Asymptomatic Bacteriuria Not a Predictor of Clinical Failure in Uncomplicated Urinary Tract Infections (uUTI): A Prospective Analysis of Women Treated for uUTI from the REASSURE Trial

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ABSTRACT

Background

Per FDA *Guidance*, the primary efficacy endpoint for trials evaluating antimicrobials for treatment of UTI is a combined clinical/microbiologic response. Overall success requires both resolution of UTI symptoms and demonstration that the causative uropathogen is reduced to < 10^3 CFU/mL at a fixed time point after randomization, regardless of whether the patient is asymptomatic. Previously, we retrospectively evaluated the impact of post treatment asymptomatic bacteriuria (ASB) for Phase 3 clinical trial patients with UTI and found that ASB was not a predictor of subsequent clinical failure. In this study, we prospectively assessed the impact of post treatment ASB on subsequent clinical response for adult women with uUTI.

Methods

Study IT001-310 was a Phase 3 randomized, double-blind, double-dummy, active controlled trial to evaluate the safety and efficacy of sulopenem/probenecid (SUL) versus amoxicillin/clavulanate (AMC) for the treatment of uncomplicated UTI (uUTI). Adult women were randomized to receive SUL or AMC, both bid for 5 days. The primary efficacy outcome was overall success (combined clinical/microbiologic success) at the Test of Cure (TOC) visit in the mMITT population. ASB at TOC was prespecified as an additional efficacy endpoint to be assessed, and the presence of ASB at the End of Treatment (EOT) and TOC visit was evaluated to see if it impacted clinical response at the following visit.

Results

2,222 women were randomized; 990 (44.6%) were in the mMITT population. ASB was the reason for nonresponse in 74 (14.2%) and 93 (19.9%) patients treated with SUL and AMC, respectively. As shown in Table 1, for both treatment arms, the presence of ASB at the EOT and TOC visit did not lead to clinical failure at the following visit.

Table: Association of Asymptomatic Bacteriuria at the End of Treatment and Test of Cure Visits and Clinical Response at the Following Visits, micro-MITT Population

micro-MITT patients treated with sulopenem			micro-MITT patients treated with amoxicillin/clavulanate		
Overall Response at EOT (D5)	Clinical Success at TOC (D12) n/N (%)	p-value	Overall Response at EOT (D5)	Clinical Success at TOC (D12) n/N (%)	p-value
Success	259/272 (95.2)	0.721	Success	226/243 (93.0)	0.527
Fail: ASB	29/30 (96.7)		Fail: ASB	43/45 (95.6)	
Overall Response at TOC (D12)	**Clinical Success at FV (D28)**	**p-value**	**Overall Response at TOC (D12)**	**Clinical Success at FV (D28)**	**p-value**
Success	296/318 (93.1)	0.656	Success	247/260 (95.0)	0.208
Fail: ASB	69/73 (94.5)		Fail: ASB	85/93 (91.4)	

*Reasons for failure include death, receipt of an antibiotic (which includes any antibiotic for a UTI based on investigator assessment or programmatic outcomes), clinical symptoms alone or both urine culture positive plus clinical symptoms. Note: micro-MITT = microbiologic modified intent-to-treat; EOT = end of treatment; TOC = test of cure; FV = final visit; ASB = asymptomatic bacteriuria

Conclusions

SUL and AMC, both β-lactams, appear to have similar effects on the frequency of post treatment ASB. For patients in both treatment arms, the presence of ASB a week after completing UTI therapy was not a marker of subsequent clinical failure. The inclusion of ASB as part of the primary endpoint for studies of UTI should be reconsidered. Inclusion of microbiologic results from asymptomatic patients after complete resolution of uUTI symptoms is a practice inconsistent with available treatment recommendations.

INTRODUCTION

Per FDA *Guidance*[1,2], the primary efficacy endpoint for trials evaluating antimicrobials for treatment of uncomplicated urinary tract infection (uUTI) and complicated urinary tract infection (cUTI) is a combined clinical and microbiologic outcome response. Overall success requires both resolution of UTI symptoms and demonstration that the causative uropathogen is reduced to <10^3 CFU/mL at a fixed time point after randomization, regardless of whether the patient is symptomatic.

Previously, we retrospectively evaluated the impact of post treatment asymptomatic bacteriuria (ASB) for Phase 3 clinical trial patients with uUTI (Study 301) and found that ASB was not a predictor of subsequent clinical failure. In the REASSURE trial (Study 310), we prospectively assessed the impact of post treatment ASB on subsequent clinical response for adult women with uUTI.

METHODS

Study IT001-310

- Multicenter, double-blind, active-controlled, Phase 3 randomized trial
- 2222 adult women with uUTI
  - Pyuria, bacteriuria, and clinical signs/symptoms of uUTI
- Compared sulopenem etzadroxil/probenecid (oral sulopenem) 500 mg/500 mg PO BID x 5 days to amoxicillin/clavulanate 875 mg/125 mg PO BID x 5 days
- Primary endpoint: overall (clinical + microbiologic) response in the micro-MITT population at the Test-of-Cure (Day 12) Visit
- Additional endpoint: rate of post-treatment ASB at End-of-Treatment (D5), Test-of-Cure (D12) and Final Visit (D28).
  - ASB was defined as clinical cure (resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms) and microbiologic persistence (≥ 10^3 CFU/mL of the baseline uropathogen

RESULTS

Table 1: Study 310 Outcomes at TOC and EOT and Reasons for Failure at TOC in the micro-MITTS Populations

	micro-MITTS Population		
Outcome	**Sulopenem n (%) N=480**	**Amoxicillin/ clavulanate n (%) N=442**	**Difference (%), (95% CI)**
Overall response of success at TOC	296 (61.7)	243 (55.0)	6.7 (0.3, 13.0)
Overall response of failure at TOC	160 (33.3)	177 (40.0)	
Reason for failure: ASB only	**70 (14.6)**	**91 (20.6)**	
Clinical failure only	63 (13.1)	47 (10.6)	
Both clinical and microbiologic failure	26 (5.4)	35 (7.9)	
Receipt of non-study antibacterial therapy for uUTI	8 (1.7)	4 (0.9)	
Antibacterial therapy alone	1 (0.2)	4 (0.9)	
Indeterminate	24 (5.0)	22 (5.0)	
Clinical success at TOC	371 (77.3)	339 (76.7)	0.6 (-4.8, 6.1)
Microbiologic success TOC	361 (75.2)	295 (66.7)	8.5 (2.6, 14.3)
Overall response of success at EOT	252 (52.5)	226 (51.1)	1.4 (-5.1, 7.8)

Table 2: Study 310 Asymptomatic Bacteriuria and Subsequent Clinical Response to Treatment, Sulopenem- and Amoxicillin/clavulanate-Treated Patients, micro-MITTS Population

Patients treated with sulopenem			Patients treated with amoxicillin/clavulanate		
Overall Response at EOT (D5)	**Clinical Success at TOC (D12) n/N (%)**	**p-value**	**Overall Response at EOT (D5)**	**Clinical Success at TOC (D12) n/N (%)**	**p-value**
Success	241/252 (95.6)	0.872	Success	210/226 (92.9)	0.538
Fail: ASB	26/27 (96.3)		Fail: ASB	42/44 (95.5)	
Overall Response at TOC (D12)	**Clinical Success at FV (D28)**	**p-value**	**Overall Response at TOC (D12)**	**Clinical Success at FV (D28)**	**p-value**
Success	274/296 (92.6)	0.634	Success	231/243 (95.1)	0.186
Fail: ASB	65/69 (94.2)		Fail: ASB	83/91 (91.2)	

RESULTS

Table 3: Summary of Asymptomatic Bacteriuria in Recent uUTI Trials

	Combined Response at TOC			Clinical Response at TOC			Asymptomatic Bacteriuria	
Study / Population	**Regimen A**	**Regimen B**	**Difference (95%CI)**	**Regimen A**	**Regimen B**	**Difference (95%CI)**	**Regimen A**	**Regimen B**
IT001-301 / FQ-S population	Sulopenem etzadroxil/ probenecid 247/370 (66.8)	Ciprofloxacin 326/415 (78.6)	-11.8 (-18.0, -5.6)	Sulopenem etzadroxil/ probenecid 300/370 (81.1)	Ciprofloxacin 349/415 (84.1)	-3.0 (-8.4, 2.3)	Sulopenem etzadroxil/ probenecid 12.7%	Ciprofloxacin 3.9%
IT001-310 / A/C-S population	Sulopenem etzadroxil/ probenecid 296/480 (61.7)	Amoxicillin/ clavulanate 243/442 (55.0)	6.7 (0.3, 13.0)	Sulopenem etzadroxil/ probenecid 371/480 (77.3)	Amoxicillin/ clavulanate 339/442 (76.7)	0.6 (-4.8, 6.1)	Sulopenem etzadroxil/ probenecid 14.6%	Amoxicillin/ clavulanate 20.6%
EAGLE 2 / NFT-S Population[5*]	Gepotidacin 162/320 (50.6)	Nitrofurantoin 135/287 (47.0)	4.3 (-3.6, 12.1)	Gepotidacin 210/320 (65.6)	Nitrofurantoin 187/287 (65.2)	1.2 (-6.3, 8.7)	Gepotidacin 15%*	Nitrofurantoin 18.1%*
EAGLE 3 / NFT-S Population[5*]	Gepotidacin 162/277 (58.5)	Nitrofurantoin 115/264 (43.6)	14.6 (6.4, 22.8)	Gepotidacin 188/277 (67.9)	Nitrofurantoin 167/264 (63.3)	4.4 (-3.5, 12.3)	Gepotidacin 9.4%*	Nitrofurantoin 19.7%*

* Data for gepotidacin and nitrofurantoin taken from Table 2 of Wagenlehner F, et al[5] where ASB patients are referred to as 'clinical success, microbiological failure'. NOTE: no formal head-to-head study has been conducted between sulopenem and gepotidacin or nitrofurantoin.

Table 4: Study 301 Asymptomatic Bacteriuria and Subsequent Clinical Response to Treatment Among Sulopenem-Treated Patients, micro-MITTS Population

Patients treated with sulopenem		
Overall Response at EOT (D5)	**Clinical Failure at TOC (D12) n/N (%)**	**p-value**
Success	22/240 (9.3)	0.993
Fail: ASB	1/11 (9.1)	
Overall Response at TOC (D12)	**Clinical Failure at FV (D28) n/N (%)**	**p-value**
Success	15/247 (6.1)	0.533
Fail: ASB	4/47 (8.5)	

Table 5: Summary of Asymptomatic Bacteriuria in Recent cUTI Trials

	Combined Response at TOC			Clinical Response at TOC			Asymptomatic Bacteriuria	
	Regimen A	Regimen B	Difference (95%CI)	Regimen A	Regimen B	Difference (95%CI)	Regimen A	Regimen B
Study 302	**Sulopenem→ PO sulopenem** 301/444 (67.8)	**Ertapenem→ PO Cipro/AC** 325/440 (73.9)	-6.1 (-12.0, -0.1)	**Sulopenem→ PO sulopenem** 397/444 (89.4)	**Ertapenem→ PO Cipro/AC** 389/440 (88.4)	1.0 (-3.1, 5.1)	**Sulopenem→ PO sulopenem** 22%	**Ertapenem→ PO Cipro/AC** Cipro - S: 5% Amox-clav: 22%
Wagenlehner et al (CID 2016)	**CTZ-AVB→ PO Cipro or TMP-SMX** 280/393 (71.2)	**Doripenem→ PO Cipro or TMP-SMX** 269/417 (64.5)	6.7 (0.30, 13.12)	**CTZ-AVB→ PO Cipro or TMP-SMX** 332/393 (84.5)	**Doripenem→ PO Cipro or TMP-SMX** 360/417 (86.3)	-1.9 (-6.78, 3.02)	**CTZ-AVB→ PO Cipro or TMP-SMX** 13%	**Doripenem→ PO Cipro or TMP-SMX** 22%
Kaye et al (JAMA 2018)	**Meropenem Vaborbactam→ PO Levo[1]** 143/192 (74.5)	**Piperacillin Tazobactam→ PO Levo** 128/182 (70.3)	4.1 (-4.9, 9.1)	**Meropenem Vaborbactam→ PO Levo[1]** 174/192 (90.6)	**Piperacillin Tazobactam→ PO Levo** 157/182 (86.3)	4.4 (-2.2, 11.1)	**Meropenem Vaborbactam→ PO Levo[1]** 16%	**Piperacillin Tazobactam→ PO Levo** 16%
Wagenlehner et al (NEJM 2019)	**Plazomicin→ PO Levo or other** 156/191 (81.7)	**Meropenem→ PO Levo or other** 138/197 (70.1)	11.6 (2.7, 20.3)	**Plazomicin→ PO Levo or other** 170/191 (89.0)	**Meropenem→ PO Levo or other** 178/197 (90.4)	-1.4 (-7.9, 5.2)	**Plazomicin→ PO Levo or other** 7%	**Meropenem→ PO Levo or other** 20%
Wagenlehner et al (Lancet 2015)	**Ceftolozane tazobactam** 306/398 (76.9)	**Levofloxacin*** 275/402 (68.4)	8.5 (2.3, 14.6)	**Ceftolozane tazobactam** 366/398 (92.0)	**Levofloxacin*** 356/402 (88.6)	3.4 (-0.7, 7.6)	**Ceftolozane tazobactam** 15%	**Levofloxacin*** Levo-R: 38%* Levo-S: 13.4%*
Eckburg et al (NEJM 2022)	**Oral tebipenem pivoxil hydrobromide** 264/449 (58.8)	**Ertapenem** 258/419 (61.6)	−3.3 (−9.7, 3.2)	**Oral tebipenem pivoxil hydrobromide** 418/449 (93.1)	**Ertapenem** 392/419 (93.6)	−0.6 (−4.0 to 2.8)	**Oral tebipenem pivoxil hydrobromide** 34%	**Ertapenem** 32%

CONCLUSIONS

- In the REASSURE trial (Study 310), sulopenem and amoxicillin/clavulanate, both β-lactams, appear to have similar effects on the frequency of post treatment ASB
  - For patients in both treatment arms, the presence of ASB a week after completing UTI therapy was not a marker of subsequent clinical failure.
  - These findings align with retrospective results from Study 301 where post treatment ASB was not a predictor of subsequent clinical failure for Phase 3 clinical trial patients with uUTI[3]
- Inclusion of ASB as part of the primary endpoint for studies of UTI should be reconsidered
  - The degree and duration of post treatment ASB likely differs for each antibiotic and is not currently defined
  - Inclusion of microbiologic results from asymptomatic patients after complete resolution of uUTI symptoms is a practice inconsistent with available treatment recommendations
    - Screening for and treatment of ASB is not recommended for most patients, except for those who are pregnant or undergoing an endourologic procedure[6-8]
    - Obtaining "proof of cure" urine cultures after symptomatic resolution is not standard of care in clinical practice[9-11]

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