Indications of a New Antibiotic in Clinical Practice: Results of the Tigecycline Initial Use Registry

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Tigecycline is the first of a new class of antibiotics named glycylcyclines and it was approved for the treatment of complicated intra-abdominal infections and complicated skin and skin structure infections. Notwithstanding this, tigecycline's pharmacological and microbiological profile which includes multidrug-resistant pathogens encourages physicians' use of the drug in other infections. We analyzed, during the first months after its launch, the tigecycline prescriptions for 113 patients in 12 institutions. Twenty-five patients (22%) received tigecycline for approved indications, and 88 (78%) for "off label" indications (56% with scientific support and 22% with limited or without any scientific support). The most frequent "off label" use was ventilator associated pneumonia (VAP) (63 patients). The etiology of infections was established in 105 patients (93%). MDR-*Acinetobacter* spp. was the microorganism most frequently isolated (50% of the cases). Overall, attending physicians reported clinical success in 86 of the 113 patients (76%). Our study shows that the "off label" use of tigecycline is frequent, especially in VAP. due to MDR-*Acinetobacter* spp., where the therapeutic options are limited (eg: colistin). Physicians must evaluate the benefits/risks of using this antibiotic for indications that lack rigorous scientific support.

Key-Words: Tigecycline, off-label, ventilator-associated pneumonia.

In, 2006 the Information System of Bacterial Resistance (SIR), which includes 27 centers from Argentina, published worrisome rates of nosocomial bacterial resistance: 50% of methicillin-resistant *Staphylococcus aureus* (MRSA), 50%-70% of *Klebsiella pneumoniae* resistant to third-generation cephalosporins, and 25% of *Pseudomonas aeruginosa* and 60% of *Acinetobacter* spp. carbapenem-resistant [1].

This increasing medical issue calls for a more effective solution by means of new antimicrobial agents, especially those with novel mechanisms of action and activity against multidrug-resistant (MDR) bacteria.

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 nosocomial resistant pathogens such as MRSA, extended spectrum β-lactamases (ESBLs)-producing Enterobacteriaceae (EB), and MDR-*Acinetobacter* spp [2].

It has been approved by the US Food and Drug Administration (FDA) for the treatment of complicated intra-abdominal infections (cIAI), and complicated skin and skin structure infections (cSSSI) [2]. Notwithstanding this, tigecycline's pharmacological and microbiological profiles encourage physicians' use of the drug in other infections caused by resistant pathogens featuring limited therapeutic options.

Considering this, we designed the Tigecycline Initial Use Registry (TIUR), a multicenter prospective observational study designed to characterize the indication types, pathogens, and outcomes of patients who were treated with tigecycline in 12 Argentinean institutions.

We hypothesized that a systematic analysis of tigecycline prescriptions in our country might help us understand the clinical outcomes of patients who were treated for indications other than cIAI and cSSSI.

Material and Methods

Study Design

The TIUR included patients treated with tigecycline from November 1, 2006 to March 31, 2007. Patients were eligible for the TIUR if they received at least one dose of tigecycline and were not part of a clinical trial.

Attending physicians collected, in an *ad hoc* case report form, the following patient's information: sex, age, admission setting (general ward or intensive care unit), infection type for which tigecycline was indicated, severity of illness at admission (measured by the Mortality Probability Model – MPM- II_0 score [3]), microbiological documentation, previous and concomitant antibiotic therapy -defined as a patient who received at least one dose of another antibiotic before or during the treatment with tigecycline, respectively- and clinical outcome to the tigecycline treatment.

To analyze the data, we divided the tigecycline indications into three categories: type I, labeled indications (cIAI and cSSSI); type II, not approved indications ("off label"), with pharmacological and microbiological evidence that the drug is useful for a particular indication (eg. community-acquired pneumonia and hospital-acquired pneumonia); and type III, "off label" indications with, up to the moment, insufficient data regarding that particular use of the drug (eg. bacteremia, osteomyelitis).

Study Population

The analysis was restricted to patients whose form had been accurately completed by their attending physicians.

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Outcome Assessment

The attending physician evaluated the patient's clinical response to therapy as: cure if the patient's resolution of signs and symptoms was such that no further antibiotic therapy was required; improved if a patient showed partial resolution of clinical signs and symptoms; failure if the patient had an inadequate response to therapy; and undetermined if no evaluation was possible for any reason (e.g. a patient who received tigecycline for less than 72 hs). Clinical success (CS) was defined as an outcome of cure or improved.

Statistics

Results are expressed as proportions and presented with their corresponding 95% confidence interval. When applicable, two tailed hypothesis testing for difference in proportions was used.

Results

Twelve institutions participating in the TIUR reported a total of 133 patients receiving at least one dose of tigecycline. The population under study consisted of 113 patients (84.9%). Twenty patients were excluded from the analysis because the case report form was not complete.

Only 25 patients (22%) received tigecycline for labeled indications (type I). Eighty- eight patients (78%) received tigecycline for "off label" indications (type II 56% -63/113- and type III 22% -25/113). The most frequent "off label" indication was ventilator-associated pneumonia (VAP) (100% of type II indications) (Table 1).

Patients' mean age was 58 years (range 17-93) without significant differences between indications. Sixty-two patients were male (55%) (Table 1).

Patients in the type-II indication group were admitted more frequently to intensive care unit (ICU) (98%) than those included in type I or III indication groups ($p<0.0001$); showing MPM-II_0 score values significantly higher than patients of type I and III indications (52 *vs.* 32 and 29 respectively, p=0.0001). The length of stay for patients with type III indications was significantly higher than for those with type I and II indications (57 days *vs.* 35 and 38 days respectively, p=0.05) (Table 1).

Of the 113 patients, 149 isolates were identified. MDR-*Acinetobacter* spp. (only susceptible to colistin and minocycline) was the microorganism most frequently isolated (50% of the cases) whose proportion rates were significantly higher in patients with type II indications (VAP) than in those with type I and III indications (p=0.0005) (Table 1).

There was no significant difference between the three indication groups regarding the proportion of patients with previous and concomitant antibiotic therapy (Table 1). Vancomycin, carbapenems (imipenem or meropenem) and piperacillin-tazobactam, alone or in combination, were the most frequent antibiotics previously used. The most common concomitant antibiotics were antipseudomonal antibiotics (colistin, carbapenems -imipenem or meropenem-, ceftazidime, amikacin and ciprofloxacin).

The evaluated patients received tigecycline (initial dose of 100mg and then 50mg every 12 h) for an average of 14 days (range 1-67). The median length of treatment for type III indications (21 days) was significantly higher than type I (15 days) and type II (11 days) indications (p=0.015) (Table 1).

Overall, attending physicians reported CS in 86 of the 113 patients (76%, range 68–84%). The CS rates observed in type I and III indications was significantly higher than in type II indications (88% and 84% *vs*. 66% respectively, p=0.032) (Table 2).

The clinical success rate showed no significant difference between the 82 patients with prior antibiotic therapy and 31 patients without such therapy (74% in both cases). In contrast, the success rate was markedly different in 35 patients with concomitant antibiotic therapy and 78 without such treatment (57% and 95% respectively, $p<0.00001$) (Table 2).

Global CS (76%) was not affected by the presence of MDR-*Acinetobacter* spp. (67%, range 56-77%), SAMR (68%, range 47-85%), or ESBLs-producing enterobacteria (81%, range 62-100%). Patients with VAP (100% of type II indications) due to MDR-*Acinetobacter* spp. showed a CS rate of 64% (range 52-75%).

In patients with CS, the median of duration of tigecycline therapy and the lengths of stay were 16 days and 42 days, respectively. Taking into account the different indications, patients with type III indications had a duration of treatment with tigecycline significantly longer than type I and type II indications (22 days *vs*. 15 and 12 days, respectively, p=0.015) (Table 2).

Global mortality proportion was 26.5% (30/113 patients). The crude mortality of type II indications was significantly higher than type I and III indications (38% -24/63- *vs*. 12% -3/25- and 12% -3/25- respectively, p=0.037).

Discussion

Our study (TIUR) provides information about how tigecycline was used in clinical practice during the first months after its commercialization in Argentina.

This analysis showed that tigecycline was commonly used for "off label" indications (78%), especially in patients admitted to ICU (78%) with VAP (56%) due to MDR-*Acinetobacter* spp. (61%).

"Off label" indication use is defined as prescribing the drug for an indication other than the one approved by regulatory authorities. The American Medical Association estimates that 40%-60% of all prescriptions in the United States are issued for drugs being used in a fashion other than their approved purpose with "off-label" prescribing being particularly common for infectious diseases [4].

The mere 22% use of tigecycline for labeled indications, in our country, could be based on the other effective and less expensive antibiotic treatment options which physicians have for treating cIAI[22] and cSSSI[23]. In contrast, ICU-physicians have the daily challenge of treating patients with VAP due to MDR-bacteria.

Table 1. Patient demographic and clinical characteristics.

Characteristics	Global	Indications		
		Type I	Type II	Type III
Number of patients, n (%)	113 (100)	25 (22) -cSSSI[1] 17 -cIAI[2] 8	63 (56) -VAP[3] 63	25 (22) -bacteremia 12 -osteomyelitis 4 -mediastinitis 2 -others 7
Age; mean years (range)	58 (17-93)	52 (19-93)	62 (17-89)	55 (29-79)
Male; n (%)	62 (55)	13 (52)[4]	37 (59)[5]	14 (54)[6]
ICU[7] location, n (%)	88 (78)	10 (40)[8]	62 (98)[9]	16 (64)[10]
MPM II_0[11], median (†)[12]	45 (38)	32 (14)[13]	52 (55)[14]	29 (11)[15]
LOS[16], median	41	35[17]	38[18]	57[19]
Isolates, n	149	37	82	30
-AB-MDR[20] (%)	74 (50)	12 (32)[21]	50 (61)[22]	12 (40)[23]
-MRSA[24] (%)	25 (17)	9 (24)	9 (11)	7 (23)
-ESBL-EB[25] (%)	21 (14)	7 (19)	10 (12)	4 (14)
-Others (%)	32 (19)	12 (25)	13 (18)	7 (23)
Prior ABX[26], n (%)	82 (72)	18 (72)[27]	42 (67)[28]	22 (88)[29]
Concomitant ABX, n (%)	35 (31)	9 (36)[30]	20 (32)[31]	6 (24)[32]
Tigecycline treatment, mean days	14	15[33]	11[34]	21[35]

[1]Skin and skin structure infections; [2]Intra-abdominal infections; [3]Ventilator-associated pneumonia; [4 *vs.* 5 *vs.* 6] No significant difference was found; [7]Intensive care unit; [8 *vs.* 9 and 10] p<0.0001; [11]Mortality probability model; [12]Mortality probability; [14 *vs.* 13 and 15] p=0.0001; [16]Length of stay; [18 *vs.* 17 and 19] p=0.05; [20]Multidrug-resistant *Acinetobacter* spp.; [22 *vs.* 21 and 23] p=0.0005; [24]Methicillin-resistant *S.aureus*; [25]Extended-spectrum β-lactamases-producing enterobacteriaceae; [26]Antibiotic; [27 *vs.* 28,*vs.* 29] No significant difference was found; [30 *vs.* 31,*vs.* 32] No significant difference was found; [35 *vs.* 33 and 34] p=0.015.

Table 2. Proportion of patients with clinical success (CS) criteria.

Characteristics	Global	Indications		
		Type I	Type II	Type III
All patients, CS/total (%)	86/113 (76)	22/25 (88)[1]	42/63 (66)[2]	21/25 (84)[3]
Prior ABX[4], CS/total (%)				
-Yes	61/82 (74)[5]	16/18 (89)	27/42 (64)	18/22 (82)
-No	24/31 (74)[6]	6/7 (87)	14/21 (68)	2/3 (66)
Concomitant ABX, CS/total (%)				
-Yes	20/35 (57)[7]	8/9 (89)	10/20 (50)	4/6 (66)
-No	74/78 (95)[8]	14/16 (87)	35/43 (82)	19/19 (100)
Isolates, CS/total (%)				
-AB-MDR[9]	50 (67)[12]	9 (75)	32 (64)	9 (75)
-MRSA[10]	17 (68)[13]	7 (77)	6 (66)	4 (57)
-ESBL-EB[11]	17 (81)[14]	7 (100)	7 (70)	3 (75)
-Others	23 (79)	9 (100)	8 (61)	6 (86)
Tigecycline treatment, mean days	16	15[15]	12[16]	22[17]

[1 and 3 *vs.* 2] p=0.032; [4]Antibiotic; [5 *vs.* 6] No significant difference was found; [7 *vs.* 8] p=< 0.00001; [9]Multidrug-resistant *Acinetobacter* spp.; [10]Methicillin-resistant *S.aureus*; [11]Extended-spectrum β-lactamases-producing enterobacteriaceae; [12 *vs.* 13 and 14] No significant difference was found; [17 *vs.* 15 and 16] p=0.015.

The high intrapulmonary concentration of tigecycline [5] as well as the prevalence in our study of VAP due to MDR-*Acinetobacter* spp. (61%), ESBL-producing EB (12%), and MRSA (11%) -all of them susceptible to tigecycline (at least *in vitro*)- seem to explain the reasons why physicians choose the drug to treat these patients. Furthermore, while VAP due to MRSA or ESBL-producing EB have other therapeutic options (linezolid [6] and carbapenems [7], respectively), VAP due to *Acinetobacter* spp. resistant to almost all groups of commercially available antimicrobials, creates a serious clinical problem [8]. Several studies, most of them with small samples, have shown good outcomes in patients with VAP due to MDR-*Acinetobacter* spp. treated with colistin [9], high-dose ampicillin-sulbactam [10], tetracyclines [11](doxycycline or minocycline) or aerosolized tobramycin [12]. However, the recorded clinical experience with these antibiotics is still limited

and the reported studies of their use in the treatment of VAP are not randomized controlled clinical trials. Tigecycline can thus be considered an alternative.

The proportion of global CS in our patients was 76%. Tigecycline´s CS proportion observed in patients with type I indications (88%) was similar to those reported in the phase III clinical trials (86.5% in cSSSI and 86.1% in cIAI) [2].

The administration of prior antibiotic therapy has not been associated with significant differences in the proportion of CS. In contrast, patients who received concomitant antibiotic treatment showed a CS rate significantly lower than patients who did not received concomitant antibiotic treatment (57% *vs*. 95%, respectively, p=0.05). These findings cannot be easily explained but the small sample size might be the reason behind this finding, and does not allow us to draw any definite conclusion.

The CS rate for patients with VAP was significantly less than the global rate -66%- (MDR-*Acinetobacter* spp. 64%, MRSA 66% and ESBL-producing EB 70%), reflecting a severity of illness significantly higher than that of the other indications. Ninety-eight percent (98%) of patients with VAP were in the ICU, as expected, and they had a mortality rate of 38%, less than that predicted by the MPM II_0 (55%). A possible explanation is that the MPM II_0 overestimates the mortality of patients who have probabilities of death of ≥ 40% [13]. In that sense, Heyland et al. [14] reported that in patients with VAP there is a 20% to 55% mortality rate which increases to 76% if the infection is caused by MDR pathogens, evidencing the fact that our data should be taken into account.

Adverse event and microbiological eradication data, was not specifically collected in our study.

In summary, "off label" use of tigecycline in Argentina is frequent especially in severe infections, such as VAP due to MDR-*Acinetobacter* spp., based on the pharmacological and microbiological profile of the drug.

Finally, we know that our study is not a rigorous trial with specific inclusion and exclusion criteria, close case monitoring and strict follow-up, however, the results obtained in this prospective observational study provide some initial evidence that tigecycline may be an acceptable option for indications that have not yet been approved.

Tigecycline Initial Use Registry Group

Members of the Tigecycline Initial Use Registry Group include Liliana Calanni. (Hospital Dr. Eduardo Castro Rendón, Neuquén, Argentina); Francisco Nacinovich (Instituto Cardiovascular de Buenos Aires e Instituto Medico de Alta Complejidad, Buenos Aires, Argentina); Martin Christin and Claudia Tosello (Instituto Medico de Alta Complejidad, Buenos Aires, Argentina); Marcelo del Castillo and Andrea Mora (FLENI Instituto de Investigaciones Dr.Raúl Carrea, Buenos Aires, Argentina); Jorge Calderón (Policlínico Neuquén, Neuquén, Argentina); Jorge Vergara (Hospital Ramos Mejía, Buenos Aires, Argentina); Walter Vázquez (Hospital Español, Mendoza, Argentina); Ana Colombini (Clínica San Camilo, Buenos Aires, Argentina); Pablo Bonvehí (CEMIC, Buenos Aires, Argentina); Paulo Chinchilla (Clínica Ciudad, Buenos Aires, Argentina); Laura Barcán (Hospital Italiano, Buenos Aires), Daniel Curcio and Francisco Fernández (Sanatorio San José, Buenos Aires, Argentina).

References

1. Quinteros M., Radice M., Famiglietti A., et al. Análisis de la sensibilidad a los antimicrobianos en los aislamientos de pacientes internados años 2004-2005. Boletín de la Asociación Argentina de Microbiología **2006**;172:13-6.
2. Pankey G.A. Tigecycline. J Antimicrob Chemother. **2005**;56(3):470-80
3. Lemeshow S., Teres D., Klar J., et al. Mortality probability models (MPM II) based on an international cohort of intensive care patients. JAMA **1993**;270:2478-86.
4. Pritchard R.H. Off-Label Uses of Approved Drugs: A New Compromise Is Needed, (March 25, **1999**) available at leda.law.harvard.edu/leda.
5. Conte J.E., Golden J.A., Kelly M.G., Zurlinden E. Steady-state serum and intrapulmonary pharmacokinetics and pharmacodynamics of tigecycline. Int J Antimicrob Agents **2005**;25(6):523-9.
6. Grau S., Alvarez-Lerma F., del Castillo A., et al. Cost-effectiveness analysis of the treatment of ventilator-associated pneumonia with linezolid or vancomycin in Spain. J Chemother **2005**;17(2):203-11.
7. Lorente L., Lorenzo L., Martin M., et al. Meropenem by continuous *versus* intermittent infusion in ventilator-associated pneumonia due to Gram-negative bacilli. Ann Pharmacother. **2006**;40(2):219-23.
8. Li J., Nation R.L., Turnidge J.D., et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infect Dis **2006**;6(9):589-601.
9. Kallel H., Hergafi L., Bahloul M., et al. Safety and efficacy of colistin compared with imipenem in the treatmentof ventilator-associated pneumonia: a matched case-control study. Intensive Care Med **2007**;33(7):1162-7.
10. Betrosian A.P., Frantzeskaki F., Xanthaki A., Georgiadis G. High-dose ampicillin-sulbactam as an alternative treatment of late-onset VAP from multidrug-resistant *Acinetobacter baumannii*. Scand J Infect Dis **2007**;39(1):38-43.
11. Wood G.C., Hanes S.D., Boucher B.A., et al. Tetracyclines for treating multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia. Intensive Care Med **2003**;29(11):2072-6.
12. Hallal A., Cohn S.M., Namias N., et al. Aerosolized tobramycin in the treatment of ventilator-associated pneumonia: a pilot study. Surg Infect (Larchmt) **2007**;8(1):73-82.
13. Rué M., Artigas A., Alvarez M., et al. Performance of the mortality probability models in assesing severity of iones during the first week in the intensive care unit. Crit Care Med **2000**;28(8):2819-24.
14. Heyland D.K., Cook D.J., Griffith L., et al. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. Am J Respir Crit Care Med **1999**;159(4 Pt 1):1249-56.