

DALBAVANCIN FOR THE TREATMENT OF COMPLICATED SKIN AND SOFT TISSUE INFECTIONS IN PATIENTS WITH AND WITHOUT DIABETES MELLITUS IN THE DISCOVER STUDIES

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ABSTRACT

Objective: To compare outcomes of patients with complicated skin and soft tissue infections (cSSTI) treated with dalbavancin versus vancomycin or linezolid in diabetic and non-diabetic patients.

Methods: Data from two randomized, double-blinded cSSTI clinical trials were analyzed for investigator assessed clinical outcome at the end of treatment (EOT) based on a subset analysis of patients with and without diabetes mellitus. Patients were randomized to receive either intravenous dalbavancin or IV vancomycin with option to switch to oral linezolid for a total duration of treatment of 10–14 days. Fasting as well as random glucose measurements were to be performed at baseline for all patients.

Results:

Table 1. Prevalence of Diabetes Mellitus in cSSTI Studies (ITT population)

| | DISCOVER 1 | | DISCOVER 2 | |
|----------------------------------------------------------------------------------|---------------------|------------------------------|---------------------|------------------------------|
| | Dalbavancin n/N (%) | Vancomycin/Linezolid n/N (%) | Dalbavancin n/N (%) | Vancomycin/Linezolid n/N (%) |
| Past medical history of diabetes mellitus at Baseline | 43/288 (14.9) | 30/285 (10.5) | 35 (9.4) | 62 (16.8) |
| Baseline fasting blood glucose consistent with diabetes mellitus | 52/288 (18.0) | 47/285 (16.5) | 51/371 (13.8) | 67/368 (18.2) |
| Baseline fasting blood glucose consistent with pre-diabetes | 74/288 (25.7) | 86/285 (30.2) | 97/371 (26.2) | 83/368 (22.6) |
| Baseline fasting blood glucose consistent with diabetes mellitus or pre-diabetes | 126/288 (43.6) | 133/285 (46.7) | 148/371 (39.8) | 150/368 (40.8) |

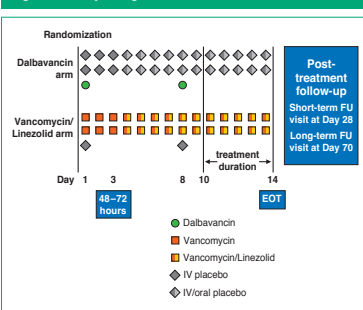
Table 2: Investigator Assessment of Clinical Success at EOT in Patients with Diabetes Mellitus

| | DISCOVER 1 | | DISCOVER 2 | |
|------------------------------------------------|---------------------|------------------------------|---------------------|------------------------------|
| | Dalbavancin n/N (%) | Vancomycin/Linezolid n/N (%) | Dalbavancin n/N (%) | Vancomycin/Linezolid n/N (%) |
| Patients with diabetes mellitus at Baseline | 33/37 (89.2) | 22/24 (91.7) | 32/34 (94.1) | 49/52 (94.2) |
| Difference (95 CI) | -2.5 (-18.3, 16.6) | | -0.1 (-14.1, 10.9) | |
| Patients without diabetes mellitus at Baseline | 200/209 (95.7) | 215/219 (98.2) | 282/290 (97.2) | 241/250 (96.4) |
| Difference (95 CI) | -2.5 (-6.4, 0.9) | | 0.8 (-2.3, 4.3) | |

Conclusions: A history of diabetes mellitus significantly underrepresents the true incidence of diabetes mellitus in this population. Clinical success rates were marginally lower in patients with a history of diabetes compared to non-diabetic patients with cSSTI. Comparable success rates were seen for patients treated with dalbavancin versus comparator antibiotics.

METHODS

Figure 1. Study Design: Studies DUR001-301/302



- Patients had:
 - cellulitis, abscess or wound infection with erythema >75cm² and
 - either a fever, an elevated white blood cell count >12k cells/mm³ or immature neutrophils >10%
- Patients received:
 - Dalbavancin 1 gram IV over 30 minutes on Day 1 and 500 mg IV on Day 8, or
 - Vancomycin 1 gram (or 15 mg/kg) IV every 12 hours (q12h) for at least three days with an option to switch to oral linezolid 600 mg q12h to complete 10–14 days of therapy
- The primary endpoint was measured at 48–72 hours of therapy with success requiring both cessation of spread of the lesion and complete resolution of fever.
 - Secondary endpoints included an investigator assessment of outcome at Day 14 and Day 28
 - Efficacy results from both trials were pooled
- Data was analyzed by history of diabetes as well as fasting glucose measurements at baseline.
 - A case-controlled substudy of fructosamine, a measure of recently glycosylated albumin, at baseline was also performed
 - Patients with either a history of diabetes mellitus, a fasting plasma glucose of >7 mmol/L at baseline (or on day 3 for those with missing baseline values) or a random plasma glucose >11.1 mmol/L (for those with missing fasting glucose values only) were considered to have diabetes for purposes of this analysis

RESULTS

Table 1. Correlation of a History of Diabetes Mellitus with Elevated Plasma Glucose (PG)

| Plasma Glucose (PG) | History of Diabetes N=170 n/N (%) | No History of Diabetes N=1141 n/N (%) |
|------------------------------------------------------------------------------------|-----------------------------------|---------------------------------------|
| Fasting PG values available at baseline or Day 3 | 110/170 (64.7) | 788/1141 (69.1) |
| Fasting PG values not available at baseline or Day 3 | 60/170 (35.3) | 353/1141 (30.9) |
| Fasting PG consistent with Diabetes ¹ | 82/110 (74.6) | 140/788 (17.8) |
| Fasting PG consistent with pre-diabetes ² | 15/110 (13.6) | 345/788 (43.8) |
| Fasting PG not elevated | 13/110 (11.8) | 303/788 (38.5) |
| Any elevated Fasting PG | 97/110 (88.1) | 485/788 (61.5) |
| Random Plasma Glucose (at baseline, only for those with missing fasting PG) | | |
| Random PG available at baseline | 59/60 (98.3) | 333/353 (94.3) |
| Random PG not available at baseline | 1/60 (1.7) | 20/353 (5.7) |
| Random PG consistent with Diabetes ³ | 22/59 (37.3) | 8/333 (2.4) |
| Random PG not consistent with Diabetes | 37/59 (62.7) | 325/333 (97.6) |
| Fasting or random PG consistent with Diabetes | 104/170 (61.2) | 148/1121 (13.2) |

¹Fasting plasma glucose >7 mmol/L; ²Fasting plasma glucose ≥5.6 to <7 mmol/L; ³Random plasma glucose >11.1 mmol/L

Table 2. Demographics

| Category | With Diabetes N=317 | Without Diabetes N=973 | p value |
|------------------------------------------|---------------------|------------------------|---------|
| Mean Age (years) | 56.3 | 47.5 | <0.001 |
| Male Gender, n (%) | 158 (49.8) | 595 (61.2) | <0.001 |
| Region, n (%) | | | <0.001 |
| North America | 77 (24.3) | 390 (40.1) | |
| Rest of World | 240 (75.7) | 583 (59.9) | |
| Intravenous drug use, n (%) | 15 (4.7) | 182 (18.7) | <0.001 |
| Creatinine clearance <30 mL/min, n/N (%) | 15/310 (4.8) | 18/950 (1.9) | 0.005 |
| Mean BMI (kg/m ²) | 31.7 | 28.4 | <0.001 |

Table 3. Systemic Signs of Infection

| Systemic Signs | With Diabetes n/N (%) | Without Diabetes n/N (%) | p value |
|-----------------------------------|-----------------------|--------------------------|---------|
| Temperature ≥38°C | 268/314 (85.4) | 817/964 (84.8) | 0.797 |
| WBC >12,000 cells/mm ³ | 140/302 (46.4) | 344/928 (37.1) | 0.004 |
| Bands ≥10% | 74/229 (32.3) | 139/713 (19.5) | <0.001 |

Table 4. Presence of Diabetes in Subtypes of Infections

| | Cellulitis N=693 n (%) | Major Abscess N=329 n (%) | Wound Infection N=268 n (%) |
|------------------|------------------------|---------------------------|-----------------------------|
| Diabetes | 198 (28.6) | 62 (18.8) | 57 (21.3) |
| Without diabetes | 495 (71.4) | 267 (81.2) | 211 (78.7) |

Table 5. Clinical Success by Diabetes Status

| Timepoint | With Diabetes | | | Without Diabetes | | | Difference for "All" category (95% CI) |
|---------------------------------------------|---------------------|------------------------------|----------------|---------------------|------------------------------|----------------|----------------------------------------|
| | Dalbavancin n/N (%) | Vancomycin/Linezolid n/N (%) | All n/N (%) | Dalbavancin n/N (%) | Vancomycin/Linezolid n/N (%) | All n/N (%) | |
| Clinical response at 48–72 hours | 125/151 (82.8) | 127/166 (76.5) | 252/317 (79.5) | 396/497 (79.7) | 387/476 (81.3) | 783/973 (80.5) | -1.0 (-6.3, 3.9) |
| ≥20 reduction in lesion size at 48–72 hours | 131/151 (86.8) | 139/166 (83.7) | 270/317 (85.2) | 445/497 (89.5) | 428/476 (89.9) | 873/973 (89.7) | -4.5 (-9.2, -0.5) |
| Investigator Success at Day 14 | 123/133 (92.5) | 134/141 (95.0) | 257/274 (93.8) | 416/429 (97.0) | 384/393 (97.7) | 800/822 (97.3) | -3.5 (-7.2, -0.9) |
| Investigator Success at Day 28 | 114/124 (92.9) | 118/126 (93.7) | 232/250 (92.8) | 373/389 (95.9) | 355/365 (97.3) | 728/754 (96.6) | -3.8 (-7.8, -0.7) |

Fructosamine Substudy

- Of 898 patients with fasting plasma glucose values available:
 - 582 (64.8%) had a fasting plasma glucose ≥5.6 mmol/L
 - 222 (24.7%) had a fasting plasma glucose >7 mmol/L
- To address the question as to whether diabetes was pre-existing or coincident with the skin infection, 154 of those patients with an elevated glucose (≥5.6 mmol/L) had a baseline fructosamine level obtained
 - These 154 patients were compared to 54 patients with normal baseline glucose levels (<5.6 mmol/L)

Table 6. Fructosamine Substudy

| Fructosamine | Fasting Glucose | | | | History of Diabetes | |
|--------------|-----------------|----------------|----------------|--------------|---------------------|----------------|
| | <5.6 n/N (%) | ≥5.6 n/N (%) | ≤7 n/N (%) | >7 n/N (%) | Yes n/N (%) | No n/N (%) |
| <285 | 54/54 (100.0) | 123/154 (79.9) | 110/112 (98.2) | 67/96 (69.8) | 16/38 (42.1) | 161/170 (94.7) |
| ≥285 | 0 | 31/154 (20.1) | 2/112 (1.8) | 29/96 (30.2) | 22/38 (57.9) | 9/170 (5.3) |

DISCUSSION

- Patients with cSSTI who had diabetes mellitus were older and more likely to be obese.
- A higher proportion of patients with diabetes mellitus had leukocytosis and left shift compared to those without diabetes mellitus.
- A higher proportion of those with diabetes mellitus had cellulitis as the sub-type of infection and were less likely to present with major abscess.
- 20.1% and 30.2% of patients with elevated fasting glucose ≥5.6 and >7, respectively, had evidence of diabetes by fructosamine.
- No patient with normal glucose at baseline had evidence of diabetes by fructosamine.
- Of the 170 patients who did not have diabetes and in whom a fructosamine assay was performed, 5.3% of the patients had serum fructosamine levels consistent with diabetes.
- 13.2% of patients presenting with an ABSSTI without a history of diabetes had an elevated glucose diagnostic of diabetes
- Patients treated with dalbavancin in those with and without diabetes had similar outcomes to those on comparator

CONCLUSIONS

- Assessment of diabetes based only on history would significantly underrepresent the actual incidence of diabetes mellitus in this population as elevated glucose, even in the setting of acute infection, may be a sign of underlying diabetes.
- The proportion of patients achieving >20% reduction in lesion size at 48–72 hours and clinical success rates at the end of treatment and 2 weeks post treatment were lower in patients with a history of diabetes compared to non-diabetic patients.
- Comparable success rates were seen for patients treated with dalbavancin versus comparator antibiotics.

