Readmissions Can Fall Along With Length of Stay

BY PATRICE WENDLING

CHICAGO — With hospitals under pressure to improve efficiency by reducing patient length of stay, findings from a new study suggest that this effort does not necessarily lead to increased readmission rates.

That's what Dr. Jorge Go and his colleagues at the Iowa City Veterans Affairs Medical Center found in an analysis of all 3,709,103 medical admissions to 129 VA hospitals from 1997 to 2007. Approximately 18% of patients (692,599) were excluded for reasons such as death, terminal cancer, or transfer to other facilities, leaving 3,016,504 patients for the final analysis.

Among patients in the analysis, 97% were male and 72% were white; the mean age was 65 years, and 46% had three to five comorbidities. Patients were stratified by five common conditions: heart failure, chronic obstructive pulmonary disease (COPD), acute myocardial infarction, community acquired pneumonia, and gastrointestinal hemorrhage.

During the 10-year interval, there was a 25% reduction in average length of stay (LOS) and a 7% reduction in hospital readmissions, Dr. Go reported at the annual meeting of the Society of Hospital Medicine.

The unadjusted mean LOS decreased significantly for all diagnoses, from 6 days in 1997 to 4.5 days in 2006-2007. The biggest reduction was in MI and pneumonia cases, with LOS dropping by 2 full days.

The unadjusted readmission rate also declined significantly for all diagnoses, from 13.9% in 1997 to 12.7% in 2007. The biggest decrease was in COPD patients (17.3% to 14.3%), while readmissions remained constant among those with GI hemorrhage.

"Decreasing LOS and readmissions seem to reflect secular trends—that we're providing more efficient and better care," Dr. Go said. "It's reassuring to show that increasing patient efficiency has not resulted in increased hospital readmission."

A multivariate analysis that adjusted for age, sex, income level, comorbidities, admission source, and VA facility showed that the decrease in readmission risk occurred earlier for chronic conditions than for acute conditions.

'It's reassuring ... that increasing patient efficiency has not resulted in increased hospital readmission.'

DR. GO

Compared with 1997, the readmission rate began to decrease significantly among heart failure patients from 2002-2003 (OR 0.93) to 2006-2007 (OR 0.90), and among COPD patients from 1998-1999 (OR 0.91) to 2006-2007 (OR 0.79).

In contrast, significant declines in readmission rates occurred only in 2006-2007 for the acute conditions of MI (OR 0.88) and GI hemorrhage (OR 0.87), with no improvement for pneumonia during the study period, Dr. Go reported.

Possible explanations for this finding are that medical advances and improvements in delivery of care have been greater for chronic conditions than for acute conditions, or that care for acute conditions was already very good and thus more difficult to improve, Dr. Go said in an interview.

The observed pattern of changes in readmission rates for chronic and acute diseases could be useful to policymakers using readmission rates as a quality improvement measure. The National Quality Forum already endorses using 30-day all-cause heart failure readmissions as a quality measure and plans to use it for other conditions as well, he said.

Although the sample size was large, Dr. Go acknowledged that the study could not account for severity of illness, differentiate planned from unplanned readmissions, or capture readmissions by VA patients to private or university hospitals.

The researchers disclosed no relevant conflicts of interest. ■

TYGACIL® (tigecycline) Brief Summary
See package insert for full Prescribing Information. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.
INDICATIONS AND USAGE
TYGACIL is indicated for the treatment of adults with complicated skin and skin structure infections caused by *Escherichia coli, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae, Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Streptococcus pyogenes, Enterobacter cloacae, Klebsiella pneumoniae,* and *Bacteroides fragilis.*
TYGACIL is indicated for the treatment of adults with complicated intra-abdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*), *Bacteroides fragilis, Bacteroides thetaiotaomicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens,* and *Peptostreptococcus micros.*
TYGACIL is indicated for the treatment of adults with community-acquired pneumonia infections caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila.*
CONTRAINDICATIONS
TYGACIL is contraindicated for use in patients who have known hypersensitivity to tigecycline.
WARNINGS AND PRECAUTIONS
Anaphylaxis/Anaphylactoid Reactions
Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including TYGACIL, and may be life-threatening. TYGACIL is structurally similar to tetracycline-class antibiotics and should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics.
Hepatic Effects
Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.
Mortality Imbalance and Lower Cure Rates in Ventilator-Associated Pneumonia
A study of patients with hospital acquired pneumonia failed to demonstrate the efficacy of TYGACIL. In this study, patients were randomized to receive TYGACIL (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received TYGACIL had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 14/122 [11.5%]) than the comparator.
Use During Pregnancy
TYGACIL may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline [see **USE IN SPECIFIC POPULATIONS**].
Tooth Development
The use of TYGACIL during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Results of studies in rats with TYGACIL have shown bone discoloration. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.
***Clostridium difficile* Associated Diarrhea**
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile. C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.
Patients With Intestinal Perforation
Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In cIAI studies (n=1642), 6 patients treated with TYGACIL and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with TYGACIL had higher APACHE II scores (median = 13) versus the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.
Tetracycline-Class Effects
TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL.
Superinfection
As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.
Development of Drug-Resistant Bacteria
Prescribing TYGACIL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In clinical trials, 2514 patients were treated with TYGACIL. TYGACIL was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. Table 1 shows the incidence of treatment-emergent adverse reactions through test of cure reported in ≥2% of patients in these trials.

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in ≥2% of Patients Treated in Clinical Studies

Body System Adverse Reactions	TYGACIL (N=2514)	Comparators[a] (N=2307)
Body as a Whole		
Abdominal pain	6	4
Abscess	3	3
Asthenia	3	2
Headache	6	7
Infection	8	5
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	4	5
Metabolic and Nutritional		
Alkaline Phosphatase Increased	4	3
Amylase Increased	3	2
Bilirubinemia	2	1
BUN Increased	3	1
Healing Abnormal	4	3
Hypoproteinemia	5	3
SGOT Increased[b]	4	5
SGPT Increased[b]	5	5
Nervous System		
Dizziness	3	3
Skin and Appendages		
Rash	3	4

[a] Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid.
[b] LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.
In Phase 3 double-blind studies that included a comparator and employed a 1:1 randomization, death occurred in 4.7% (107/2274) of patients receiving TYGACIL and 3.8% (85/2264) of patients receiving comparator drugs. In a pooled analysis of these studies, the risk difference of all-cause mortality was 1.0% (95% CI -0.3, 2.2) between TYGACIL and comparator treated patients. No significant differences were observed between treatments by infection type (see Table 2). Generally, deaths represented complications of the underlying disease or progression of disease. A causal relationship to TYGACIL has not been established.

Table 2. Patients with Adverse Events with Outcome of Death by Infection Type

Infection Type	TYGACIL n/N	TYGACIL %	Comparator n/N	Comparator %	Risk Difference* % (95%CI)
cSSSI	6/566	1.1	1/550	0.2	0.9 (-0.3, 2.2)
cIAI	24/817	2.9	17/825	2.1	0.9 (-0.8, 2.6)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.3, 2.7)
HAP	65/467	13.9	56/467	12.0	1.9 (-2.6, 6.4)
Non-VAP[a]	40/336	11.9	42/345	12.2	-0.3 (-5.4, 4.9)
VAP[a]	25/131	19.1	14/122	11.5	7.6 (-2.0, 16.9)

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI=Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP=Ventilator-associated pneumonia.
* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups.
[a] These are subgroups of the HAP population.
Note: The Phase 3 Studies include 300 and 305 (cSSSI), 301 and 306 (cIAI), 308 and 313 (CAP), and 311 (HAP).
In comparative clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with TYGACIL (7%) versus comparators (6%). Serious adverse events of sepsis/septic shock were more frequently reported for subjects treated with TYGACIL (2%) versus comparators (1%). Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established [see **WARNINGS AND PRECAUTIONS**].
The most common treatment-emergent adverse reactions were nausea and vomiting which generally occurred during the first 1 – 2 days of therapy. The majority of cases of nausea and vomiting associated with TYGACIL and comparators were either mild or moderate in severity. In patients treated with TYGACIL, nausea incidence was 26% (17% mild, 8% moderate, 1% severe) and vomiting incidence was 18% (11% mild, 6% moderate, 1% severe).
In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35% for TYGACIL and 9% for vancomycin/aztreonam; vomiting incidence was 20% for TYGACIL and 4% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25% for TYGACIL and 21% for imipenem/cilastatin; vomiting incidence was 20% for TYGACIL and 15% for imipenem/cilastatin. In patients treated for community-acquired bacterial pneumonia (CABP), nausea incidence was 24% for TYGACIL and 8% for levofloxacin; vomiting incidence was 16% for TYGACIL and 6% for levofloxacin.
Discontinuation from tigecycline was most frequently associated with nausea (1%) and vomiting (1%).
For comparators, discontinuation was most frequently associated with nausea (<1%).
The following adverse reactions were reported infrequently (<2%) in patients receiving TYGACIL in clinical studies:
Body as a Whole: injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis
Cardiovascular System: thrombophlebitis
Digestive System: anorexia, jaundice, abnormal stools
Metabolic/Nutritional System: increased creatinine, hypocalcemia, hypoglycemia, hyponatremia
Special Senses: taste perversion
Hemic and Lymphatic System: partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia
Skin and Appendages: pruritus
Urogenital System: vaginal moniliasis, vaginitis, leukorrhea
Post-Marketing Experience
The following adverse reactions have been identified during postapproval use of TYGACIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. Anaphylaxis/anaphylactoid reactions, acute pancreatitis, hepatic cholestasis, and jaundice.
DRUG INTERACTIONS
Warfarin
Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].
Oral Contraceptives
Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.
USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects—Pregnancy Category D [see **WARNINGS AND PRECAUTIONS**]
Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ^{14}C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bony structures. The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg·hr/mL and 6 mcg·hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.
There are no adequate and well-controlled studies of tigecycline in pregnant women. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers
Results from animal studies using ^{14}C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman [see **WARNINGS AND PRECAUTIONS**].
Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of effects on tooth development, use in patients under 8 years of age is not recommended [see **WARNINGS AND PRECAUTIONS**].
Geriatric Use
Of the total number of subjects who received TYGACIL in Phase 3 clinical studies (n=2514), 664 were 65 and over, while 288 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.
No significant difference in tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of tigecycline [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].
Hepatic Impairment
No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response [see **CLINICAL PHARMACOLOGY (12.3)** and **DOSAGE AND ADMINISTRATION (2.2)** in full Prescribing Information].
OVERDOSAGE
No specific information is available on the treatment of overdosage with tigecycline. Intravenous administration of TYGACIL at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose intravenous toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD_{50}) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD_{50} was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.
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