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CONCORDANCE OF CLINICAL RESPONSE AT 48–72 HOURS AFTER INITIATION OF THERAPY AND END OF TREATMENT (EOT) IN PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTION (ABSSSI) IN THE DISCOVER STUDIES

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ABSTRACT

Background: Recent guidance from FDA recommends that the assessment timepoint for determination of non-inferiority in registrational abSSSI studies be made at 48–72 h after initiation of treatment. Historically, timepoints for assessment of clinical response have typically been at the end of treatment (EOT) or thereafter, at days 14–28. We performed an analysis of these two endpoints from data generated in the phase 3 DISCOVER program, which compared dalbavancin (DAL) to vancomycin/linezolid (V/L) for treatment of abSSSI.

Methods: The two DISCOVER trials were randomized, double-blinded studies in which patients with skin infection lesions >75cm^2 in area and either fever, WBC >12k cells/mm^3 or bands >10% were randomized to receive either DAL 1g IV over 30 mins on D 1 followed by 500 mg IV on D 8 or V 1 gm or 15 mg/kg IV every 12 h (q12h) with an option to switch to L 600 mg po q12h after 3 days of therapy. Measurements obtained at 48–72 h recorded the cessation of spread of the lesion and absence of fever. Patients were not required to discontinue therapy based on these assessments. Clinical status was assessed programmatically based on the resolution of signs and symptoms of infection at EOT on D 14.

Results: The majority (945/1046, 90.3%) of patients who responded favorably to treatment by 72 h were ultimately cured. Most (129/182, 70.9%) patients who were non-responders on D 3 were also subsequently cured. 72/1046 patients (6.9%) who were early responders were clinical failures at EOT while 50/182 (27.5%) early non-responders were clinical failures at EOT.

Clinical Status at EOT (D14)	Early Clinical Response (D3) Clinical Responder		Clinical Non-Responder		Intermediate		Total	
	n	%	n	%	n	%	n	%
Clinical Success	945	72.0	129	9.8	53	4.0	1127	(85.9%)
Clinical Failure	72	5.5	50	3.8	10	0.8	132	(10.1%)
Indeterminate	29	2.2	3	0.2	21	1.6	53	(4.0%)
Total	1046	(79.7%)	182	(13.9%)	84	(6.4%)	1312	

Conclusion: The majority of early responding patients were ultimately cured. Early non-responders were more likely to require a change in treatment. While the rigorous early response definition used for registrational purposes allows justification of a non-inferiority trial design, it does not capture all the factors clinicians consider in deciding whether to continue or discontinue therapy at that time.

BACKGROUND

- Recent guidance from FDA recommends that the assessment timepoint for determination of non-inferiority in registrational ABSSSI studies be made at 48–72 h after initiation of treatment. Historically, timepoints for assessment of clinical response have typically been at the end of treatment (EOT) or thereafter, at days 14–28. We performed an analysis of these two endpoints from data generated in the phase 3 DISCOVER program, which compared dalbavancin (DAL) to vancomycin/linezolid (V/L) for treatment of ABSSSI.

METHODS

- The two DISCOVER trials were randomized, double-blinded studies in which patients with skin infection lesions >75cm^2 in area and either fever, WBC >12k cells/mm^3 or bands >10% were randomized to receive either dalbavancin 1000 mg IV over 30 minutes on Day 1 followed by 500 mg IV on Day 8 or vancomycin 1 gm or 15 mg/kg IV every 12 h with an option to switch to linezolid 600 mg po q12h after 3 days of therapy.
- Measurements obtained at 48–72 h recorded the size of the erythema associated with infection site to document cessation of spread of the lesion and temperature measurements to document absence of fever. Patients were not required to continue or discontinue therapy based on these early response assessments. The primary endpoint in FDA Draft Guidance is cessation of spread and absence of fever.
- Clinical status in the evaluable population was assessed programmatically based on the resolution or improvement of a prespecified set of signs and symptoms of infection at the end of treatment on Day 14.
- Data from both DISCOVER studies was pooled and a number of assessments at 48–72 hours were compared with those at EOT. Sensitivity, specificity, positive predictive value and negative predictive value of the early response were calculated. Missing data were excluded.
- The 'test' under consideration is the early response at 48–72 hours and the outcome of interest is clinical success at end of treatment. Sensitivity (the probability of a successful early response given the patient will actually be a clinical success at EOT) and specificity (the probability of an early non-response given the patient will be a clinical failure at EOT) are defined as follows:

$$\text{Sensitivity} = \frac{\text{true positives (responder early and success at EOT)}}{\text{true positives (responder early and success at EOT)} + \text{false negatives (non-responders but success at EOT)}}$$

$$\text{Specificity} = \frac{\text{true negatives (non-responders early and failures at EOT)}}{\text{true negatives (non-responders early and fail at EOT)} + \text{false positives (responders early but failure at EOT)}}$$

$$\text{Positive predictive value} = \frac{\text{true positives (responder early and success at EOT)}}{\text{true positives (responder early and success at EOT)} + \text{false positives (responders early but failure at EOT)}}$$

$$\text{Negative predictive value} = \frac{\text{true negatives (non-responders early and failures at EOT)}}{\text{true negatives (non-responder and failure at EOT)} + \text{false negatives (non-responder but success at EOT)}}$$

RESULTS

Figure 1. Outline of Lesion to Assist in Determination of Cessation of Spread

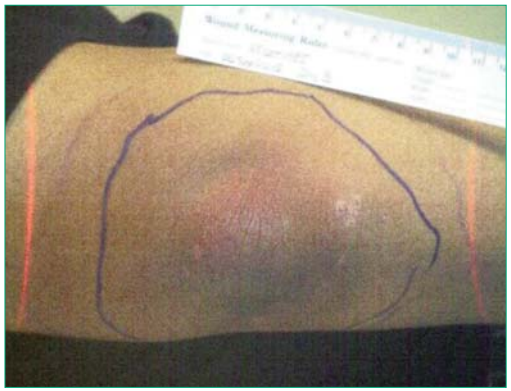

Table 1. Comparison of Early Assessments and Clinical Status at End of Treatment

Type of 48–72 hour Assessment	EOT Outcome	48–72 hour Assessment: Clinical Responder	48–72 hour Assessment: Clinical Non-Responder
Cessation of spread of the lesion and absence of fever	Clinical Success	945	129
	Clinical Failure	72	50
>20% reduction in lesion size	Clinical Success	1046	81
	Clinical Failure	78	54
Cessation of spread of lesion	Clinical Success	1093	34
	Clinical Failure	94	38
Absence of Fever	Clinical Success	998	129
	Clinical Failure	88	44

Table 2. Sensitivity, Specificity, Positive and Negative Predictive Value of an Early Response Assessment for Predicting Clinical Success at End of Treatment

48–72 hour Analysis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Cessation of spread + absence of fever	88%	41%	93%	28%
Cessation of spread	97%	29%	92%	53%
Cessation of spread + worsening pain	99%	43%	92%	80%
Absence of fever	89%	33%	91%	25%
>20% reduction in lesion size	93%	41%	93%	40%

- Addition of the criteria of 'worsening pain relative to baseline' improved the negative predictive value and specificity of the Day 3 assessment of cessation of spread.

DISCUSSION

- Based on Cessation of spread alone:
  - Sensitive (98%) marker of ultimate clinical success with positive predictive value (>90%)
  - Negative predictive value of 53% because some early failures will ultimately be successes at EOT
  - Addition of pain assessment increases NPV to 80%
  - Given that the pretest probability of failure is low, it is not surprising that the negative predictive value was lower than the PPV
- In other words:
  - Patients achieving cessation of spread of the lesion after 72 hours of antibiotic treatment have a >90% chance of being cured at the end of treatment
  - Patients who do **not** achieve cessation of spread at 72 hours and have worsening of pain have an 80% chance of ultimately failing therapy

CONCLUSION

- A measurement of early clinical response at 48–72 hours after initiation of treatment can help predict outcome and guide treatment of ABSSSI in addition to anchoring a non-inferiority trial design
  - All combinations of cessation of lesion spread and/or absence of fever had >90% sensitivity and could help identify patients who would ultimately be cured
  - Cessation of lesion spread with an assessment of pain can help predict those patients who might ultimately fail treatment
- Additional work is needed to improve the predictive value of these early response assessments

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