


Research letters

**Journal of Antimicrobial Chemotherapy**
doi:10.1093/jac/dkp342

Advance publication 16 September 2009

**Off-label use of antibiotics in hospitalized patients: focus on tigecycline**

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Keywords: randomized clinical trials, APACHE II, intensive care units

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Sir,

Tigecycline is the first of a new class of antibiotics named glycylcyclines and is active *in vitro* against a variety of Gram-positive and Gram-negative organisms, including vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamase-producing *Enterobacteriaceae* and multidrug-resistant (MDR) *Acinetobacter* spp. 

It has been approved by the US FDA for the treatment of complicated intra-abdominal infections (cIAIs), complicated skin and skin structure infections (cSSSIs) and community-acquired bacterial pneumonia (CABP).

Notwithstanding these indications, tigecycline’s pharmacological and microbiological profiles encourage physicians’ use of the drug for off-label indications.

The definition of off-label use is not limited to prescribing an antibiotic for an indication that is not approved by regulatory authorities. The off-label use of a medication may include other parameters such as age, severity of illness, dose and route of administration and drug combinations, among others.

Taking this into consideration, we have evaluated some characteristics of a group of patients treated with tigecycline for the approved indications (cSSSIs, cIAIs and CABP) and compared them with the patients included in the randomized clinical trials (RCTs) developed by the pharmaceutical company for each indication.

Between 16 September 2007 and 11 May 2009, I developed the LatinUser Project (Latin America Tigecycline Initial Use Registry), which included patients treated with tigecycline in 21 institutions from Argentina, Chile, Colombia and Ecuador.

Patients were eligible for the LatinUser Project if they received tigecycline for ≥72 h and were not part of a clinical trial.

For the present analysis, patients who received tigecycline for approved indications (cSSSIs, cIAIs and CABP) were extracted from the LatinUser database. The following data were analysed for each patient: and compared with those from the RCTs for each indication (cSSSIs, cIAIs and CABP) (Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA): (i) admission setting [general ward or intensive care unit (ICU)]; (ii) severity of illness at admission [measured by the APACHE II (Acute Physiology and Chronic Health Evaluation II) score]; (iii) source of infection; (iv) previous and concurrent antibiotic therapy (defined as a patient who received at least one dose of another
antibiotic before or during the treatment with tigecycline, respectively); and (v) clinical success at the end of treatment [defined as cure (complete resolution of signs and symptoms) or improvement (partial resolution)].

The institutions participating in the LatinUser Project reported a total of 209 patients. Only 66 of them (31.6%) received tigecycline for approved indications (cSSSIs, n = 38, 18.2%; cIAIs, n = 18, 8.6%; and CABP, n = 10, 4.8%). Fifty-six patients (84.8%) were admitted to an ICU. The mean APACHE II score at admission was 14.5 (range 10–30). In patients with CABP the mean CURB-65 score was 4 (range 2–4). Among patients with cSSSIs and cIAIs, 64.3% of infections were nosocomial infections (36/56).

All patients received previous antibiotic therapy; in 57.6% of cases for ≥3 days (38/66). Vancomycin, carbapenems (imipenem or meropenem) and piperacillin/tazobactam, alone or in combination, were the most frequent antibiotics previously used (60.6% of patients, 40/66).

Tigecycline and a concurrent antibiotic were used in 22 patients (33%). The most common concurrent antibiotics were anti-pseudomonal agents [carbapenems (imipenem or meropenem), broad-spectrum cephalosporins and ciprofloxacin]; 72.7% of patients, 16/22. Overall, attending physicians reported clinical success in 50 patients (75.8%; range 64%–86%); the comparison between our data and the data from the RCTs is shown in Table 1.

While off-label prescribing is not illegal, and may sometimes be clinically appropriate, it does, however, raise a number of clinical, safety and ethical issues. Off-label use can be justified if there is sufficient evidence (e.g. in vitro activity, pharmacodynamics and well-designed observational studies) to suggest an overall reasonable risk–benefit ratio for a given clinical context.

I have demonstrated in two sequential studies that the off-label use of tigecycline in Argentina is frequent (79% and 78% of total prescriptions), especially in ventilator-associated pneumonia due to MDR Acinetobacter spp.3,4

Considering the approved indications, we found that when tigecycline was used in cIAIs, cSSSIs and CABP, patients showed characteristics very different from those of patients included in the RCTs. Most of them had: (i) nosocomial infections and required hospitalization in an ICU (data not described in the RCTs); (ii) higher values of severity score index (APACHE II, CURB-65); and (iii) a high percentage of previous antibiotic use for ≥3 days and concurrent antibiotic use in one-third of patients (both conditions were a criterion for patient exclusion in the RCTs).

By definition, my patients have received tigecycline for approved indications, but, in most of them, within parameters of off-label use.

In summary, although RCTs are used extensively to characterize the efficacy and safety of new treatment options, the characteristics of the trial participants often do not reflect those of the wider patient population. In most cases, one or more patient subgroups (whether defined by severity of illness, source of infection, or previous and concomitant medication) would be under-represented.

Acknowledgements
I acknowledge Karen Todel for manuscript translation and development.

Funding
No funding of any kind has been received by the author.

Transparency declarations
D. C. is speaker of Wyeth Laboratories Argentina for Tygacil®.

References
2. Wyeth. FDA Approves New Indication for Wyeth’s TYGACIL (tigecycline) for the Treatment of Adult Patients with Community-Acquired

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<td>Admission to ICU</td>
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cSSSIs, complicated skin and skin structure infections; cIAIs, complicated intra-abdominal infections; CABP, community-acquired bacterial pneumonia; RCT, randomized clinical trial (Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA); ICU, intensive care unit; NA, not available; EC, exclusion criteria by protocol.
aClinically evaluable patients.
bMicrobiologically evaluable patients.
cAt admission.
dModified intent-to-treat population.
eExcluding CABP patients.
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