Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis

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CRD summary
The review found that tigecycline was no more effective than standard antimicrobial regimens for treating serious complicated infections and was associated with a higher rate of adverse effects, especially vomiting and nausea. The review was generally well conducted and these conclusions appear reliable.

Authors' objectives
To assess the safety and efficacy of tigecycline for treating adults with serious bacterial infection.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, ISRCTN, Nederlands Trial Register, UMIN-CTR, ANZCTR, ClinicalTrials.gov and Clinical Study Results Database were searched to March 2011 without language restrictions. Reference lists of retrieved articles were checked. Database search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared clinical efficacy, safety and eradication efficiency of tigecycline versus other antimicrobial agents for bacterial infection were eligible for inclusion. The primary outcome was treatment success (cure or significant improvement in the clinically assessable population). Secondary outcomes included treatment success in the microbiologically assessable population, eradication of pathogens, adverse events, discontinuation of treatment due to adverse effects and all-cause mortality.

The mean age of participants in the included studies was 37 to 60 years. About 65% were male. Most were white. Diagnoses included complicated skin and skin structure infections, complicated intra-abdominal infection, community- or hospital-acquired pneumonia and diabetic foot infection. Tigecycline was usually given as a loading dose of 100mgs followed by 50mgs over 12 hours. A wide range of antibiotics were used as comparators, usually given in combination (such as imipenem plus cilastatin). Duration of treatment ranged from two to 28 days. Time to test of cure was from seven to 92 days. Infections were as defined in the primary studies; definitions were fairly consistent across the studies. The primary studies excluded participants with known or suspected drug resistance. All studies were multicentred and nearly all were pharmaceutical industry funded.

Two reviewers independently selected the studies.

Assessment of study quality
The aspects of study validity assessed in the published RCTs were: clearly described sequence generation; allocation concealment; blinding; completeness of outcome data and avoidance of selective outcome reporting; and discussion of other potential sources of bias. Points were awarded for each of these according to a modified Jadad score. Studies that scored 3 points or more were deemed to be high quality. Unpublished studies were not assessed for quality as information on study design was not available.

The authors did not state how many reviewers conducted the assessment. [A: The authors have clarified that this assessment was performed in duplicate.]

Data extraction
Odds ratios (ORs) were extracted for each outcome in each study. The population used for each analysis varied according to the type of outcome (as detailed in the review) and included the modified intention-to-treat population (mITT) (those who received at least one dose of study drug and were followed up by intention-to-treat), the clinically assessable mITT population and the subset of that population who were microbiologically assessable. Drug manufacturers were contacted to obtain the results of unpublished studies. Primary study authors were not contacted due to time constraints.

Two reviewers independently extracted the data. Disagreements resolved by discussion with a third reviewer.
Methods of synthesis
The data were combined in a random-effects model to calculate pooled odds ratios (ORs) and 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the Q and I² statistics. Substantial heterogeneity was explored with a Galbraith plot to identify potential outliers. Subgroup and sensitivity analyses were conducted to examine the effects of pathogen, infection type, comparator drug (for adverse events) and exclusion of outliers. Meta-regression was used to explore the effects of treatment duration, time to test-of-cure assessment and study quality using median values or ranges to estimate means if necessary. Publication bias was assessed using funnel plots and the Arcsine Thompson test.

Results of the review
Fourteen RCTs (7,409 participants, range 101 to 1,061) were included in the meta-analysis. Ten RCTs (5,375 participants) were published and four (2,034 participants) were unpublished. The median quality score in the 10 published RCTs was 3 (range 3 to 5) and six RCTs scored at least 3 points out of 5. Eight RCTs were double blinded.

In the clinically assessable mITT population there was no significant difference in treatment success between tigecycline and other antibiotics (OR 0.87, 95% CI 0.74 to 1.02; 14 RCTs, 5,642 participants; I²=0%). In the (larger) mITT population, treatment success was significantly less likely in the tigecycline group (OR 0.82, 95% CI 0.73 to 0.93; 11 RCTs, 6,053 participants; I²=0%). There was no significant difference between the groups in the rate of eradication of individual pathogens. The findings of subgroup and sensitivity analyses did not differ significantly from the main findings for the clinically assessable mITT population.

Tigecycline was associated with a higher rate of total adverse events (OR 1.45, 95% CI 1.11 to 1.88; 11 RCTs, 6,078 participants; I²=79%), vomiting (OR 3.35, 95% CI 2.12 to 5.30; 13 RCTs, 7,004 participants; I²=84%), nausea (OR 3.06, 95% CI 2.02 to 4.63; 13 RCTs, 7,004 participants; I²=87%) and discontinuation due to adverse events (OR 1.48, 95% CI 1.17 to 1.88; 11 RCTs, 6,158 participants; I²=5%). There was no significant difference between the groups for rates of diarrhoea (OR 1.05, 95% CI 0.82 to 1.35; 12 RCTs; I²=49%) and all-cause mortality (OR 1.28, 95% CI 0.97 to 1.69; 12 RCTs; I²=0%). Heterogeneity was high (I²≥75%) for several of the analyses of adverse events. The findings of Galbraith plots and the effects of excluding outlying studies were discussed in the review. No evidence of publication bias was found.

Authors' conclusions
Tigecycline was no more effective than standard antimicrobial regimens for treating serious complicated infections and was associated with a higher rate of adverse effects, especially vomiting and nausea.

CRD commentary
The objectives and inclusion criteria of the review were clear and relevant sources were searched for published and unpublished studies in any language. Formal tests showed no evidence of publication bias. Steps were taken to limit the risk of reviewer bias in the process of study selection and data extraction; it was not stated clearly whether quality assessment was undertaken in duplicate. Relevant methods were used to assess the quality of the published studies but few details were reported about the quality of individual studies.

There was marked clinical heterogeneity between the primary studies. Statistical heterogeneity was absent or low for efficacy outcomes. Appropriate methods were used to combine data, assess heterogeneity and explore differences between studies. The authors noted that the review was limited by incomplete data for some outcomes and failure to contact primary authors for missing data.

The review was generally well conducted and the authors' conclusions appear reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated a need for more RCTs to compare tigecycline with other treatments for different types of infection, RCTs should assess the efficacy of tigecycline for treating infections caused by multidrug-resistant bacteria and assessment with unpublished studies was required in order to make decisions about new drugs.

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