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Original Research Article

A retrospective observational study of the impact of Tigecycline in treating multidrug resistant pneumonia

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ABSTRACT

Background: Few antimicrobials are currently active to treat extensively drug resistant (XDR) gram-negative bacilli infections. This represents a serious global public health concern. Critically ill patients face the brunt of majority of these infections. Tigecycline has coverage for a majority of these XDR infections (with the exception of *Pseudomonas aeruginosa*), but is not currently approved for hospital-acquired pneumonia. Nevertheless it is being commonly used for this indication though many meta-analysis have suggested an increased risk of death in patients receiving this antibiotic.
Methods: In this retrospective analysis we compared the mortality rates between a Tigecycline based and a non Tigecycline based therapy for XDR infections in the critically ill over a period of 12 months. A total of 93 patients were included in the study.
Results: Tigecycline group had significantly increased risk for in hospital mortality with an odds ratio of 6.0 and 95% CI of 1.37 to 26.12 with a p value of 0.01. But such a difference was not evident in 14 day mortality.
Conclusions: Initiation of Tigecycline for multidrug resistant, pneumonia needs to be re-thought. Only a small percentage of patients with pneumonia with *in-vitro* sensitivity having low minimum inhibitory concentration (MIC) would benefit from the drug. Even in this group the risk of increased mortality needs to be carefully considered before Initiation of therapy.

Keywords: Hospital acquired, Pneumonia, Resistant, Tigecycline

INTRODUCTION

The growing impact of multidrug resistance has led to an increased need for newer antibiotics in the critically ill patients. The lack of research for developing new antibiotics makes future gloomy. Currently, few therapeutic options remain for extensively drug resistant (XDR) gram negative infections in the critically ill. Colistimethate sodium (Colistin) based mono/combination therapy is the regimen remaining for many a clinical scenario. But colistin monotherapy is associated with nephrotoxicity and possible reinfection.

Study of experimental models has shown synergy of colistin and agents like rifampicin, fosfomycin etc.[1-3] Although these studies show better microbiological response with combination therapy, clinical cure and mortality remains unaffected.

Tigecycline is another drug which is commonly prescribed for resistant organisms. It is the first of a novel class of minocycline derivatives known as glycylcyclines. It has broad spectrum coverage of aerobic and anaerobic gram positive and gram negative bacilli. Only notable exceptions are *Proteus* and *Pseudomonas* showing in vitro resistance.[4]

Tigecycline is licensed for use in complex skin and soft tissue infection and abdominal infections. But XDR organisms like *Acinetobacter* are infrequently responsible for the approved indications of Tigecycline. Off - label use of Tigecycline have met with much controversy. One benefit which is often cited is the potential prevention of re-emergence of infection when colistin is combined with Tigecycline. But this has not yet been substantiated.

The approved standard dose of Tigecycline is an intravenous loading dose of 100 mg followed by 50 mg twice daily. Tigecycline has a large volume of distribution and serum maximum concentration (C max) has found to rarely cross 0.87 mg/dl.[5] With the above standard dose, many clinical studies have noted poor outcome of patients treated with gram negative bacteraemia.[6]

The Food and Drug Administration (FDA) have issued boxed warning in both 2010 and 2013 for its use citing independent increase in mortality rates citing unknown reasons. Many studies have since been published both supporting and refuting the FDA warning.

This formed the basis for a retrospective analysis to evaluate the mortality rate of critically ill pneumonia patients getting treated with the standard dose of Tigecycline.

METHODS

We conducted a retrospective, chart based observational study in mixed adult intensive care units i.e. medical, neurology, surgical non -cardiac and neurosurgery critical care units of a tertiary care teaching Hospital in India. Patients admitted to the hospital having HAP or VAP due to gram negative bacilli between November 2015 to October 2016 were Included. Institutional Ethical committee review was not taken due to the retrospective nature of the study and since anonymised patient data was collected.

Table 1: Patient demographics in the study groups.

Patient demographics	Tigecycline group	Non – Tigecycline group	P value
Number of patients 'n'	9	84	0.06
Male%	6 (66.6%)	75 (89.2%)	0.05
Age in years (Mean ± SD)	65.5 ± 10.4	71.3 ± 6.7	0.42
Weight (kg) (Mean ± SD)	68.6 ± 20.3	71.8 ± 12.2	0.85
APACHE II score	19.9 ± 8.5	18.4 ± 7.5	0.44
14 day mortality (%)	2 (22.2%)	17 (20.23%)	0.09
In hospital mortality (%)	6 (66.67%)	21 (25%)	0.01

Table 2: MIC of Tigecycline in the study groups.

Organism	Sensitive (n)	MIC <1 mg/L	MIC =1 mg/L	MIC >1 mg/L and ≤4 mg/L
Acinetobacter Baumannii	64	13 (20.3%)	10 (15.6%)	41 (64%)
Klebsiella Pneumonia	29	1 (0.03%)	7 (24%)	21 (72.4%)
Total	93	14 (15%)	17 (18.2%)	62 (66.6%)

Table 3: MIC breakpoint values of Tigecycline.

	MIC breakpoint		MIC breakpoint	
Validating agency	For *Enterobacteriaceae*		For *Acinetobacter*	
	Sensitive	Resistant	Sensitive	Resistant
CLSI	Undetermined	Undetermined	Undetermined	Undetermined
FDA	≤2 mg/L	8	≤2 mg/L	8
EUCAST	1	2	Insufficient evidence	Insufficient evidence

Clinical and Laboratory Standards Institute (CLSI), Food and Drug Administration (FDA), European Committee on Antimicrobial Susceptibility Testing (EUCAST).

In addition to patient demographics and mortality, MIC levels of different XDR organisms in critically ill patients were collected (Table 1). A total of 93 cases were included during this study period in Figure 1.

HAP and VAP were defined as per Centre for Disease Control (CDC) guidelines. The study group included extensively drug resistant gram negative bacilli which were sensitive only to colistin and Tigecycline. A comparative study of patients harbouring XDR organisms who were treated with either Tigecycline or non Tigecycline based therapy was done. Patient demographics weight and disease severity were comparable between the groups. 14 day and in hospital mortality were compared between the groups.

The sensitivity and MIC levels of Tigecycline for *Enterobacteriaceae* and *Acinetobacter* were checked using the Vitek 2™ automated machine. The results and the treatment strategies were noted.

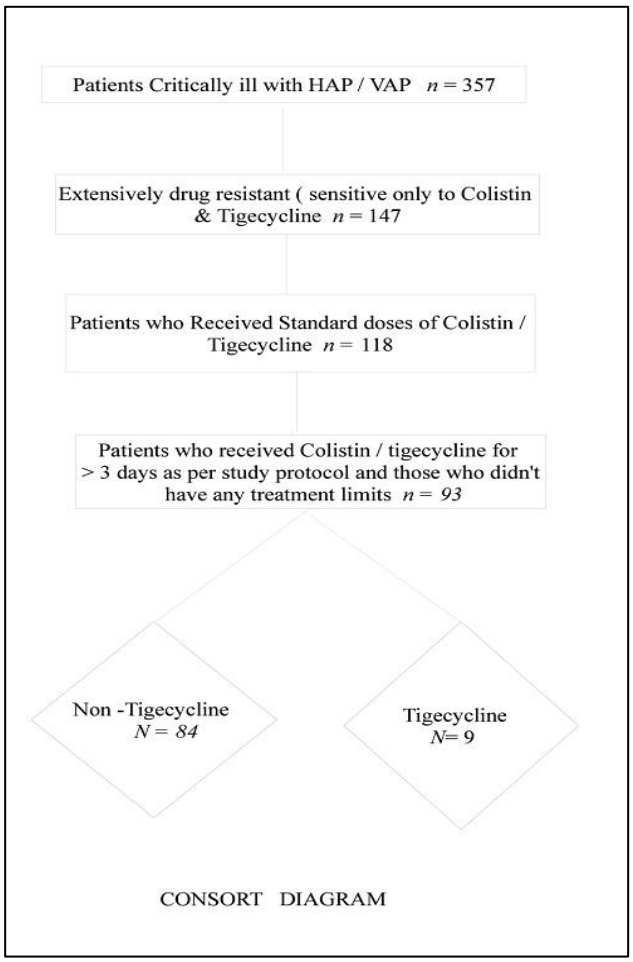

Figure 1: CONSORT diagram.

Primary outcomes

Comparison of 14 day mortality and in-hospital mortality between the two antimicrobial therapy group patients.

The patients who meet the following criteria were included in the study.

1) Patients aged 18 and above admitted in the critical care units.
2) HAP/VAP due to XDR gram negative bacilli-sensitive only to colistin and Tigecycline.
3) Treatment with antimicrobial regimen >72 hours - with drug dosages as per current recommendations.

Patients were excluded from the study if they met any of the following exclusion criteria.

1) Co-existence of other infections or polymicrobial infection
2) Pregnancy

Multidrug resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[7] Extensively drug resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories i.e. bacterial isolates remain susceptible to only one or two categories –in our case colistimethate sodium (colistin) and Tigecycline.[7]

Pan drug resistant (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories.[7] To ensure correct application of these definitions, bacterial isolates should be tested against all or nearly all of the antimicrobial agents within the antimicrobial categories and selective reporting and suppression of results should be avoided.

As per hospital policy, colistin and Tigecycline being reserve drugs, therapy with these drugs is started as per culture and sensitivity results with consensus from Clinical Microbiologists who are leading hospital infection control committee.

Statistical analysis was analysed using Medcalc clinical statistics software. The data with a non-normal distribution were assessed with Mann–Whitney test. Data with a normal distribution were assessed with the Student t-test. Categorical variables are presented as proportions and were analysed with the use of the Chi square test or Fisher exact test, as appropriate.

RESULTS

Of the total no of sensitive isolates, only 15% 0f the organisms had an MIC of <1 mg/L for Tigecycline. If the organisms with MIC levels ≤1 mg/L were considered, it included 33% 0f the organisms. Detailed sensitivity details of *Acinetobacter* and *Klebsiella* are shown in Table 2.

Patient demographics, 14 day mortality and in hospital mortality are detailed in Table 1. The two groups were matched in terms of disease severity and APACHE II score. Tigecycline group had a statistically significant increased risk for in hospital mortality, with an odds ratio of 6.0 and 95% CI of 1.37 to 26.12 and a p value of 0.01. Both groups had similar mortality risk at 14 days. The odds ratio was 1.12 with a 95% CI of 0.21 to 5.91 and a p value of 0.088.

DISCUSSION

HAP/VAP caused by all XDR organisms treated with Tigecycline appeared to have questionable therapeutic benefit since the isolates with favourable MIC values amounted to only a small percentage.

One possible explanation for the reduced therapeutic benefit of Tigecycline is that antibiotic concentrations in the extracellular fluid (ECF) in critically ill patients with

HAP or VAP may be more important than previously recognized. Burkhart et al have tested the alveolar endothelial lining fluid (ELF) concentration of Tigecycline after the standard dose in hospital acquired pneumonia (HAP).[8] The low levels (0.01 to 0.02 mg/L) would suggest that unless the MIC levels were <1 mg/L and the isolate is resistant to most other agents, the standard dosing of Tigecycline as antimicrobial therapy would be inappropriate.

It is likely that, at the recommended doses, these antibiotics do not achieve the desired pharmacodynamic targets when pharmacokinetic parameters are altered as occurs in critically ill patients.[9]

Tigecycline also needs higher area under curve (AUC)/MIC ratios for efficacy, possibly due to extracellular fluid leak in septic patients with HAP or VAP.[10] This change in lung exposure, in the presence of similar serum exposure, could explain a reduced response with Tigecycline.

In MDR infections, the experimental dose of twice the standard dose, i.e. 100 mg twice daily has yet to find evidence. Ramirez et al compared a higher dose regimen of Tigecycline in a phase two trial for HAP/VAP showing higher clinical efficacy for the higher dose group.[11] But since adequate numbers of patients were not enrolled, the results could not be statistically analysed to be significant. Furthermore, *Acinetobacter* was not an etiologic agent in the patient group.

Better success rates with a high dose regimen of Tigecycline in (loading dose 200 mg followed by 100 mg every 12 h) in severe infections due to MDR bacteria seems promising, but in these series Tigecycline was almost always administered in combination with other antimicrobials.[12]

In our study all the patients who were treated with Tigecycline had an MIC of 2 mg/L or more. The excess mortality in the Tigecycline-based treatment may be because the organisms isolated were of higher Tigecycline MICs (>1 mg/L).

Tigecycline has microbiological issues even after a decade of its introduction. Routine microbiological sensitivity tests like disc diffusion have shown major errors in estimating minimum inhibitory concentration (MIC) values for Tigecycline.[13] Zone diameter breakpoints are validated for E. coli only. For other *Enterobacteriaceae*, an MIC method is recommended. Thus the disk diffusion methods should either be confirmed with broth micro dilution or other automated methods should be used. Even in this regard serious discrepancies exist between MIC breakpoints by various agencies (Table 3).

Our study is limited by its small numbers, retrospective design, and the lack of any pharmacokinetic and pharmacodynamics data due to our inability to measure Tigecycline levels. Also in most cases, Tigecycline was administered with one or more other drugs which is a confounding factor.

Studies including a comprehensive PK/PD analysis of its role in a higher dose both alone and with other antibiotics may be warranted.

CONCLUSION

In the absence of consensus breakpoint criteria between different agencies for *Enterobacteriaceae* and *Acinetobacter baumannii*, blindly using Tigecycline for the treatment of multidrug resistant pneumonia showing in vitro susceptibility might be counterproductive. Only a fraction of patients with pneumonia having in-vitro sensitivity would benefit from the drug. Even in this group the risk of increased mortality needs to be carefully considered before Initiation of therapy.

A well-designed prospective clinical trial for comparing different antimicrobial treatment groups for XDR organisms especially in the critical care setting is clearly required.

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