Systematic Review and Meta-Analysis

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The efficacy and safety of omadacycline in treatment of acute bacterial infection

A systemic review and meta-analysis of randomized controlled trials

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Abstract

Background: This study aims to assess the clinical efficacy and safety of omadacycline for the treatment of acute bacterial infections in adult patients through meta-analysis.

Methods: PubMed, Embase, ClinicalTrials.gov, and Cochrane databases were searched up to May 2019. Only randomized controlled trials (RCTs) that evaluated omadacycline and other comparators for treating acute bacterial infections in adult patients were included. The primary outcome was the clinical response rate at the posttreatment evaluation, whereas the secondary outcomes were risk of an adverse event (AE) and mortality.

Results: Four RCTs were included. Overall, omadacycline had a clinical response rate noninferior to comparators in the treatment of acute bacterial infection in the modified intent-to-treat population (odds ratio [OR], 1.31; 95% confidence interval [CI], 1.04–1.65; I^2 = 0%) and in the clinically evaluable population (OR, 1.53; 95% CI, 1.11–2.11; I^2 = 0%). Furthermore, no significant differences were found between omadacycline and comparators for the risk of treatment-emergent AEs (OR, 1.13; 95% CI, 0.60–2.14; I^2 = 93%), treatment-related AEs (OR, 0.70; 95% CI, 0.46–1.04; I^2 = 56%), serious AEs (OR, 1.01; 95% CI, 0.64–1.58; I^2 = 0%), and discontinuation of study drug due to an AE (OR, 0.78; 95% CI, 0.47–1.29; I^2 = 0%). However, in the clinical trial, NCT02877927, in which omadacycline was used in only oral form, the reported incidence of nausea and vomiting were 30.2% (111/368) and 16.9% (62/368), respectively. Finally, the mortality rate was similar between omadacycline and comparator in the treatment of acute bacterial infection (OR, 1.32; 95% CI, 0.47–3.67; I^2 = 0%).

Conclusion: The clinical efficacy of omadacycline is not inferior to that of comparators in the treatment of acute bacterial infections in adult patients, and this antibiotic is also well tolerated.

Abbreviations: ABSSSI = acute bacterial skin and skin structure infection, AE = adverse event, CABP = community-acquired bacterial pneumonia, CE = clinically evaluable, MITT = modified intent-to-treat, MRSA = methicillin-resistant *Staphylococcus aureus*, RCT = randomized controlled trial.

Keywords: omadacycline, acute bacterial infection, complicated skin and skin structure infection, community-acquired bacterial pneumonia

1. Introduction

Omadacycline is a new aminomethylcycline, a semisynthetic compound derived from tetracycline class.[1] Like older tetracyclines, omadacycline exhibits activity against a broad spectrum of bacteria, including gram-positive, gram-negative, anaerobic, and atypical pathogens.[2–8] More, omadacycline has the additional advantage than older tetracyclines that it remains active against antibiotic-resistant bacteria carrying the major efflux and target protection resistance determinants.[9,10] In the global surveillance investigations,[2–5,8,10,11] omadacycline exhibits potent in vitro activity against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, penicillin-resistant *S pneumoniae*, and extended-spectrum β-lactamase-producing Enterobacteriaceae. Recently, several randomized trials have assessed the clinical efficacy and safety of omadacycline for treating acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP) in adult patients.[12–15] However, an updated meta-analysis comparing the efficacy and safety of omadacycline and other comparators for the treatment of acute bacterial infection in adult patients is lacking.

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Therefore, we conducted this meta-analysis to provide a real-time evidence on the efficacy and safety of omadacycline in adult patients with acute bacterial infection.

2. Methods

2.1. Study search and selection

All clinical studies were identified through a systematic review of the literature in PubMed, Embase, ClinicalTrials.gov, and Cochrane databases until May 2019 using the following search terms: "omadacycline," "Nuzyra," and "PTK-0796." Only randomized controlled studies that compared the clinical efficacy and adverse effects of omadacycline and other comparators in the treatment of adult patients with acute bacterial infections were included. All languages of publication could be included. However, we excluded articles if they were in vitro studies or pharmacokinetic–pharmacodynamic assessment. Two reviewers (SHL and SPC) searched and examined publications independently to avoid bias. Any disagreement was resolved and decided by a 3rd reviewer (Lai). The following data were extracted from all the included studies: authorship, year of publication, study design, countries, antibiotic regimens of omadacycline and comparators, outcomes, and adverse events (AEs). The modified intent-to-treat (MITT) population consisted of all patients in the ITT population who had a confirmed diagnosis in accordance with the study protocol criteria. The clinically evaluable (CE) population included patients from the MITT population who had a qualifying infection as per the criteria for trial entry, received a trial drug, did not receive any antibacterial agent not assigned within the trial that could confound interpretation of the results, and had an assessment of outcome during the protocol-defined window. The microbiologically evaluable population included patients in the CE population from whom at least 1 bacterial pathogen was isolated from blood or infected tissue at baseline. For evaluating safety, the ITT population that included all patients who received any amount of intravenous study drug was used. The ethical approval was not necessary for meta-analysis in our institute.

2.2. Definitions and outcomes

The primary outcome was investigator-assessed clinical response at the posttreatment evaluation (7–14 days after the last dose of a trial drug) in the MITT and the CE population, and clinical response was defined as the resolution of clinical signs and symptoms of acute bacterial infection, or improvement to the extent that no further antimicrobial therapy was necessary. Secondary outcomes included early clinical responses, the risk of AEs, including treatment-emergent AEs (TEAEs), treatment-related AEs, serious AEs, and discontinuation because of AEs and mortality.

2.3. Data analysis

This study used the Cochrane Risk of Bias Assessment tool to assess the quality of enrolled randomized controlled trials (RCTs) and the risk of bias.[16] Statistical analyses were conducted using the software Review Manager, version 5.3. The degree of heterogeneity was evaluated with the Q statistic generated from the Chi-squared test. The proportion of statistical heterogeneity was assessed using the I^2 measure. Heterogeneity was considered significant when the P was $<.10$ or I^2 was $>50\%$. The random-effect model was used when data were significantly heterogeneous, and the fixed-effect model was used when data were homogenous. Pooled odds ratio (OR) and 95% confidence intervals (CIs) were calculated for outcome analyses.

3. Results

3.1. Study selection and characteristics

The search program yielded 172 references. After excluding 69 duplications, the remaining 103 abstracts were screened. Among them, we retrieved ten articles for full-text review. Finally, 4 studies[12–15] fulfilling the inclusion criteria were included in this meta-analysis (Fig. 1). All studies[12–15] were randomized, multicenter studies designed to compare the clinical efficacy and safety of omadacycline with other comparators for adult patients with acute bacterial infection (Table 1). All studies[12–15] were multicenter, and 2 studies[13,14] were multinational. Three studies[12,13,15] focused on ABSSSIs, in which linezolid was the comparator and 1 study[14] focused on CABP in which moxifloxacin was the comparator. Except 1 study[15] comparing oral omadacycline and linezolid, 3 studies[12–14] focused on the initially intravenous, injection of omadacycline, and comparators. However, the antibiotics used in these RCTs are not 1st-line antibiotics commonly used to treat SSTIs. Almost all the domains in each study were classified as having a low risk of bias (Fig. 2).

3.2. Clinical efficacy

Overall, omadacycline had a clinical response rate in MITT population not inferior to comparators in the treatment of acute bacterial infection (OR, 1.31; 95% CI, 1.04–1.65; $I^2=0\%$; Fig. 3) in the pooled analysis of 4 studies.[12–15] In the CE population, omadacycline remained noninferior to comparators in terms of clinical response rate in the pooled analysis of five studies (OR, 1.53; 95% CI, 1.11–2.11; $I^2=0\%$). The noninferiority of omadacycline remained the same in sensitivity test after randomly excluding individual study. In the subgroup analysis of patients with ABSSSIs, omadacycline exhibited noninferior clinical response rate to linezolid among both MITT and CE populations (MITT populations, OR, 1.35; 95% CI, 1.02–1.77; $I^2=28\%$. CE population, OR, 1.60; 95% CI, 1.08–2.38; $I^2=0\%$). According to different type of ABSSSIs, no significant difference regarding clinical response rate was observed between omadacycline and linezolid in terms of major abscess (OR, 1.44; 95% CI, 060–3.49; $I^2=52\%$), wound infection (OR, 2.02; 95% CI, 0.26–15.96; $I^2=53\%$) and cellulitis (OR, 1.83; 95% CI, 0.83–4.07). Among overall ME population, no significant difference was observed between omadacycline and comparator in the pooled analysis of 3 studies[12–14] (OR, 1.71; 95% CI, 0.97–3.03; $I^2=3\%$). The similar trend between omadacycline and comparator was noted for treating infection with *S aureus* (OR, 1.06; 95% CI, 0.62–1.83; $I^2=0\%$), and MRSA (OR, 0.95; 95% CI, 0.38–2.34; $I^2=0\%$).

3.3. Adverse events

No significant differences were found between omadacycline and comparators for the risk of TEAEs (OR, 1.13; 95% CI, 0.60–2.14; $I^2=93\%$), treatment-related AEs (OR, 0.70; 95% CI, 0.46–1.04; $I^2=56\%$), serious AEs (OR, 1.01; 95% CI, 0.64–1.58; $I^2=0\%$), and discontinuation of study drug due to an AE (OR, 0.78; 95% CI, 0.47–1.29; $I^2=0\%$) (Fig. 4). Regarding common AEs,

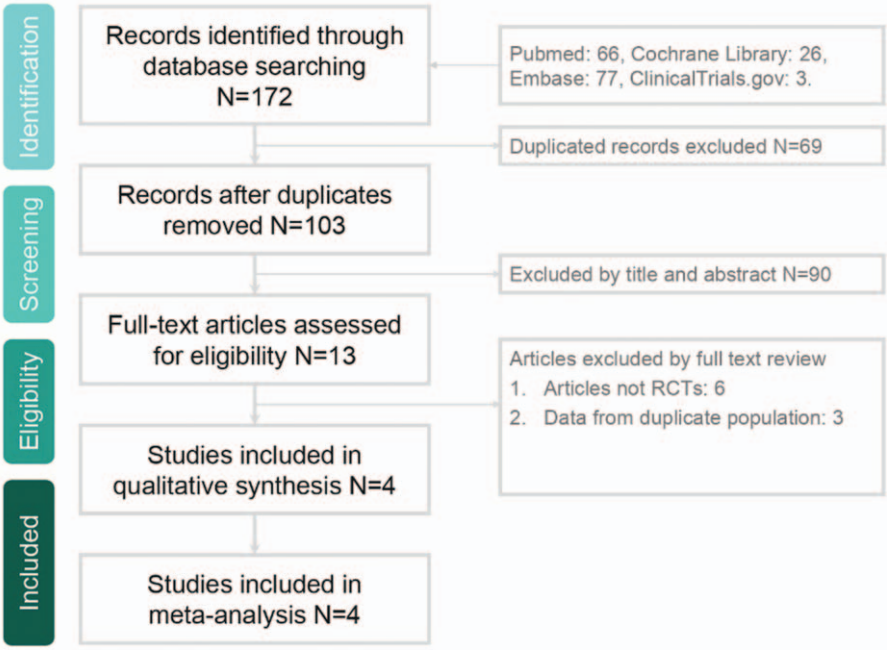

Figure 1. Study selection process flow.

no significant difference was observed between omadacycline and comparators in terms of nausea (OR, 1.51; 95% CI, 0.52–4.40; $I^2=92\%$), vomiting (OR, 2.04; 95% CI, 0.75–5.59; $I^2=81\%$), diarrhea (OR, 0.51; 95% CI, 0.16–1.60; $I^2=79\%$), constipation (OR, 1.38; 95% CI, 0.66–2.88; $I^2=0\%$), and headache (OR, 1.08; 95% CI, 0.67–1.74; $I^2=0\%$). Finally, the mortality rate was similar between omadacycline and comparator in the treatment of acute bacterial infection (OR, 1.32; 95% CI, 0.47–3.67; $I^2=0\%$).

4. Discussion

This 1st meta-analysis based on 4 RCTs found that the clinical efficacy of omadacycline was not inferior to that of other comparators in the treatment of patients with acute bacterial infection. First, the overall pooled clinical response rate of omadacycline in treating acute bacterial infections including ABSSSI and CABP was 86.2% in MITT population and 93.0% in CE population, and it was not inferior than that of comparator (82.7% in MITT population and 89.6% in CE population). Second, pooled clinical response rate of omadacycline for treating ABSSSI in this meta-analysis was also not inferior to that of linezolid in both MITT and CE population. Third, in the subgroup analysis of different type of ABSSSI and pathogens, omadacycline exhibited the clinical response rate similar to linezolid. Finally, the mortality of patients with acute bacterial infection treated with omadacycline was only 0.84%, which was not significantly different from that seen in comparators (0.65%).

Table 1

Characteristics of included studies.

Study, published year	Study design	Study site	Study period	Type of infection	No of patients		Dose regimen	
					Omadacycline	Comparator	Omadacycline	Comparator
Noel et al, 2012	Randomized, controlled, evaluator-blinded study	11 sites in the United States	2007–2008	Complicated skin and skin structure infection	118	116	100 mg qd (iv)	Linezolid 600 mg q12h (iv) ± aztreonam (iv)
O'Riordan et al, 2019	Double blind, randomized controlled trial	55 sites in the United States, Peru, South Africa and Europe	2015–2016	Acute bacterial skin and skin-structure infection	323	322	100 mg q12h × 2 doses then 100 mg qd (iv)	Linezolid 600 mg q12h (iv)
Stets et al, 2019	Double blind, randomized controlled trial	86 sites in Europe, North America, South America, the Middle East, Africa, and Asia	2015–2017	Community-acquired pneumonia in PSI risk II, III, or IV	386	388	100 mg q12h × 2 doses then 100 mg qd (iv)	Moxifloxacin 400 mg (iv)
NCT02877927	Double blind, randomized controlled trial	Multicenter in the United States	May 2017–June 2017	Acute bacterial skin and skin-structure infection	368	367	450 mg qd × 2 doses then 300 mg qd (oral)	Linezolid 600 mg q12h (oral)

iv = intravenous, PSI = pneumonia severity risk.

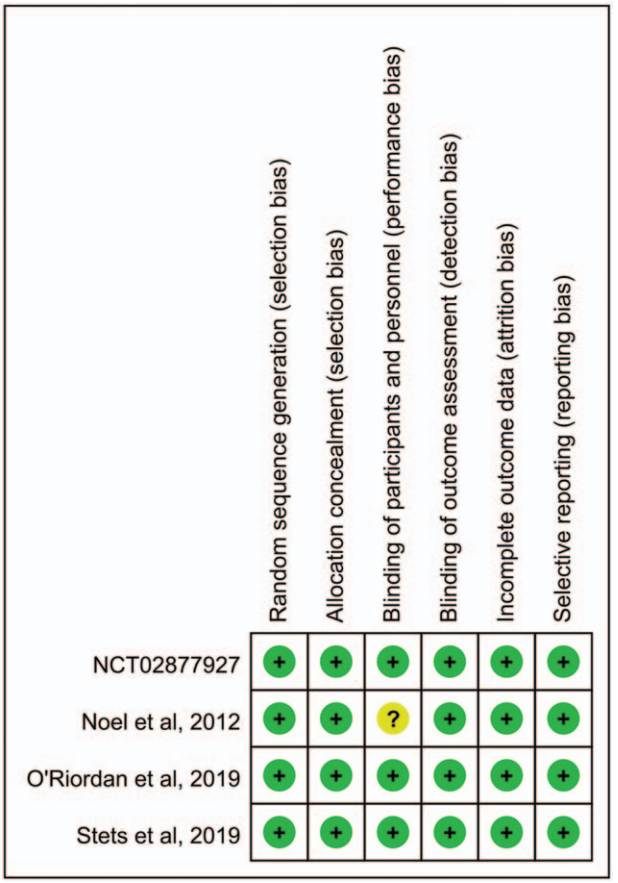

Figure 2. Risk of bias per study and domain.

In summary, all these findings indicated that omadacycline can be an effective therapeutic option in the treatment of acute bacterial infection, particularly ABSSSI.

The effectiveness of omadacycline in the treatment of acute bacterial infections including ABSSSI and CABP in adult patients can be supported by in vitro studies. In a global surveillance[3] of 69,246 clinical isolates during 2010 and 2011, 99.9% of *S aureus* isolates, including MRSA were inhibited by 2 mg/dL of omadacycline, and its potencies were comparable for *Streptococcus pneumoniae* ($MIC_{50/90}$ 0.06/0.06 mg/dL), and viridans streptococci ($MIC_{50/90}$ 0.06/0.12 mg/dL). In addition, omadacycline remains active against commonly encountered Enterobacteriaceae, including *Escherichia coli* ($MIC_{50/90}$ 0.5/2 mg/dL), *Klebsiella* spp ($MIC_{50/90}$ 1/4 mg/dL), and *Citrobacter* spp ($MIC_{50/90}$ 1/4 mg/dL). Another surveillance[17] of 14,000 clinical isolates from the United States and Europe during 2017 demonstrated similar findings that 96.5% of MRSA, 99.8% of methicillin-susceptible *S aureus*, 98.6% of *S pneumoniae*, ≥97.7% of other *Streptococcus* spp, 99.8% of *Hemophilus influenzae*, 99.1% of *E coli*, 87.5% of *K pneumoniae* can be inhibited by omadacycline. Overall, the potent in vitro activity of omadacycline against clinical isolates, including MRSA, can help explained the great in vivo clinical response in this meta-analysis.

In addition to clinical efficacy, we should consider AE risk while prescribing omadacycline. Nausea, vomiting, and headache were the most common AEs, and the overall incidence of these AEs was comparable with comparators. However, in the clinical trial, NCT02877927,[15] in which omadacycline was used in only oral form, the reported incidence of nausea and vomiting could be up to 30.2% (111/368) and 16.9% (62/368), respectively. In addition to these common AEs, the pooled risks of TEAEs, treatment-related AEs, and serious AEs were similar between omadacycline and comparators. Finally, no significant difference was observed between omadacycline and comparators in terms of discontinuation of the study drug due to an AE. Therefore, the findings of this meta-analysis suggest that omadacycline is as safe as other comparators in the treatment of acute bacterial infection.

This study has several limitations. Only 4 RCTs were considered in this meta-analysis, and only 2 types of acute bacterial infections, ABSSSI and CABP, were included. Fortunately, 2 additional trials[15,18] aim to investigate the efficacy of omadacycline in the clinical setting of acute pyelonephritis and cystitis are ongoing. We can obtain more data to analyze after these trials are completed in the near future. In addition, this study did not assess the cost effect; however, it should be an important issue in the use of novel antibiotics.

In conclusion, omadacycline is as good as comparators in terms of efficacy and tolerance in the treatment of acute bacterial infection in adult patients. Thus, omadacycline is an appropriate option for antibiotic therapy in adult patients with acute bacterial infection.

Author contributions

Conceptualization: Shao-Huan Lan, Shen-Peng Chang, Chih-Cheng Lai, Chien-Ming Chao.

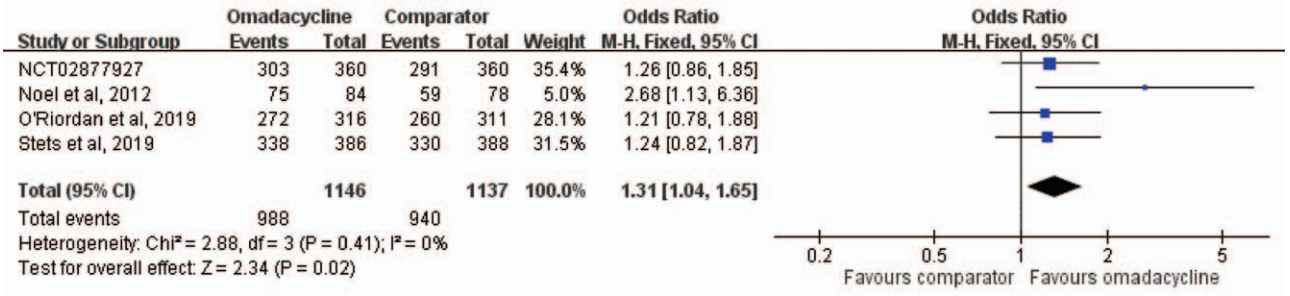

Figure 3. Overall clinical response rates for omadacycline and comparators in the treatment of acute bacterial infections. CI = confidence interval.

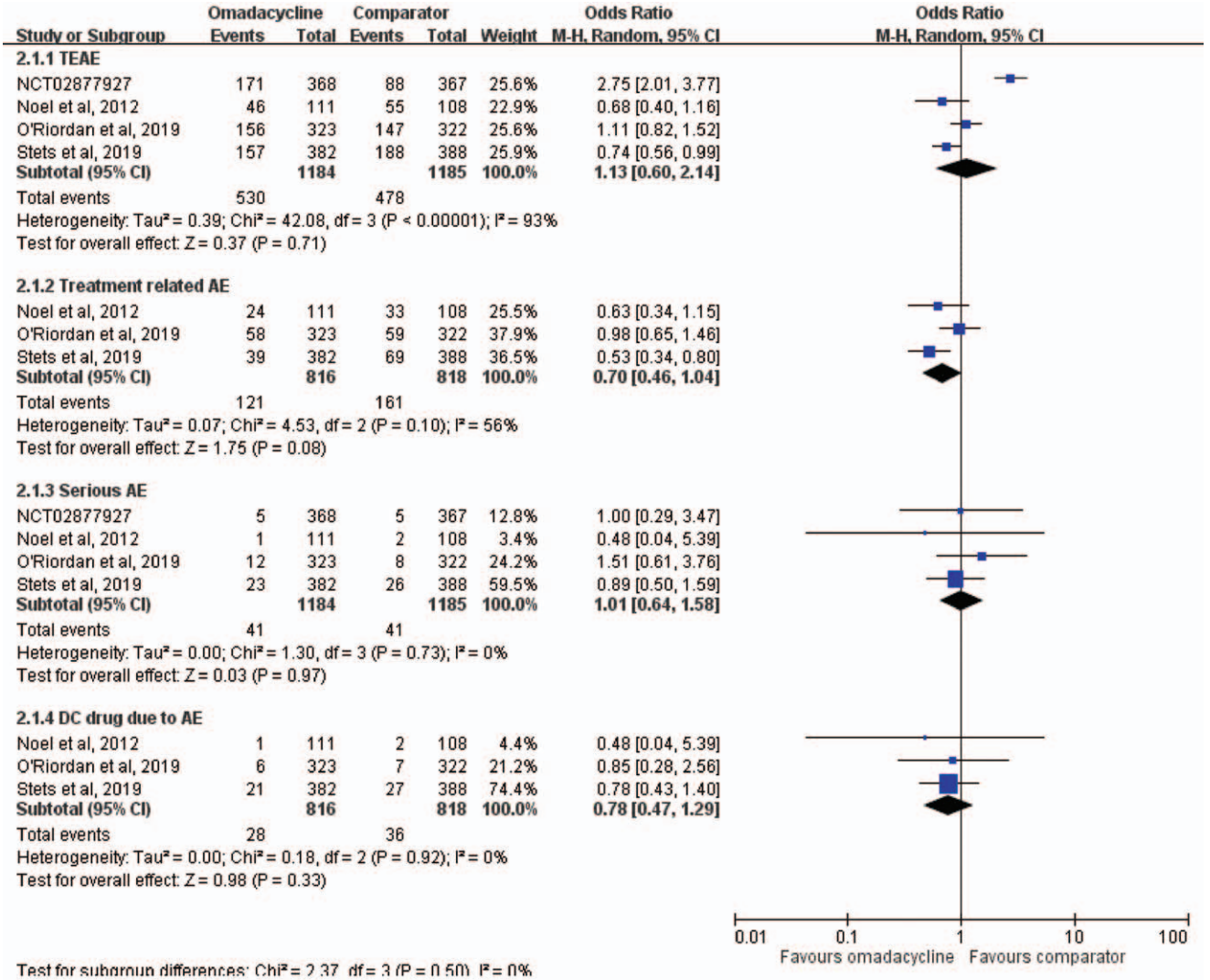

Figure 4. Adverse event risks with omadacycline and comparators in the treatment of acute bacterial infections. AE = adverse event, CI = confidence interval, TEAEs = treatment-emergent AEs.

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Formal analysis: Shao-Huan Lan, Shen-Peng Chang, Li-Chin Lu.
Writing – original draft: Chih-Cheng Lai.
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