Presentation 266
Monday

Risk Factors for Change in Outcome Between the End of Therapy (EOT) and Post-Treatment (PT) Evaluations in Patients with Complicated Urinary Tract Infections (cUTI) Treated with Eravacycline (ERV): Analysis from a Randomized, Double Blind, Phase 3 Trial (IGNITE2)

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Abstract

Background: IGNITE2 compared ERV to levofloxacin (LEV) for cUTI. Although ERV achieved a higher response rate (clinical cure and microbiological success) at the end of therapy (EOT), ERV did not demonstrate non-inferiority to LEV at the post-treatment evaluation (PT, 6-8 days after EOT). Since response was driven by microbiological outcome, we investigated factors associated with microbiological failure at PT despite initial response at EOT.

METHODS: Outcomes in patients classified as microbiological success at EOT were examined. We compared those who remained successes at PT to patients who converted to failure. Risk factors including demographics, type of infection, study drug, and duration of IV therapy while on study drug were assessed. We employed logistic regression to identify variables independently associated with microbiological failure at PT despite success at EOT.

RESULTS: In the microbiological-ITT population, at EOT, 90.6% (270/298) and 84.8% (256/302) subjects were microbiological successes in the ERV and LEV groups, respectively. Crude failure rates between EOT and PT were 25.5% and 14.3 %, for ERV and LEV, respectively. Independent variables associated with conversion to failure at PT are shown in the table below. The adjusted Odds Ratios (OR) for loss of efficacy between EOT and PT among patients who received ≤ 3 days IV study drug were 1.61 (95% CI=0.90, 2.88, p=0.1102) and 1.34 (95% CI=0.67, 2.67, p=0.4135) for ERV and LEV, respectively, suggesting an interaction between duration of IV therapy and study drug.

Table. Factors associated with failure at post-treatment visit in multivariate analysis

Factor	Adjusted OR	95% CI	p-value
Treatment	0.68	0.44 - 1.06	0.0900
Diagnosis (AP vs other cUTI)	0.57	0.36 - 0.92	0.0200
Gender	1.55	0.96 - 2.50	0.0716
IV study drug ≤ 3 days	1.45	0.93 - 2.26	0.0977

CONCLUSIONS: Treatment with ≤ 3 days of IV ERV was identified as a potentially modifiable, independent risk factor for a change in microbiologic outcome between EOT and PT in patients enrolled in this study. Further investigation of IV-only ERV for the treatment of cUTI is warranted.

Introduction

IGNITE2 was a phase 3 study designed to assess the safety and efficacy of eravacycline (ERV) administered as an intravenous (IV) to oral (PO) transition therapy compared with levofloxacin (LEV) in subjects diagnosed with cUTI (Refer to P264). In the pivotal portion of the study, responder rates were 60.4% for the ERV arm and 66.9% for the LEV arm in the microbiological intent-to-treat (micro-ITT) population at the Post-Treatment (PT) visit. The resulting difference was −6.5% (95% CI: −14.1, 1.2). The lower limit of the 95% CI did not exceed −10%, and non-inferiority was not demonstrated.

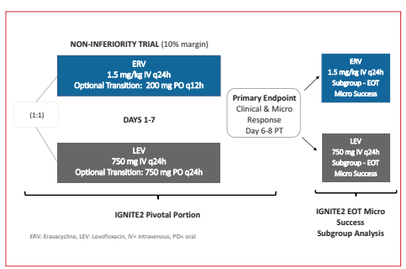
However, at all timepoints prior to the PT visit, clinical cure rates, microbiological success rates, and combined responder rates, were higher in the ERV group compared to the LEV group (between-treatment group differences 5.5 – 9.7%, favoring eravacycline). Between the end of therapy (EOT) and PT visits, responder rates fell 26.2% in the ERV group, compared with 14.2% in the LEV group.

To explore the reasons for the disproportionate loss of efficacy in the ERV group, a logistic regression model was developed. Since the combined responder rate was determined primarily by the microbiologic outcome, a subset of subjects with microbiologic success at EOT was identified and analyzed to determine independent risk factors associated with conversion to microbiologic failure at PT.

Methods

- Post hoc assessment of subjects enrolled in IGNITE2 who had a microbiologic outcome of success at the EOT visit
- Key Inclusion Criteria
  - Male and female subjects >18 years of age who were able to provide informed consent
  - Had either pyelonephritis and normal urinary tract anatomy or cUTI with at least one of the following conditions:
    - Indwelling urinary catheter
    - Urinary retention (at least approximately 100 mL of residual urine after voiding)
    - History of neurogenic bladder
    - Partial obstructive uropathy (e.g., nephrolithiasis, bladder stones, and ureteral strictures)
    - Azotemia of renal origin (not congestive heart failure or volume related) such that the serum blood urea nitrogen (BUN) was elevated (> 20 mg/dL) AND the serum BUN:creatinine ratio was < 15
    - Surgically modified or abnormal urinary tract anatomy (e.g., bladder diverticula, redundant urine collection system, etc.) EXCEPT urinary tract surgery within the month prior to screening (placing of stents or catheters was not considered to be surgical modification)
  - Had at least two of the following signs or symptoms:
    - Chills, rigors, or warmth associated with fever (oral, rectal, tympanic, or temporal artery temperature > 100.4°F/38°C) or hypothermia (oral, rectal, tympanic, or temporal artery temperature < 95°F/35°C)
    - Flank pain (pyelonephritis) or pelvic pain (cUTI)
    - Nausea or vomiting
    - Dysuria, urinary frequency, or urinary urgency
    - Costovertebral angle tenderness on physical examination
  - Had a urine specimen with evidence of pyuria as indicated by any of the following:
    - Dipstick analysis positive for leukocyte esterase (where positive result was at least "++" as indicated on the urine dipstick provided in the laboratory kit), OR
    - At least 10 white blood cells (WBCs) per cubic millimeter, OR
    - ≥ 10 WBCs per high power field
- Key Exclusion Criteria
  - Concurrent use of non-study antibacterial drug therapy that would have had a potential effect on outcome evaluations in subjects with cUTI, including:
    - Subjects who had a history of levofloxacin-resistant urinary tract infection
    - Were likely to receive ongoing antibacterial drug prophylaxis prior to the LPT visit (e.g., subjects with vesiculo-ureteral reflux)
    - Had use of systemic antibiotics effective in cUTI within 72 hours prior to enrollment except under specific circumstances
  - Complicated pyelonephritis with complete obstruction or known or suspected renal or perinephric abscess, emphysematous pyelonephritis, OR
    - Any condition that was likely to have required surgery to achieve cure (this did NOT include procedures to place catheters or obtain diagnosis)
  - Subjects who had a high risk for cUTI due to *Pseudomonas* spp.
  - Neutropenia (absolute neutrophil count < 1,000 PMNs/µL)
  - Creatinine clearance of < 50 mL/min as estimated by the Cockcroft-Gault equation (eCCr)
  - Had a known or suspected hypersensitivity to tetracyclines or fluoroquinolones

Figure 1. IGNITE2 Study Design with Post-hoc Analysis of Outcomes in EOT Microbiological Successes

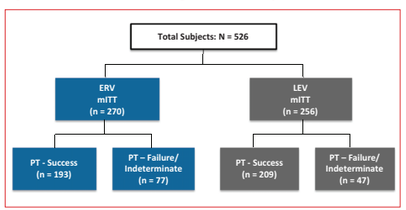


- The following potential predictors of microbiological response were included in the initial full logistic regression model: treatment group, primary site of infection (pyelonephritis and normal urinary tract anatomy, cUTI with indwelling catheter, cUTI with urinary retention, cUTI with neurogenic bladder, cUTI with partial obstructive uropathy, cUTI with azotemia of renal origin, cUTI with surgically modified or abnormal urinary tract anatomy, other cUTI), indwelling urethral or suprapubic catheter, stent, nephrostomy tube or other urinary tract device present at any time within the past 48 hours of EOT, retained urinary tract stone present at any time within the past 48 hours of EOT, gender, age (as a continuous variable), weight (as a continuous variable), race (White versus non-White), creatinine clearance (as a continuous variable), highest MIC to study drug administered, negative urinalysis at time of oral drug step down (defined as urine WBCs < 10/mm^3 or urine leukocyte esterase negative), and receipt of IV study drug for ≤ 3 days.
- A backwards stepwise procedure was used to identify the potential predictors of microbiological response at PT. The covariate with the highest p-value was excluded from the model, and the model was re-run. A p-value of < 0.15 was used to retain a covariate in the model, with treatment group retained in the model regardless of p-value.
- The model was further refined to focus only on variables expected clinically to be associated with microbiological failure and with a strong association with failure on univariate analysis. The following variables were excluded from the model: highest MIC to study drug, negative urinalysis, and weight; and the primary site of infection variables were combined as pyelonephritis and normal urinary tract anatomy versus cUTI. The same procedure for building the model was used (backwards selection procedure), but a p-value of < 0.10 was used to retain a covariate in the model with treatment group retained in the model regardless of the p-value. In addition, an interaction term for study drug and receipt of IV study drug for ≤ 3 days was included in the model, but it was not retained in the final model given a high p-value. Variables included in the final model are presented in Table 1, which predicted loss of efficacy from EOT to PT, are presented in with their associated odds ratios.

Results

- In the microbiological-ITT population, at EOT, 90.6% (270/298) and 84.8% (256/302) subjects were microbiological successes in the ERV and LEV groups, respectively. Crude failure rates between EOT and PT were 25.5% and 14.3 %, for ERV and LEV, respectively.

Figure 2. IGNITE2 EOT Microbiological Success Subjects



- As shown in Table 1, in addition to treatment group, two baseline characteristics, diagnosis and gender, and one post-randomization factor, duration of IV study drug, were identified as independent predictors of conversion to microbiological failure from EOT to PT.

Table 1. Results of Logistic Regression - Predictors of Microbiological Failure at PT

	Adjusted Odds Ratio	95% Confidence Interval	p-value
Treatment (levofloxacin)	0.68	0.44 – 1.06	0.0900
Diagnosis (acute pyelonephritis versus other cUTI)	0.57	0.36 – 0.92	0.0716
Gender (male)	1.55	0.96 – 2.50	0.0716
IV study drug ≤ 3 days	1.45	0.93 – 2.26	0.0977

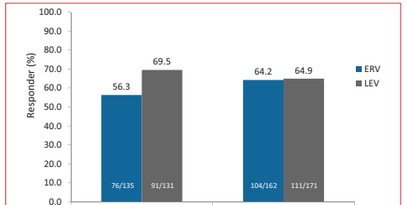
- The adjusted Odds Ratios (OR) for loss of efficacy between EOT and PT for patients who received ≤ 3 days IV study drug were 1.61 (95% CI=0.90, 2.88, p=0.1102) and 1.34 (95% CI=0.67, 2.67, p=0.4135) for ERV and LEV, respectively, suggesting an interaction between duration of IV therapy and study drug. However, when an interaction term for duration of IV therapy and study drug was included in the model shown in Table 1, the interaction term was not statistically significant (p=0.5755).
- Outcomes were tabulated among subjects with and without the identified independent risk factors. As shown in Table 2, in the LEV group, subjects with a diagnosis of other cUTI, male subjects, and subjects who received > 3 d IV study drug had lower PT responder rates. In the ERV group, a similar pattern was seen, with the notable exception that the responder rate was higher among subjects who received > 3 d IV study drug. Among subjects with other cUTI, among males, and among subjects who received > 3 d IV study drug, responder rates at PT were similar between the ERV and LEV groups. In contrast, among subjects with AP, among females, and among subjects who received ≤ 3 d IV study drug, responder rates were higher in the LEV group than the ERV group.

Table 2. PT Responder Outcome by Risk Factors (micro-ITT Population)

	Primary Diagnosis							
	AP				Other cUTI			
	ERV (N = 142)		LEV (N = 146)		ERV (N = 176)		LEV (N = 156)	
	n	%	n	%	n	%	n	%
Responder	92	64.8	116	79.5	88	56.4	86	55.1
Non-responder	41	28.9	24	16.4	59	37.8	67	43.0
Indeterminate	9	6.3	6	4.1	9	5.8	3	1.9
	Gender							
	Female				Male			
	ERV (N = 194)		LEV (N = 211)		ERV (N = 104)		LEV (N = 91)	
	n	%	n	%	n	%	n	%
Responder	123	63.4	154	73.0	57	54.8	48	52.8
Non-responder	58	29.9	50	23.7	42	40.4	41	45.1
Indeterminate	13	6.7	7	3.3	5	4.8	2	2.2
	IV SD Days							
	≤ 3 d IV				> 3 d IV			
	ERV (N = 135)		LEV (N = 131)		ERV (N = 162)		LEV (N = 171)	
	n	%	n	%	n	%	n	%
Responder	76	56.3	91	69.5	104	64.2	111	64.9
Non-responder	48	35.6	36	27.5	52	32.1	55	32.2
Indeterminate	11	8.2	4	3.1	6	3.7	5	2.9

Abbreviations: N = number of subjects in the micro-ITT population; n = number of subjects in the specific category.
Notes: Percentages are calculated as 100 x (n/N).

Figure 3. Responder Outcome at PT Visit By Days of IV Study Drug



- Among subjects who received > 3 days of IV study drug, there was no disproportionate loss of efficacy in the ERV group compared with the LEV group. It is also notable that the PT responder rate among subjects in the LEV group who received ≤ 3 days of IV study drug was higher compared with those who received > 3 days IV study drug. This was expected because subjects in the former group were more likely to have had faster clinical responses following initiation of study drug therapy, allowing them to step down to PO study drug after the minimum 3 days of IV study drug. In contrast, in the eravacycline group, the opposite pattern was observed; EOT responders who received ≤ 3 days of IV study drug had a lower responder rate at PT compared with those who received > 3 days of IV study drug.

Conclusions

- Primary diagnosis of other cUTI, male gender, and receipt of ≤ 3 days of IV study drug were identified as independent risk factors for loss of efficacy between EOT and PT
- Among subjects with other cUTI, male gender, and receipt of > 3 days of IV study drug, responder rates were similar between the ERV and LEV groups
- Among ERV subjects, responder rates were higher in those who received > 3 days of IV study drug than in those who received ≤ 3 days of IV study drug; among LEV subjects, the opposite pattern was seen
- Further investigation of the efficacy and safety of IV-only eravacycline therapy for the treatment of cUTI is warranted

References

1. *Tsai L, Zervos M, Miller L, et al. Abstract 264. ASM Microbe 2016, Boston, MA, June 16-20, 2016*