**Increased Mortality Related to Tigecycline (Tygacil®)**

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On 9/1/2010, the U.S. Food and Drug Administration (FDA) notified healthcare professionals of a finding of increased all-cause mortality across Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparators. The report of increased mortality was noted to be most apparent in patients treated for hospital-acquired pneumonia (HAP), particularly VAP.[1,2] Due to the increased risk of all cause mortality, clinicians must weigh the risk and benefit of the use of tigecycline and consider the use of other agents.[1] However, a role for tigecycline still exists, particularly in patients with multidrug resistant (MDR) pathogens where a limited number of effective antibiotics are available.

In a pooled analysis of all 13 Phase 3 and 4 trials of tigecycline vs. comparators; vancomycin plus aztreonam for complicated skin and skin structure infection (cSSSI); vancomycin or linezolid for resistant pathogens (RP); imipenem for complicated intra-abdominal infections (cIAI) and hospital acquired pneumonia [including ventilator associated pneumonia (VAP)]; levofloxacin for community acquired pneumonia (CAP); and ertapenem for diabetic foot infection (DFI)[1,2], death occurred in 4.0% (150/3788) of patients receiving tigecycline compared with 3.0% (110/3646) of patients receiving other antibiotics, with an adjusted risk difference of all-cause mortality of 0.6% (95% CI 0.1, 1.2), Table 1.[1,2]

| Patients with outcome of death by infection type[1] | | | | | | |
|---|---|---|---|---|---|---|
| **Infection** | | **Tigecycline** | | **Comparator** | | **Risk difference** |
| | | **n/N** | **%** | **n/N** | **%** | **% (95% CI)** |
| cSSSI | | 12/834 | 1.4 | 6/813 | 0.7 | 0.7 (-0.3-1.7) |
| cIAI | | 42/1382 | 3 | 31/1393 | 2.2 | 0.8 (-0.4-2) |
| CAP | | 12/424 | 2.8 | 11/422 | 2.6 | 0.2(-2-2.4) |
| HAP | Non-VAP | 66/467 | 14.1 | 57/467 | 12.2 | 1.9 (-2.4-6.3) |
| | VAP | 25/131 | 19.1 | 15/122 | 12.3 | 6.8 (-2.1-15.7) |
| RP | | 11/128 | 8.6 | 2/43 | 4.7 | 3.9 (-4-11.9) |
| DFI | | 7/553 | 1.3 | 3/508 | 0.6 | 0.7 (-0.5-1.8) |
| Overall adjusted | | 150/3788 | 4 | 110/3646 | 3 | 0.6 (0.1-1.2) |
| RP = resistant gram positive pathogens, namely vancomycin resistant enterococci (VRE) and methicillin resistant *Staphylococcus aureus* (MRSA); DFI = with or without osteomyelitis | | | | | | |

Unpublished data reported to the FDA noted increased mortality and lower cure rates in patients with HAP treated with tigecycline. Lower cure rates were particularly observed among patients with VAP who were treated with tigecycline versus a comparator; 47.9% vs. 70.1%. Mortality was also greater in tigecycline treated VAP patients; 25/131 (19.1%) vs. 15/122 (12.3%). Particularly high mortality was seen among patients with VAP and associated bacteremia [9/18 (50.0%) vs. 1/13 (7.7%)].[1,2]

The cause of this increased mortality is yet to be determined. Possible explanations offered by the FDA included progression of the underlying infection, patient related factors such as underlying co-morbidities or difference in complication rates, but there are concerns the difference in mortality may be related to the pharmacokinetic properties of the drug.[1] Tigecycline is a glycylcycline, a tetracycline like-class antibiotic and thus is a bacteriostatic agent (inhibits the growth of bacteria as opposed to

killing the organisms). While tigecycline has excellent tissue penetration, it also has very low plasma concentrations, suggesting it may not be an ideal agent for treatment of bacteremia or other endovascular infections.[2]

Tigecycline is currently approved for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired pneumonia. It has activity against susceptible gram positive bacteria, anaerobes, *Mycobacterium abscessus* and *Mycobacterium fortuitum*, and gram negative organisms, but is not active against *Pseudomonas aeruginosa, Proteus spp. Providencia spp,* and *Morganella morganii*.[1,2] A labeling change has been updated for tigecycline to reflect this new finding of increased mortality.[2] Due to the increased risk of all-cause mortality in patients with certain severe infections, clinicians should consider alternative intravenous antibiotics.[1]

References


1. Food and Drug Administration. Drug Safety Announcement-Tigecycline. Available at http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm. Accessed 9/1/10
2. Tygacil® (tigecycline) Prescribing Information, Pfizer Pharmaceuticals Inc.


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