Systematic Review and Network Meta-analysis of Tedizolid for the Treatment of Acute Bacterial Skin And Skin Structure Infections (ABSSSI) due to Methicillin-Resistant *Staphylococcus aureus* (MRSA)

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INTRODUCTION

- Acute bacterial skin and skin structure infections (ABSSSI) include cellulitis/erysipelas, wound infection, and major cutaneous abscess, as defined by the U.S. Food and Drug Administration (FDA) in 2010.[1]
- Common bacterial pathogens causing ABSSSI include *Streptococcus pyogenes* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA).[1,2]
- MRSA is a significant cause of healthcare-associated and community-associated ABSSSI.[4]
- ABSSSI caused by MRSA are associated with worse outcomes and higher costs of care than those caused by methicillin-sensitive *S. aureus* (MSSA).[4]
- The standard therapy for complicated MRSA infections is usually vancomycin; however, its efficacy has come into question due to concerns about its slow bactericidal activity and the emergence of resistant strains.[4]
- Tedizolid phosphate, the prodrug of the novel oxazolidinone tedizolid, is approved for the treatment of ABSSSI in the United States, the European Union, and Canada.[5,6]
  - Two Phase 3 trials, ESTABLISH-1 (NCT01170221) and ESTABLISH-2 (NCT01421511), demonstrated the noninferior efficacy of tedizolid (200 mg once daily for 6 days) to linezolid (600 mg twice daily for 10 days) in patients with ABSSSI.[7,8]
- Because of the absence of head-to-head data comparing tedizolid with agents other than linezolid, we conducted a systematic review and developed a network meta-analysis (NMA) to compare the relative effectiveness of tedizolid with that of other antibacterials approved for treating MRSA-associated ABSSSI.

METHODS

Systematic Review

- A systematic review was conducted according to the principles established in the Centre for Reviews and Dissemination (CRD)[9] and National Institute for Health and Care Excellence (NICE) guidance.[10]
  - A literature search was conducted in 10 relevant databases of research: MEDLINE, EMBASE, Science Citation Index Expanded (SCI-EXPANDED), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database, ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), and metaRegister of Controlled Trials (mRCT). The initial search was not limited by date range or language.
  - Search records were assessed for relevance on the basis of the title and abstract by one reviewer, and checked by a second reviewer; any disagreements were discussed with a third reviewer.

Eligibility Criteria

- Randomized, controlled trials (RCTs) of any size and duration
- Studies published in English that evaluated tedizolid, vancomycin, linezolid, daptomycin, teicoplanin, tigecycline, ceftaroline, or telavancin for the treatment of ABSSSI in adults with suspected or documented MRSA-associated ABSSSI, complicated skin and soft tissue infections (cSSTI), or complicated skin and skin structure infections (cSSSI)
  - Because ABSSSI is a definition proposed by the FDA in 2010, trials conducted before that year were conducted using the cSSSI or cSSTI terminology. For the purposes of these analyses, ABSSSI, cSSTI, and cSSSI are considered equivalent.
- Studies that assessed combination treatments were excluded from the analysis.

Outcomes of Interest

- Clinical response (defined by all but 1 trial as resolution or improvement in key clinical symptoms or a cessation of infection spread) at (1) early assessment (48-72 hours after the first dose), (2) end of treatment (within 48 hours of the final dose), and (3) post-therapy evaluation (PTE)/test of cure (TOC) (1 to 3 weeks following treatment)
- Rates of gastrointestinal events, nephrotoxicity, hepatotoxicity, and neurotoxicity (including optic neuropathy)
- Rates of adverse events (AEs) as defined by the author
- Discontinuation due to AEs
  - For the purpose of these analyses, it was assumed that AEs were defined similarly across studies.
- Recurrence of infections and antibacterial resistance
- Sustained response as defined by the author

Network Meta-analysis (NMA)

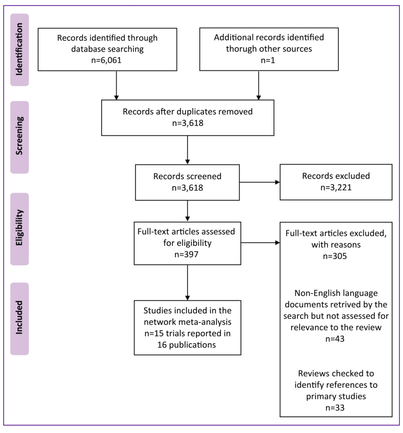
- Networks were developed based on similarity in study design, outcome measures, and available data according to guidance from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force and the Australian Pharmaceutical Benefits Advisory Committee (PBAC) on best practice for the conduct of indirect and mixed treatment comparisons.
- The following outcomes were selected as priorities for the NMA: clinical response at early assessment (48-72 hours after the first dose of study medication), end of treatment (EOT), and PTE or test of cure (TOC); AEs leading to discontinuation; and nephrotoxicity.
- Standard Bayesian methodology for NMA was applied for all outcomes using fixed and random effects models.
  - Because of the limited information available to estimate the between-study variance, only results for the fixed effect models are presented.
- For each outcome, the NMA synthesized the results across studies to give overall estimates of the odds ratios (ORs) and 95% credible interval (CrI) for each pair of treatments within the network.
- All analyses were conducted using WinBUGS version 1.4.3 and R version 3.1.1 software. The package R2WinBUGS was used to run WinBUGS from within R.[13]

RESULTS

Systematic Review

- Of 6,061 identified records, 3,618 non-duplicate studies were assessed for relevance. Of these, 397 reports were further assessed for relevance against the pre-defined criteria. Fifteen trials met the inclusion criteria for the systematic review and NMA (**Figure 1**).
  - Of these 15 trials, 7 were open-label, 3 were single blind, 4 were double blind, and 1 trial did not report blinding.
- Across the 15 eligible trials, similar treatment time periods were assessed, and the follow-up time was generally similar for the EOT and end-of-study time points.

Figure 1. Flow Chart for the Systematic Review and Network Meta-analysis



Network Meta-analysis

- The following networks were explored, when possible, for each outcome:
  - All trials: a network of all trials that reported data for the particular outcome (if data were reported for multiple populations, those for the intention-to-treat [ITT] population were used).
  - ITT/modified ITT (mITT): a network that included only trials that reported data for the ITT or mITT (only patients who received treatment, had evidence of disease criteria, or had a positive pathogen screening at baseline).
  - MRSA only: a network with only trials reporting data for patients or subgroups of patients with confirmed MRSA.
- The interventions and outcomes assessed in the 15 eligible RCTs included in the NMA are presented in **Table 1**.
  - Networks varied depending on the data available in each trial, and none of the networks included all 15 trials.
  - The following outcomes had connected networks and were selected for analysis in the NMA: clinical response at EOT and PTE/TOC and AEs leading to discontinuation.
  - Only 2 trials reported data for early clinical response and trials reporting data for rates of nephrotoxicity did not share a common treatment arm. Therefore, no networks were developed for these outcomes.
  - The proportion of patients with cellulitis, wound infection, abscess, other types of infections, and confirmed MRSA varied among trials.

Table 1. Summary of Treatments Assessed in Each Trial and the Networks Possible for Analyses

	Treatments								Outcomes Assessed (Network)					
Study Reference	Tedizolid	Tigecycline	Ceftaroline	Teicoplanin	Linezolid	Vancomycin	Daptomycin	Telavancin	Clinical Response at EOT (all trials)	Clinical response at EOT (ITT/mITT)	Clinical response at PTE/TOC (all trials)	Clinical response at PTE/TOC (ITT/mITT)	Clinical response at EOT/PTE/TOC (MRSA only)[a]	Discontinuation due to AE (all trials)
Aikawa 2013						X	X				X	X	X	X
Evers 2013							X	X			X	X		
Florescu 2008		X				X					X	X	X	
Itani 2010					X	X			X	X	X	X	X	
Kohno 2007					X	X			X		X		X	
Lin 2008					X	X			X		X			
Moran 2014	X				X				X	X	X	X		X
Pertel 2009						X	X				X	X		X
Prokocimer 2013	X				X				X	X	X	X	X	X
Sharpe 2005					X	X					X	X	X	
Stevens 2002					X	X					X	X	X	
Stryjewski 2008						X		X			X	X	X	X
Talbot 2007			X			X			X		X	X		X
Weigelt 2005					X	X					X	X		X
Wilcox 2004				X	X				X	X				

AE, adverse event; EOT, end of treatment; ITT, intention-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; mITT, modified intention-to-treat; PTE, post-therapy evaluation; TOC, test of cure.
[a]An additional post-hoc analysis of the MRSA-only population was conducted that included a study (Corey 2010) that compared ceftaroline to combination treatment with vancomycin and aztreonam for the clinical response at PTE/TOC.

Clinical Response at End of Treatment

- **Table 2** shows the results for clinical response at EOT for tedizolid versus each of the comparator treatments for the all-trials and ITT/mITT networks.
- Based on the network that includes all of the trials, the results suggest that tedizolid is superior to vancomycin with respect to clinical response rate at EOT (OR: 1.7 [95% CrI: 1.0, 3.0]) (**Table 2**).
- There was no evidence of a difference between tedizolid and any of the other comparators (**Table 2**).

Table 2. Fixed Effect Model Comparing Tedizolid with Comparators[a] with Respect to Clinical Response at End of Treatment: All-trials and ITT/mITT Networks

	Odds Ratio, Tedizolid versus Comparator Drug (95% Credible Interval[a])						
Network	Ceftaroline	Daptomycin	Linezolid	Teicoplanin	Telavancin	Tigecycline	Vancomycin
All trials	0.7 (0.0, 30.6)	–	1.0 (0.7, 1.3)	2.2 (0.6, 9.0)	–	–	1.7 (1.0, 3.0)
ITT/mITT	–	–	1.0 (0.7, 1.3)	2.2 (0.6, 9.0)	–	–	1.5 (0.8, 2.6)

ITT, intention-to-treat; mITT, modified intention-to-treat.
[a]95% credible interval that is above 1 is in favor of tedizolid.

Clinical Response at Post-therapy Evaluation or Test of Cure

- The NMA for clinical response at PTE/TOC included all 6 comparator antibacterials in the all-trials and ITT/mITT networks and 5 comparator drugs in the MRSA-only network (**Table 3**).
- The odds of a clinical response at the PTE/TOC were higher for tedizolid compared with vancomycin in the all-trials and ITT/mITT networks (OR: 1.6 [95% CrI: 1.1, 2.5]) (**Table 3**).
- There was no evidence of a difference between tedizolid and any of the other comparators (**Table 3**).
- A post-hoc analysis of clinical response at PTE/TOC in the MRSA-only network included an additional study that assessed ceftaroline versus combination treatment with vancomycin and aztreonam (this study was excluded per the eligibility criteria in the original analysis).
  - In this post-hoc analysis, no difference was seen between tedizolid and comparator treatments.

Table 3. Fixed Effect Model Comparing Tedizolid with Comparators with Respect to Clinical Response at Post-therapy Evaluation or Test of Cure: All-trials, ITT/mITT Networks, and MRSA Only Networks

	Odds Ratio, Tedizolid versus Comparator Drug (95% Credible Interval[a])					
Network	Ceftaroline	Daptomycin	Linezolid	Telavancin	Tigecycline	Vancomycin
All trials	1.0 (0.3, 3.5)	1.4 (0.5, 3.8)	1.0 (0.7, 1.4)	1.4 (0.9, 2.3)	3.2 (0.8, 16.9)	1.6 (1.1, 2.5)
ITT/mITT	1.0 (0.3, 3.5)	1.4 (0.5, 3.8)	1.0 (0.7, 1.4)	1.4 (0.9, 2.3)	3.2 (0.8, 16.7)	1.6 (1.1, 2.5)
MRSA only	–	2.1 (0.4, 13.4)	1.0 (0.4, 2.3)	1.1 (0.4, 3.0)	3.2 (0.7, 20.0)	1.6 (0.7, 4.0)

ITT, intention-to-treat; mITT, modified intention-to-treat, NMA, network meta-analysis.
[a]95% credible interval that is above 1 is in favor of tedizolid.
Post-hoc analysis results of clinical response at post-therapy evaluation or test of cure for the MRSA-only network were similar (data not shown).

Discontinuation due to Adverse Events

- When considering data from all trials, there was no evidence of a difference between tedizolid and any of the other comparators tedizolid with respect to the rate of discontinuation due to AEs (**Table 4**).

Table 4. Fixed Effect Model Comparing Tedizolid with Comparators with Respect to Discontinuation due to Adverse Events: All Trials Network

	Odds Ratio, Tedizolid versus Comparator Drug (95% Credible Interval[a])				
Network	Ceftaroline	Daptomycin	Linezolid	Telavancin	Vancomycin
All trials	0.3 (0.0, 7.1)	0.8 (0.0, 45.8)	0.5 (0.1, 1.9)	0.3 (0.1, 1.3)	0.4 (0.1, 1.8)

Teicoplanin and tigecycline were not included in the all trials analysis.

LIMITATIONS

- This model assumed that the varying definitions of ABSSSI, cSSTI, and cSSSI were equivalent.
- The variety in population characteristics, degrees of blinding, and trial definition of confirmed MRSA among the trials presented a source of heterogeneity for this model.
- The included trials differed in their definition of clinical response and adverse events.
- This model included clinical response outcomes at EOT for a limited number of comparator antibacterials.

CONCLUSIONS

- Tedizolid was superior to vancomycin and equivalent to linezolid for clinical response at EOT.
- No difference in odds of clinical response at EOT and PTE/TOC between tedizolid and other comparators were observed.
- Tedizolid was found to be equivalent to all comparators when evaluating discontinuation due to AEs.
- These NMA results suggest that tedizolid may provide an alternative treatment option for the treatment of ABSSSI caused by suspected or documented MRSA.

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