Efficacy and safety of tigecycline: a systematic review and meta-analysis

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CRD summary
The authors concluded that clinicians should avoid tigecycline monotherapy as treatment for severe infections and reserve it as a last resort. More trials investigating combination regimens including tigecycline were required. Limited patient information made it difficult to ascertain the wider applicability of the findings. Based on the findings presented, the authors’ conclusions appear to be reliable.

Authors’ objectives
To compare tigecycline versus any antibiotic regimen for the treatment of any infection.

Searching
PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and Latin American and Caribbean Health Sciences Literature (LILACS) were searched; search terms were reported. No language or date restrictions were imposed. The last search was conducted in September 2010 (dates of other searches not reported). Grey and unpublished literature were identified through searches of: reference lists of all included studies; relevant conference proceedings; new drug application documents of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) databases; trial registries and ongoing trial databases; communication with authors; and sponsoring pharmaceutical companies of the included studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared tigecycline versus any other antibiotic regimen for treatment of any infection among adults or children. The primary outcome was overall 30 day mortality. Secondary outcomes included: clinical failure (defined in individual studies); microbiological failure (per patient and per isolate); superinfections and bacterial superinfections; development of resistant pathogens; and pre-specified adverse events.

Included trials were industry-sponsored and multicentre. Trials compared tigecycline versus one or two antibiotic regimens for treatment of one infection type. The three most commonly investigated infection types were complicated intra-abdominal infections, complicated skin and skin structure infections, and community acquired pneumonia. Some trials administered additional antibiotics alongside tigecycline to complement infection coverage (range 3.4% to 39.6% of trial populations). Overall mortality data were only available at the end of follow-up. Secondary outcomes reported included: clinical failure for the clinically modified intention-to-treat and clinically evaluable populations; microbiological failure per patient and per isolate; and adverse events. All the drugs were administered intravenously. All daily doses of tigecycline totaled 150mg.

The studies were screened and selected for inclusion by two independent reviewers.

Assessment of study quality
Risk of bias was assessed using the domains suggested by the Cochrane handbook: allocation sequence generation and allocation concealment; blinding; incomplete outcome data assessment; selective outcome reporting; early stopping of the trial; and extreme baseline imbalance. Allocation sequence generation and concealment were graded as low, high or unknown risks of bias according to the Cochrane handbook grading criteria.

The authors did not state how quality assessment was conducted.

Data extraction
Outcomes (rates of overall mortality, clinical failures, microbiological failures, and adverse events by end of follow-up) were extracted from the trials to calculate relative risks (RRs) for the comparisons, with 95% confidence intervals (CIs). If mortality data were unavailable, the reviewers utilised the result data reported by the FDA after confirming the trial data through the trial registry and relevant conference proceedings. Data were extracted from the largest patient population for all outcomes (further details reported in the review).
Two reviewers independently performed data extraction; the process for resolving any disagreements was not reported.

**Methods of synthesis**
The relative risks representing the overall mortality rates of the trials were pooled using a Mantel-Haenszel fixed-effects model to provide a summary relative risk with a 95% confidence interval. This analysis was subgrouped according to infection type. Heterogeneity was assessed using $\chi^2$ and $I^2$.

For mortality and clinical failure data, subgroup analyses were planned for bacteraemic patients, patients with Gram-negative infection, and for those with APACHE II scores exceeding 15. A funnel plot was constructed to assess small-trial effects for mortality data.

The effect of risk of bias on outcomes was planned to be assessed by sensitivity analyses of individual trial components for: mean age; weight; mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score; and proportion of the trial population with co-morbidities prior antibiotic failure, a baseline resistant pathogen, bacteraemia or an APACHE II score of 15 or more).

A series of subgroup and sensitivity analyses were performed for microbiological failure and adverse events; further details are reported in the review.

**Results of the review**
Fifteen trials were included in the review and meta-analysis (7,654 patients). Mean treatment duration ranged from 8.5 to 17.5 days; mean follow-up times ranged from 12 or more days to 51 days.

Quality assessment revealed low risk of bias for allocation generation in seven trials, and low risk of allocation concealment in five trials; risks of bias for these two domains were unknown in all other trials. Eleven trials reported double-blinding and four trials were open-label. Twelve trials had protocols available, demonstrating similar primary outcomes in the protocol and publication. The remaining three trials either did not have available protocols, or did not report the primary outcome in the protocol.

Overall mortality at end of follow-up with tigecycline was statistically significantly higher compared with other antibiotic regimens (RR 1.29, 95% CI 1.02 to 1.64; $I^2=0\%$). Similar findings were shown across all types of infection, but without statistical significance. The funnel plot for overall mortality demonstrated a small-studies effect (Egger's regression intercept, two-tailed $p=0.018$).

Clinical failure rates at the end of follow-up were statistically significantly higher among the clinically modified intention-to-treat population (RR 1.16, 95% CI 1.06 to 1.27; $I^2=0\%$) and the clinically-evaluable population (RR 1.13, 95% CI 1.01 to 1.27; $I^2=20\%$) (population descriptions reported in the review). Microbiological failure rates at end of follow-up were statistically significantly higher with tigecycline than the comparator drugs per patient (RR 1.13, 95% CI 0.99 to 1.30, unsubstantial heterogeneity: $I^2$ value not reported) and per isolate (RR 1.11, 95% CI 0.97 to 1.27, $I^2=67\%$).

Adverse events were more commonly reported with tigecycline than with the comparator drugs (RR 1.11, 95% CI 1.08 to 1.14; substantial heterogeneity, $I^2$ value not reported); this finding was statistically significant.

Sensitivity analyses for overall mortality and clinical failure demonstrated no statistically significant difference between trials with low risk of bias and all other trials (results reported in review). Due to unavailability of data, the planned subgroup analyses for overall mortality were not performed. Results from the subgroup and sensitivity analyses of the secondary outcome data were reported.

**Authors' conclusions**
The authors concluded that clinicians should avoid tigecycline monotherapy as treatment for severe infections and reserve it as a last resort. RCTs investigating combination regimens including tigecycline were required.

**CRD commentary**
The review question and inclusion criteria were clear. The search included attempts to identify grey literature; some of
the included trials had only been published as conference abstracts. Publication bias was unlikely, even though a small-studies effect was demonstrated by a funnel plot of the mortality data. No date or language restrictions were imposed during the search, which reduced the likelihood of time preferences and language bias. Screening and data extraction were performed independently by two reviewers, which reduced the risk of reviewer bias; it was unclear whether quality assessment was performed independently.

The included trials were assessed for risk of bias using the Cochrane domain-based tool and results were reported. Trials judged as having low risk of bias were explored by sensitivity analyses for overall mortality and clinical failure; findings were statistically similar to results of the main analyses. Meta-analysis of overall mortality data was categorised according to infection type and appeared appropriate. No heterogeneity was indicated in the subgroup meta-analyses, although limited patient information from the individual trial meant that it was difficult to judge the appropriateness of pooling and generalisability of the main findings.

Based on the findings presented, the authors' conclusions appear to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that clinicians should avoid tigecycline monotherapy as a treatment for severe infections and prescribe it only as a last resort.

**Research:** The authors stated that further RCTs were required to investigate combination regimens that include tigecycline.

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