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A descriptive case series of the relationship between maintenance of conservative PK/PD efficacy thresholds of dalbavancin over time and clinical outcome in long-term treatment of staphylococcal osteoarticular infections

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1 **A descriptive case series of the relationship between maintenance over time of conservative PK/PD**
2 **efficacy thresholds of dalbavancin and clinical outcome in long-term treatment of staphylococcal**
3 **osteoarticular infections**

4

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24 **Running title:** Dalbavancin TDM in staphylococcal OIs

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27

28 **Abstract**

29 **Objective:** To describe the relationship between maintenance over time of
30 pharmacokinetic/pharmacodynamic (PK/PD) dalbavancin efficacy thresholds and clinical outcome in a case
31 series of patients who underwent therapeutic drug monitoring (TDM) during long-term treatment of
32 staphylococcal osteoarticular infections (OIs).

33 **Methods:** Patients who received two 1500 mg dalbavancin doses one week apart for documented
34 staphylococcal OIs, underwent TDM assessment, and had clinical outcome assessable at follow-up were
35 retrospectively included. Dalbavancin concentrations ≥ 4.02 and/or ≥ 8.04 mg/L were identified as conservative
36 PK/PD efficacy thresholds. The percentage of time of the overall treatment period with dalbavancin
37 concentrations above these efficacy thresholds was calculated and correlated with clinical outcome.

38 **Results:** A total of 17 patients were retrieved. Long-term dalbavancin was used mainly for treating
39 prosthetic joint infections (9/17; 52.9%). In 13/17 patients (76.5%), clinical outcome was assessable after at
40 least 6-month follow-up and was always successful (100.0%). In 4/17 (23.5%) patients, clinical outcome is
41 going favourably after a follow-up of 3.7, 4.8, 5.1 and 5.3 months, respectively. In most patients, both
42 dalbavancin PK/PD efficacy thresholds were granted for most of treatment duration (%time ≥ 4.02 mg/L: 100%
43 in 13 cases, 75-99.9% in 2 cases, 50-74.99% in other 2; %time ≥ 8.04 mg/L: 100% in 8 cases, 75-99.9% in 4
44 cases, 50-74.99% in other 4, and $< 50\%$ in 1 case).

45 **Conclusions:** Our findings could support the idea that maintenance of conservative PK/PD efficacy
46 thresholds of dalbavancin for most of treatment duration may represent a valuable approach in dealing
47 efficaciously with long-term treatment of staphylococcal OIs.

48 **Keywords:** dalbavancin; TDM-guided strategy; PK/PD efficacy thresholds; staphylococcal osteoarticular
49 infections

50 1. Background

51 Osteoarticular infections (OIs) represent a major health concern characterized by a remarkable
52 incidence of morbidity and disability [1,2]. OIs share several management features, ~~such as~~ including the
53 frequent need for combined surgical and medical approach and, most of all, long-term antimicrobial treatments.
54 Both methicillin-susceptible and methicillin-resistant *Staphylococci* are leading causes of OIs [1,3], showing
55 relevant virulence and ability to produce biofilm, thus making extremely challenging both antimicrobial
56 treatment and microbiological eradication [4].

57 Nowadays, several antimicrobial agents are available in the anti-staphylococcal therapeutic
58 armamentarium [3,5]. Antibiotic bone penetration, anti-biofilm activity, long-term safety, and feasibility for
59 outpatient management may play a key role in the choice of the best anti-staphylococcal agent [5].

60 Dalbavancin is a novel long-acting lipoglycopeptide active against multi-drug resistant Gram-positive
61 bacteria [6]. Good tissue penetration and uniquely long elimination half-life are the main pharmacokinetic
62 features of dalbavancin. Based on this, a single 1500 mg dose was licensed for treating acute bacterial skin and
63 skin structure infections and may cover up to 14 days of treatment [6–8].

64 However, dalbavancin could represent a valuable alternative to daily intravenous in-hospital or
65 outpatient antimicrobial regimens in the long-term treatment of Gram-positive OIs according to real-world
66 evidence [9,10]. Notably, treatment duration in these scenarios should usually last at least 6 weeks or even
67 longer [11,12]. Consequently, several questions need to be addressed for enabling proper dalbavancin use
68 under these circumstances, concerning the most appropriate dosing schedule regimen, optimal treatment
69 duration, and the right timing for eventual dalbavancin re-dosing when longer treatment duration is needed.

70 Recently, we showed that therapeutic drug monitoring (TDM) may be a helpful tool in estimating the
71 duration of optimal treatment in staphylococcal OIs, suggesting that the maintenance over time of total
72 dalbavancin concentrations ≥ 4.02 or ≥ 8.04 mg/L could represent dalbavancin PK/PD efficacy thresholds [13].
73 Furthermore, we found that two 1500 mg dalbavancin doses one-week apart could be appropriate for long-
74 term treatment of subacute and/or chronic infections, allowing to maintain dalbavancin concentrations above
75 the more conservative PK/PD efficacy threshold of ≥ 8.04 mg/L for up to 4–6 weeks in most patients. However,

76 it was also recommended that TDM should be considered as the only effective way for properly managing
77 long-term dalbavancin therapy in each single patient due to wide inter-individual pharmacokinetic variability
78 and/or to the eventual need for redosing [14].

79 The aim of this study was to describe firstly the relationship between maintenance of these PK/PD
80 dalbavancin efficacy thresholds over time and clinical outcome in a case series of patients who underwent
81 TDM during long-term treatment of staphylococcal OIs.

82 **2. Methods**

83 *2.1 Study population*

84 Patients included in this analysis were retrieved from the original database of a recently published
85 population pharmacokinetic study of dalbavancin carried out among 69 patients who received long-term
86 treatment for subacute and chronic staphylococcal infections [14]. Patients were considered eligible for this
87 analysis if all the following criteria were satisfied: 1) documented staphylococcal OIs requiring long-term
88 treatment with dalbavancin monotherapy, defined as the administration of a minimum of two 1500 mg doses
89 one week apart; 2) TDM assessment of dalbavancin serum concentration in at least one occasion during the
90 overall treatment period; 3) assessability of clinical outcome at follow-up. Patients receiving long-term
91 suppressive therapy with dalbavancin for lack of source control and/or antimicrobial combination therapy were
92 excluded. The study was approved by the local ethical committee [No. 897/2021/Oss/AOUBo on 29 November
93 2021].

94 *2.2 Data collection*

95 Demographic (age, sex, weight, height, body mass index [BMI]) and clinical/laboratory data
96 (creatinine clearance, serum albumin, presence of augmented renal clearance [ARC], C-reactive protein [C-
97 RP] at baseline and at the timing of outcome assessment, site/type of infection, isolated Gram-positive
98 pathogens, number and timing of administered dalbavancin doses, number and timing of dalbavancin TDM
99 determinations, TDM results, treatment duration, clinical outcome, occurrence of adverse events were
100 collected for each included patient.

101 *2.3 Clinical management and outcome*

102 All patients underwent diagnostic procedures before starting antimicrobial treatment. Patients with
103 hematogenous vertebral osteomyelitis underwent CT-guided vertebral biopsy and bioptic material was sent for
104 microbiological culture; those with OIs other than hematogenous vertebral osteomyelitis underwent surgical
105 debridement coupled with removal of fixation devices or prosthesis explantation whenever needed/feasible,
106 followed by intraoperative microbiological culture. After completing diagnostic procedures, all patients
107 received a 14-day empirical treatment with daptomycin plus fosfomycin, and after microbiologically

108 documentation of staphylococcal aetiology within this timeframe, they were subsequently switched to receive
109 at least two 1500 mg dalbavancin doses one week apart. This approach would have guaranteed an overall anti-
110 staphylococcal treatment duration of at least 6 weeks by means of an outpatient management.

111 The overall number of administered dalbavancin doses were established by the treating physician
112 according to a test of cure (TOC). TOC was assessed by means of monthly ambulatory visits scheduled starting
113 on day 28-35 after commencing dalbavancin treatment (namely after 42-49 days from starting anti-
114 staphylococcal treatment). TOC was defined as positive based on satisfaction of all of the following criteria:
115 absence of local (*rubor, tumor, calor, dolor*) and systemic (fever and pain) signs of infection plus normal
116 values of C-RP plus absence of suggestive findings of infection at imaging studies [15]. Whenever positive
117 TOC was documented, no additional dose of dalbavancin was administered and a follow-up period for
118 confirming clinical success was started. Dalbavancin treatment period was defined as the time elapsed between
119 the first dalbavancin dose and the date of positive TOC.

120 *2.4 Relationship between maintenance over time of conservative PK/PD efficacy thresholds of dalbavancin* 121 *and clinical outcome*

122 Dalbavancin concentrations ≥ 4.02 mg/L and 8.04 mg/L were identified as conservative PK/PD
123 efficacy thresholds of dalbavancin treatment. In a previous study we showed that concentrations equal or above
124 these thresholds may grant a very high likelihood ($\geq 90\%$) of achieving optimal pharmacodynamic target
125 attainment (defined as an $fAUC_{24h}/MIC$ ratio > 111.1) against staphylococci with an MIC value up to the MIC_{90}
126 (0.06 mg/L) or the EUCAST clinical breakpoint of susceptibility for dalbavancin (0.125 mg/L), respectively
127 [13]. These thresholds were identified on the basis of the excellent relationship that we found in a previous
128 population PK study between the daily total dalbavancin concentration and the daily total dalbavancin AUC_{24h}
129 (total concentration = $0.051 + 0.04 \times \text{total } AUC_{24h}$; $R^2 = 0.99$) [13]. The desired thresholds (4.02 mg/L and 8.04
130 mg/L) were calculated by inserting in the formula the values of total AUC_{24h} that were estimated to be needed
131 (99.2 mg·h/L and 198.3 mg·h/L) for attaining the optimal pharmacodynamic target [13].

132 TDM of dalbavancin was assessed one or more times after completing the basic regimen of two 1500
133 mg doses one week apart with timings arbitrarily chosen by the treating physician. In those cases needing
134 additional dalbavancin doses, TDM was reassessed whenever feasible.

135 Total dalbavancin plasma concentrations were measured by means of a validated liquid
136 chromatography-tandem mass spectrometry analytic method at the Clinical Pharmacology Unit of the IRCCS
137 Azienda Ospedaliero Universitaria di Bologna, Italy, as previously described [16]. The intra- and inter-day
138 coefficients of variation of the quality controls were 0.09% to 0.14% and 4.8% to 14.2%, respectively. The
139 lower limit of quantification was 0.5 mg/L.

140 The post-hoc individual concentration-time profiles of dalbavancin of each single patient eligible for
141 this analysis were extracted from the original population pharmacokinetic model [14] and subsequently
142 assessed for calculating the percentage of time of the overall treatment duration in which dalbavancin
143 concentrations were above the PK/PD efficacy thresholds of 4.02 and/or 8.04 mg/L, respectively. Proportions
144 of time above the PK/PD efficacy thresholds of dalbavancin were then correlated with clinical outcomes.

145 3. Results

146 A total of 17 patients were retrieved. Demographics and clinical characteristics of the included patients
147 are reported in **Table 1**. The median age was 59 years (interquartile range [IQR] 49-71 years), with no gender
148 preponderance (52.9% male). The median BMI and CLCr were 25.3 Kg/m² (IQR 22.0-32.1 Kg/m²) and 94
149 mL/min/1.73 m² (IQR 90-107 mL/min/1.73 m²), respectively. Median C-RP at baseline was 1.9 mg/dL (IQR
150 1.2-6.7 mg/dL). Three out of 17 patients (17.6%) had ARC at baseline, and five out of them (29.4%) had
151 hypoalbuminemia.

152 Long-term dalbavancin was used mainly for treating prosthetic joint infections (9/17 cases, 52.9%).
153 These patients received dalbavancin after prosthesis removal in the context of two-stage exchange (n=5), one-
154 stage exchange (n=1), debridement and implant retention (n=1) and re-implantation with positive culture of
155 intraoperative specimens, obtained later (n=2). Methicillin-resistant *Staphylococcus epidermidis* (MRSE) was
156 the predominant pathogen (60.0%), followed by methicillin-susceptible *Staphylococcus aureus* (MSSA;
157 15.0%), methicillin-resistant *Staphylococcus aureus* (MRSA; 15.0%), *Staphylococcus warneri* (5.0%), and
158 *Staphylococcus lugdunensis* (5.0%). Overall, 14 infections were monomicrobial (82.4%) and 3 polymicrobial
159 (17.6%; MRSE plus MSSA were isolated simultaneously in all of these).

160 The median number of dalbavancin doses per patient was 2 (IQR 2-3). Additional doses were
161 administered in 5 out of 17 patients (29.4%). Median days of TOC positivity was 62 (IQR 39-72 days). Up to
162 date, in 13 out of 17 patients (76.5%), clinical outcome was assessable after at least 6-month follow-up and
163 was always successful (100.0%). In the other 4 (23.5%), clinical outcome is going favourably after a follow-
164 up of 3.7, 4.8, 5.1 and 5.3 months, respectively. In 3 out of 17 patients (17.6%) minor transient adverse events
165 occurred (fever and eosinophilia), but they did not require treatment withdrawal.

166 The median number of dalbavancin TDM assessments per patient was 4 (IQR 2-6). Two out of 17
167 patients had a single TDM assessment after completing the two 1500 mg dalbavancin doses one week apart
168 (at day 25 and 34, respectively). **Figure 1** shows the estimated distribution of time with dalbavancin
169 concentrations above or below the lower (4.02 mg/L, **panel a**) and the upper (8.04 mg/L, **panel b**) PK/PD
170 efficacy thresholds during the overall treatment period in each single patient. Among the 17 patients, the
171 percentage duration of treatment with dalbavancin concentrations above the lower PK/PD efficacy threshold

172 was 100% in 13 cases (76.4%), 75-99.9% in 2 cases (11.8%), 50-74.99% in other 2 (11.8%), and <50% in
173 none; whereas that above the upper PK/PD efficacy threshold was 100% in 8 cases (47.1%), 75-99.9% in 4
174 cases (23.5%), 50-74.99% in other 4 (23.5%), and for <50% in 1 case (5.9%).

175

176 **4. Discussion**

177 To the best of our knowledge, this is the first study that investigated the relationship between
178 maintenance of conservative PK/PD efficacy thresholds of dalbavancin over time and clinical outcome in a
179 very homogeneous subpopulation of patients receiving dalbavancin in monotherapy for long-term treatment
180 of documented staphylococcal OIs. Although limited in size, this study is strengthened by the fact that we
181 adopted very restrictive criteria with an almost standardized approach. All of the included patients received
182 the same initial schedule dosing regimen (1500 mg dose one week apart), underwent at least one TDM
183 assessment of dalbavancin after completing the initial dosing schedule, and had clinical outcome assessed after
184 TOC and follow-up.

185 Our analysis showed that in the vast majority of patients the chosen dosing schedule regimens of
186 dalbavancin were able to grant for most of treatment duration both of the conservative PK/PD efficacy
187 thresholds of dalbavancin that we adopted. This is in line with the finding that all the patients had favorable
188 clinical outcome. Indeed, a recent retrospective study carried out among 41 patients receiving dalbavancin for
189 the treatment of different type of infections apparently found no clear relationship between these conservative
190 PK/PD efficacy thresholds of dalbavancin and clinical outcome [17]. Failure occurred among 8 patients with
191 concentration values above the proposed 8 mg/L threshold, whereas treatment success occurred among 6
192 patients with concentrations below this threshold. However, it should not be overlooked that major differences
193 between the two study designs preclude direct comparison with our findings. Just to mention the most relevant,
194 in that study dalbavancin was used in most cases as salvage therapy after previous failure, indications for
195 dalbavancin treatment (ABSSSIs, osteoarticular- or other infections) and dosing schedule regimens (one single
196 dose or two doses 1- or 2- or 3- week apart) were very heterogeneous [17].

197 Although several evidences reported an overall clinical success rate higher than 80% in patients
198 receiving dalbavancin for the management of subacute or chronic staphylococcal infections [9,10,18], no
199 consensus existed about which dalbavancin dosing schedule should be adopted in these challenging scenarios.

200 Previous population PK studies were helpful in establishing which dosing schedule regimens of
201 dalbavancin could be appropriate for theoretically granting long-term treatment up to 5-6 weeks according to
202 different classes of renal function [14,19]. According to our findings, the two 1500 mg one week apart dosing

203 regimen proposed in those studies seems promising as basic schedule for starting treatment of staphylococcal
204 OIs. However, our analysis suggests that after this fixed dosing regimen dalbavancin exposure over time may
205 vary greatly between patients. TDM may be helpful in assessing this variability and should be considered
206 mandatory whenever dealing with dalbavancin treatment duration longer than 5-6 weeks, as after this
207 timeframe the probability of having suboptimal dalbavancin exposure may consistently increase.

208 The proposal of a TDM-guided dalbavancin dosing strategy could harmonize the schedule regimens
209 for subacute and chronic staphylococcal infections. Our work firstly tested the innovative role that dalbavancin
210 TDM could have in assessing conservative PK/PD efficacy thresholds of dalbavancin. Maintenance of these
211 values over time could represent a valuable indicator associated with favorable clinical outcome in the
212 treatment of subacute and chronic staphylococcal infections with dalbavancin. It should not be overlooked that
213 in these scenarios Bayesian forecasting model based on TDM data could be helpful in estimating on real-time
214 for how long dalbavancin concentrations could be maintained above the desired PK/PD efficacy threshold in
215 each single patient and this approach could also guide the timing for eventual additional doses that could be
216 needed.

217 We are aware of some limitations of our study. The retrospective study design and the limited sample
218 size should be acknowledged. Unfortunately, the retrospective study design precluded us from assessing
219 precise PK/PD efficacy values of dalbavancin in each single patient because staphylococcal clinical isolates
220 were not tested for dalbavancin susceptibility. However, it is noteworthy that the PK/PD thresholds that we
221 adopted were very conservative as they offer the opportunity of dealing with staphylococci with an MIC up to
222 the clinical breakpoint (0.125 mg/L). Indeed, the dalbavancin MIC₉₀ for *S. aureus* and for coagulase-negative
223 staphylococci is 0.06 mg/L and 0.03 mg/L, respectively [20]. This means that whenever dealing with more
224 susceptible pathogens the dalbavancin concentrations needed for achieving the PK/PD efficacy thresholds
225 could be lower than those proposed. Finally, we recognize that a more frequent TDM reassessment would have
226 enabled to calculate dalbavancin elimination half-life with more accuracy, and thus to establish more precisely
227 the right time for eventual redosing.

228 In conclusion, our analysis may support the idea that maintenance of conservative PK/PD efficacy
229 thresholds of dalbavancin for most of treatment duration may represent a valuable approach in dealing

230 efficaciously with long-term treatment of staphylococcal OIs. The two 1500 mg doses one week apart could
231 be considered a valuable basic dosing regimen, but appropriate treatment duration should be guided by real-
232 time TDM coupled with Bayesian forecasting. This latter approach could represent an additional criterium to
233 be considered for the TOC in establishing properly duration of treatment with dalbavancin. Prospective clinical
234 studies are warranted for confirming the feasibility and the reliability of this approach.

235

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237 **Conflict of interests:** MG has received personal fees from Angelini and Shionogi, outside the submitted work.
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239 fees from Angelini, Basilea Pharmaceutica, Gilead, Hikma, MSD, Pfizer, Sanofi-Aventis, Shionogi, Thermo
240 Fisher, and Accelerate Diagnostics, outside the submitted work; has participated in speaker's bureau for
241 Accelerate Diagnostics, Angelini, Basilea Pharmaceutica, Gilead, Hikma, MSD, Pfizer, Sanofi-Aventis,
242 Shionogi, Thermo Fisher, and as consultant for Angelini, Basilea Pharmaceutica, Gilead, MSD, Pfizer,
243 Shionogi, outside the submitted work. PV has served as a consultant for bioMérieux, Gilead, Merck Sharp &
244 Dohme, Nabriva, Nordic Pharma, Pfizer, Thermo-Fisher, and Venatorx, and received payment for serving on
245 the speaker's bureaus for Correvio, Gilead, Merck Sharp & Dohme, Nordic Pharma, and Pfizer, outside the
246 submitted work. The other authors report no potential conflicts of interest for this work.

247 **Ethical approval:** The study was conducted according to the guidelines of the Declaration of Helsinki and
248 approved by the local ethical committee [No. 897/2021/Oss/AOUBo on 29 November 2021]. Informed written
249 consent was waived due to the retrospective and observational nature of the study.

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313 **Table 1** – Demographics and clinical characteristics of patients (n=17)

Demographics and clinical variables	Median (IQR) or Count (%)
<i>Patient demographics</i>	
Age (years)	59 (49-71)
Gender (male/female)	9/8 (52.9/47.1)
Body weight (Kg)	73 (60-90)
Body mass index (Kg/m ²)	25.3 (22.0-32.1)
Creatinine clearance (mL/min/1.73 m ²) ¹	94 (90-107)
Serum albumin (g/dL)	3.65 (3.48-3.90)
C-reactive protein (mg/dL)	1.9 (1.2-6.7)
Augmented renal clearance (ARC)	3 (17.6)
<i>Indication for long-term dalbavancin use</i>	
Prosthetic joint infections*	9 (52.9)
Infected non-union	3 (17.6)
Hematogenous vertebral osteomyelitis	2 (11.8)
Chronic osteomyelitis of long bones following open fracture	2 (11.8)
Spinal post-surgical infection	1 (5.9)
<i>Dalbavancin treatment</i>	
Median dalbavancin doses per patient	2 (2-3)
Dosing regimens	
1500 mg + 1500 mg	12 (70.6)
1500 mg + 1500 mg + 1500 mg**	4 (23.5)
1500 mg + 1500 mg + 1500 mg + 1500 mg + 1500 mg***	1 (5.9)
Median dalbavancin TDM assessments per patient	4 (2-6)
<i>Clinical outcome</i>	
Dalbavancin treatment duration (days)	62 (38.5-77.5)
Clinical success at ≥ 6-month follow-up	13/13 (100.0)§
Transient adverse events	3 (17.6)
Need for dalbavancin withdrawal	0 (0.0)
<p>Continuous data presented as median and interquartile range (IQR), while categorical variables expressed by count or percentage.</p> <p>* Five patients underwent two-stage exchange, one underwent one-stage exchange, one underwent debridement and implant retention, and two received dalbavancin after a prosthesis re-implantation with positive intraoperative culture</p> <p>** 1500 mg day 1 + 1500 mg day 8 + 1500 mg day 36 in 2/4 patients; 1500 mg day 1 + 1500 mg day 8 + 1500 mg day 28 in 1/4 patient; 1500 mg day 1 + 1500 mg day 8 + 1500 mg day 51 in 1/4 patient</p> <p>*** 1500 mg day 1 + 1500 mg day 8 + 1500 mg day 39 + 1500 mg day 68 + 1500 mg day 102</p> <p>§ In the 4 other patients, clinical outcome is going favourably after a follow-up of 3.7, 4.8, 5.1 and 5.3 months, respectively</p>	

315 **Figure legends**

316 **Figure 1** – Estimated distribution of time with dalbavancin concentrations above or below the PK/PD efficacy
317 thresholds of 4.02 mg/L (**panel a**) and 8.04 mg/L (**panel b**) during the overall treatment period in each single
318 patient. Green box: attainment of the PK/PD efficacy thresholds (≥ 4.02 or ≥ 8.04 mg/L, corresponding to an
319 $fAUC_{24h}/MIC$ ratio > 111.1 against staphylococci with an MIC of 0.06 and 0.125 mg/L, respectively); red
320 box: non-attainment (of PK/PD efficacy threshold (< 4.02 or < 8.04 mg/L, corresponding to an $fAUC_{24h}/MIC$
321 ratio < 111.1 against staphylococci with an MIC of 0.06 and 0.125 mg/L, respectively); arrows indicate timing
322 of additional dalbavancin doses other than basic dosing regimen (namely 1500 mg day 1 plus 1500 mg day 8).
323 Numbers in parenthesis () are the months of follow-up elapsed since positive test of cure (TOC). * Indicates
324 timing of TDM assessments

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