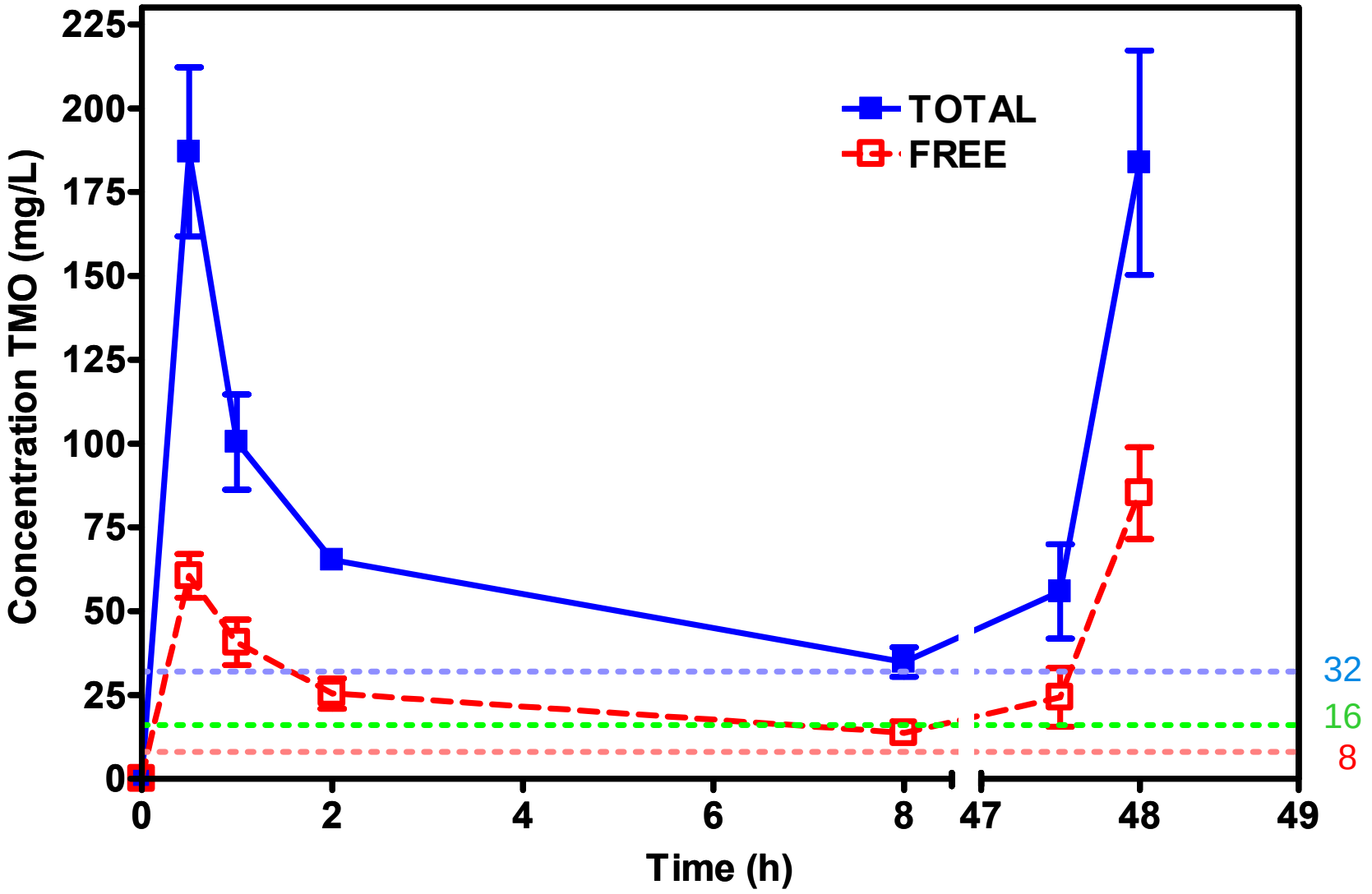
- Population : Critically ill patients with documented infection due to a Gram negative bacteria susceptible to Temocillin
- Setting : 2 Intensive care Units (1 teaching hospital, and 1 general hospital)

Patients

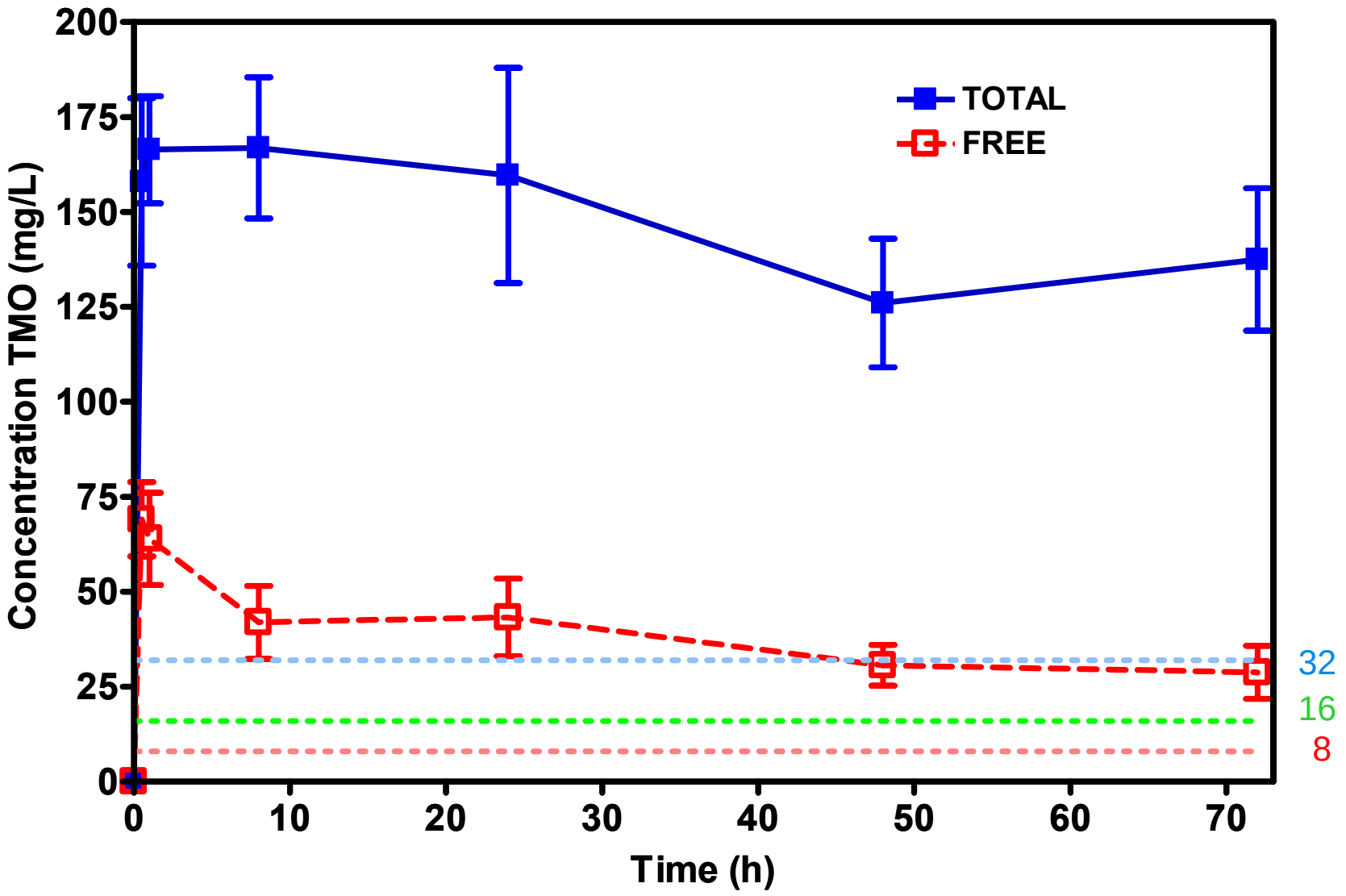
Total patients randomized : 16

	TID	CI
Type of infection (positive blood cultures)		
LRTI	4	2
IAI	3 (1)	5 (2)
UTI	1 (1)	1
age (year ± SD)	64 ± 13	70 ± 11
SOFA score (SD)	6.5 ± 3.0	8.4 ± 3.8
creatinin clearance (ml/min ± SD)	83 ± 33	51 ± 28
Treatment duration (days ± SD)	4.6 ± 1.5	5.2 ± 2.1

Conventional administration



Continuous infusion



PK/PD parameters

	TID	CI
Mean % of the time where the free fraction remains above (Monte Carlo simulation for 2g q8h, De Jongh et al. JAC 2008)		
8 mg/L (100%)	100 %	100 %
16 mg/L (80%) ← Belgian breakpoint	83 %	100 %
32 mg/L (27%)	20 %	57 %
Mean lowest free concentration ± SEM (mg/L)	14 ± 3	29 ± 7

Mean ascite concentration : 28 mg/L (range 14 – 45 mg/L)

Concentration ratio between free serum concentration and free ascite concentration : 90% [range : 42 -166%]

Outcomes

	TID (8)	CI (8)
Clinical outcome		
Cured / discharged	6	8
TMO not indicated (restrospective)	1	0
Death *	1	1
Safety outcome		
Adverse events related to temocillin	0	0

* patient under TID died of sceptic shock due to coagulase negative Staphyloccocus during treatment; patient under CI died after cure of the Gram negative infection of sceptic shock due to *E. facium* and *B. fragilis*

Conclusions

- TMO is safe at the posology of 6g per day
- If TID seems sufficient to achieve PK/PD goal for beta-lactam efficacy, CI allow a better efficacy margin considering the breakpoint (16 mg/L)
- These data suggests that the optimal dose for TMO in critically ill without renal replacement therapy should be increased to 6g daily