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Clinical experience in 52 patients with tigecycline-containing regimens for salvage treatment of *Mycobacterium abscessus* and *Mycobacterium chelonae* infections

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Objectives: We report the largest clinical experience using tigecycline-containing regimens for salvage treatment of patients with *Mycobacterium abscessus* and *Mycobacterium chelonae*.

Patients and methods: Data were collected from 52 patients on emergency/compassionate use ($n=38$) or two open-label studies ($n=7$ patients each). Based on information that was available, 46 (88.5%) of the subjects received antibiotic therapy prior to treatment with tigecycline. Treatment groups were evaluated based on length of tigecycline therapy (<1 and ≥1 month). ClinicalTrials.gov identifiers: Study 205, NCT00600600 and Study 310, NCT00205816.

Results: The most commonly used concomitant antimicrobials were macrolides, amikacin and linezolid. Pulmonary disease was the most common presentation (36/52; 69.2%), and 58.3% of these patients had underlying cystic fibrosis. The majority were *M. abscessus* complex ($n=30$) or *M. chelonae/abscessus* ($n=4$). With therapy ≥1 month (mean, 255.0 ± 265.7 days), 10/15 patients (66.7%) with cystic fibrosis and 16/26 (61.5%) overall were considered improved. Skin/soft-tissue/bone infections were the most common extrapulmonary infections. With therapy ≥1 month (mean, 143 ± 123 days), 9/12 patients (75.0%) were considered improved. Nine of the 16 cases reported as failures regardless of site of infection occurred in patients who stopped treatment due to adverse events. There were eight deaths; none was related to tigecycline.

Conclusions: Tigecycline given for ≥1 month as part of a multidrug regimen resulted in improvement in >60% of patients with *M. abscessus* and *M. chelonae* infections, including those with underlying cystic fibrosis, despite failure of prior antibiotic therapy. Adverse events were reported in >90% of cases, the most common being nausea and vomiting.

Keywords: non-tuberculous mycobacteria, atypical mycobacterial infections, cystic fibrosis, pulmonary

Introduction

Infections with non-tuberculous mycobacteria (NTM) have become a growing clinical concern over the past two decades due to their association with AIDS, recognition of the increasing incidence of NTM infections among patients without AIDS and the multidrug-resistant nature of some of the organisms.[1,2] Besides AIDS, predisposing factors for clinically significant NTM infection include immunosuppressive conditions (transplantation, chronic corticosteroid use, malignancies), structural lung disease (chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis), tumour necrosis factor-α blocking agents (infliximab, adalimumab, etanercept, golimumab, certolizumab), body morphotype, immunological defects due to genetic causes (mutations in interferon-γ and interleukin-12 pathways) and oesophageal motility disorders such as achalasia complicated by lipoid pneumonia.[2–7] The NTM infections also have been associated with use of medical devices (e.g. reusable

injection devices) and contamination of surgical solutions or equipment.[7]

Rapidly growing mycobacteria (RGM) are composed of a group of NTM species that includes *Mycobacterium abscessus* (including three subspecies), *Mycobacterium chelonae* and *Mycobacterium fortuitum* as well as other less commonly identified species. Lung infection with *M. abscessus* is most often seen among middle-aged and elderly women with bronchiectasis, although it is unclear whether bronchiectasis precedes or is a consequence of RGM infection.[8] Treatment of infection with RGM is difficult; this is especially true for chronic lung infections due to *M. abscessus*. Some RGM species are susceptible to tetracyclines (25%–40% for *M. chelonae* and *M. fortuitum*), but other species, such as *M. abscessus*, are resistant to these agents at clinically achievable levels.[9] These organisms also are resistant to first-line antituberculous agents and most other antibacterial agents.[10–13] Clarithromycin or azithromycin combined with parenteral amikacin, cefoxitin or imipenem may be effective for serious skin, soft-tissue and bone infections, but long-term sputum conversion in patients with *M. abscessus* lung infection (especially *M. abscessus* subsp. *abscessus*) has rarely been achieved with existing regimens.[2] This most likely reflects the paucity of available agents with activity against these pathogens, the toxicity of aggressive treatment regimens using any combination of the few available agents and/or expression of a functional inducible macrolide resistance gene or *erm* gene in *M. abscessus* subsp. *abscessus*.[14]

New nomenclature now differentiates three major subspecies within *M. abscessus*: *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense* and *M. abscessus* subsp. *bolletii*.[15] Species- and subspecies-level identifications are important because antibiotic susceptibility and outcomes of therapy can differ significantly depending on the RGM organism cultured. For example, *M. abscessus* subsp. *abscessus* lung disease is regarded as a chronic incurable infection for most patients given the current antibiotic options and evidence of functional inducible resistance to clarithromycin, whereas *M. abscessus* subsp. *massiliense* is less common but has a much better prognosis using macrolide multidrug regimens because of the absence of a functional *erm* gene.[14,16]

Tigecycline, the first commercially available glycylcycline, was designed to circumvent the major mechanisms of bacterial resistance to tetracyclines,[17] including those observed in RGM pathogens. Tigecycline is approved for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections in Europe and the USA;[18,19] an additional indication of community-acquired bacterial pneumonia is approved in the USA.[19] An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator.[20] The deaths were generally the result of worsening infection, complications of infection or underlying comorbidities. The studies described in this paper were not included in this mortality analysis as they were not Phase 3 or 4 comparative clinical trials.

In a comparative *in vitro* study that included 72 isolates of RGM, tigecycline MICs were ≤1 mg/L for all tested tetracycline-susceptible and tetracycline-resistant isolates of *M. abscessus*, *M. chelonae* and *M. fortuitum*.[9] In addition, tigecycline was approximately four dilutions more active than tetracycline, doxycycline and minocycline against tetracycline-susceptible organisms. In a more recent study, investigators from Spain determined the antimicrobial susceptibility of RGM using the Etest method (a non-CLSI-approved susceptibility testing method for these species[21]) in 54 clinical isolates obtained between 2000 and 2006, and found that all the strains were inhibited by tigecycline at very low MICs.[22]

We report the results of clinical experience with tigecycline in the treatment of RGM infections. The purpose of this analysis was to evaluate the efficacy and safety of tigecycline in patients with RGM infections for whom other treatment options were limited or non-existent (salvage treatment). To our knowledge, this is the largest patient series examining the effectiveness of tigecycline-containing regimens for the treatment of *M. abscessus* and *M. chelonae* infections.

Patients and methods

This report is a combined analysis of data from three settings, including patients treated with tigecycline on a single-patient emergency/compassionate-use basis and patients included in two open-label clinical trials. Available data were obtained from the investigating physicians and submitted to Wyeth Research (now part of Pfizer Inc., Collegeville, PA, USA) for compilation and summarization.

Ethics

Each protocol was reviewed and approved by each investigator's independent ethics committee or institutional review board in accordance with local regulations and good clinical practices (Study 205: The University of Texas Health Science Center Institutional Review Board, Tyler, TX, USA; Study 310: McGuire Veterans Affairs Medical Center Institutional Review Board, Richmond, VA, USA; New England Medical Center Human Investigation Review Committee, Boston, MA, USA; St Vincent Mercy Medical Center Institutional Review Board, Toledo, OH, USA; Johns Hopkins Medicine Institutional Review Board, Baltimore, MD, USA; Geisinger Institutional Review Board, Danville, PA, USA; University of Pennsylvania Committee of Studies Involving Human Beings, Philadelphia, PA, USA; Brigham and Women's Hospital Human Research Committee, Boston, MA, USA). All patients signed an institutional review board/independent ethics committee-approved informed consent form prior to study participation. For the compassionate-use programme, individual investigational new drug (IND) requests for compassionate/emergency use were submitted to the US FDA for each patient. The institutional review board at each institution was required to provide approval. Documentation of institutional review board approval was then submitted to Wyeth Research. Outside of the USA, tigecycline was provided for emergency/compassionate-use based on named-patient requests under the auspices of the sponsor's clinical research & development department.

Compassionate-use programme

Tigecycline was made available on an emergency/compassionate-use basis to patients with selected serious infections, including RGM infections, for whom prior treatment with other available antimicrobial therapies either had failed or could not be tolerated and who were believed to have lacked adequate therapeutic alternatives. Tigecycline was provided under an IND application for individual investigators in the USA and on a 'named-patient' basis (a process that allows the prescription/use of either an unlicensed drug or a drug unlicensed for a specific indication for the named patient) in other countries. Patients were allowed to receive other antimicrobial agents in combination with tigecycline. Patient data that included descriptions of demographic/baseline characteristics and outcomes were collected. Serious adverse events were to be reported ≤14 days after the last day of therapy.

Clinical studies

Study 205 (ClinicalTrials.gov identifier NCT00600600) was a Phase 2, open-label, non-comparative, single-centre, investigator-initiated study conducted at The University of Texas Health Northeast (formerly The University of Texas Health Science Center at Tyler) that investigated the efficacy, safety and tolerability of tigecycline in patients with RGM infections. Patients aged ≥10 years with positive cultures for RGM who had drug-resistant isolates or were intolerant of macrolides or had serious infections unresponsive to currently available drugs were enrolled. Patients received intravenous (iv) tigecycline 50 mg daily with daily dose adjustment allowed depending on clinical factors such as age, weight, patient-specific health status and tolerability. Patients were allowed to receive other antimicrobial agents such as clarithromycin, cefoxitin, imipenem, linezolid and/or amikacin in combination with tigecycline. Patients were to be treated until cultures were negative for 6 months. Patients were evaluated every 2 weeks while on therapy and cultures from infection sites were obtained. Final safety assessments were performed 2 weeks after the last dose of tigecycline.

Study 310 (ClinicalTrials.gov identifier NCT00205816) was a Phase 3, open-label, non-comparative, multicentre, emergency-use study to provide a mechanism for the emergency use of tigecycline in patients with resistant pathogens in appropriate clinical situations. Patients aged >8 years with a weight of >35 kg were required to have an active culture-positive bacterial infection unresponsive to other available appropriate antibiotic therapies. All patients received tigecycline at an initial iv dose of 100 mg, followed by 50 mg every 12 h administered over ∼30–60 min. Patients with RGM disease could receive a reduced total daily iv dose of 50 mg (one 50 mg dose or 25 mg every 12 h) at the investigator's discretion. Additional standard concomitant medications including antibiotics were allowed.

RGM identification

Organisms were classified by species according to information provided by local laboratories. The *M. abscessus* subspecies (*M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense* and *M. abscessus* subsp. *bolletii*) were identified only as *M. abscessus* and were referred to as *M. abscessus* complex. These subspecies can only be separated by molecular sequencing of selected genes, including *hsp65*, *rpoB* and *secA*, or PCR restriction enzyme analysis, but these techniques are not widely available or utilized. In some cases, organisms were identified as *M. abscessus/M. chelonae*, as some laboratories were unable to separate these two species.

Data analysis

Safety and efficacy data were analysed using descriptive statistics. Data from the compassionate-use programme and the two clinical studies were pooled for analysis of efficacy and safety. Efficacy outcome was assessed as improvement, failure or indeterminate. Improvement was considered to have occurred when administration of tigecycline was associated with stabilization or improvement in signs and symptoms of the RGM infection based on the information provided by the treating physicians. For lung infection, these could include reduction in cough or shortness of breath, improvement in chest CT, negative culture, reduction in density of organisms on smear or other improvements. For infections involving other sites, such as skin or bone, healing, reduction in numbers of lesions or nodules or other clinical signs were considered in the assessment of improvement. One month of therapy was considered the minimum time to see a clinical response; accordingly patients were divided into those with <1 month and those with ≥1 month of therapy. Failure was considered to have occurred in the absence of improvement after administration of tigecycline or, in some cases, premature discontinuation of treatment due to adverse events. Outcome was considered indeterminate in patients in whom neither improvement nor failure was apparent, who were not treated long enough (based on the assessment of the treating physicians) to be able to adequately evaluate response or for whom follow-up information was not provided to the sponsor. Serious adverse events were defined as adverse events that were life-threatening, prolonged hospitalization, caused disability or resulted in death.

Results

Patients

Data were available for a total of 52 patients treated with tigecycline between April 2002 and November 2006 (Table 1): 38 enrolled in the compassionate-use programme and 7 in each of the two clinical studies. Patients ranged in age from 12 to 81 years (mean, 38 years; median, 32 years) and three-quarters of patients were female. Twenty-two of the patients enrolled

Table 1. Baseline demographics and clinical characteristics

Characteristic	Lung infection (n=36)	Extrapulmonary infection (n=16)	Total (n=52)
Age (years), mean ± SD (range)	35.2 ± 22.2 (12.0–81.0)	44.4 ± 18.3 (13.0–75.0)	38.0 ± 21.3 (12.0–81.0)
Sex, *n* (%)			
female	29 (80.6)	10 (62.5)	39 (75.0)
male	7 (19.4)	6 (37.5)	13 (25.0)
Diagnosis of cystic fibrosis, *n* (%)	21 (58.3)	1 (6.3)	22 (42.3)
Country, *n* (%)			
USA	24 (66.7)	11 (68.8)	35 (67.3)
other	12 (33.3)	5 (31.2)	17 (32.7)[a]
Organism, *n* (%)			
M. abscessus complex	30 (83.3)	8 (50.0)	38 (73.1)
M. chelonae	2 (5.6)	7 (43.8)	9 (17.3)
M. abscessus/M. chelonae	4 (11.1)	1 (6.3)	5 (9.6)

[a]UK (n=5), Israel (n=4), Canada (n=2), France (n=2), Hong Kong (n=2), Denmark (n=1), Greece (n=1).

had a diagnosis of cystic fibrosis; 21 of these patients were enrolled with a lung infection. Patients with cystic fibrosis and a lung infection ranged in age from 12 to 34 years; those with a pulmonary infection and no diagnosis of cystic fibrosis were older, with an age range of 27–81 years. Approximately two-thirds of patients were enrolled in the USA and the rest were enrolled in seven other countries. Infection with *M. abscessus* complex was most common (73.1%), followed by *M. chelonae* (17.3%). Fewer than 10% of patients had infection classified as *M. abscessus*/*M. chelonae*. No patients with *M. fortuitum* infection were identified.

The most common presentation of RGM infection in this group of patients was pulmonary disease ($n=36/52$, 69.2%) and, in >90% of cases, it was due to infection with either *M. abscessus* complex or *M. abscessus*/*M. chelonae*. Patients with RGM lung infection had a median age of 26.5 years and 80.6% were female. Extrapulmonary sites of infection included skin/soft tissue ($n=7$, 13.5%), blood ($n=2$, 3.8%), CNS ($n=1$, 1.9%), bone ($n=1$, 1.9%), prosthesis ($n=1$, 1.9%), prophylaxis ($n=1$, 1.9%) and multiple sources ($n=3$, 5.8%). *M. chelonae* was more commonly found in patients with extrapulmonary infections. Patients with extrapulmonary RGM infections had a median age of 48.5 years and 62.5% were female (Table 1). For the purpose of this analysis, the site of infection was classified as extrapulmonary for one patient with *M. abscessus* infection affecting multiple sites that included the lung.

Data available indicate that 46/52 patients (88.5%) had received prior antibiotic treatment. For five of the remaining patients, no prior antibiotic use was noted in the case report form; there was no case report form for the remaining patient. The most common classes of antibiotics used before tigecycline-containing regimens were started included macrolides (clarithromycin, azithromycin), aminoglycosides (amikacin, tobramycin), agents classified as non-penicillin β-lactam antibacterials (cefoxitin, imipenem, meropenem), oxazolidinones (linezolid) and quinolones (Table 2).

Treatment

For those patients in whom the tigecycline dosage was known, slightly less than half received 100 mg daily, whereas the rest received 25 to <50 mg once or twice daily (one patient received 50 mg daily or every other day). Reasons for dosage reduction in most cases included nausea, vomiting or anorexia.

The overall mean ± SD duration of tigecycline treatment was 164.6 ± 219.7 days with a range of 3 days to ∼3.5 years (median, 84.5 days). Among the patients with lung infections, the mean ± SD duration was 188.1 ± 249.8 days, whereas for patients with extrapulmonary sites of infection, the duration was 111.8 ± 119.2 days. Ten of the 36 patients with lung infection received therapy for <1 month with a median duration of therapy of 13.5 days; the remaining 26 patients received therapy for ≥1 month with a median duration of 161.0 days (Table 3). One quarter of the patients with extrapulmonary disease ($n=4$) received therapy for <1 month with a median duration of 20.5 days; 12 patients received therapy for ≥1 month with a median duration of 87.5 days.

Table 2. Concomitant antibiotic therapy received during the study by ≥6% of all patients

Antibiotic class	Lung infection, *n* (%); *N*=36	Extrapulmonary infection, *n* (%); *N*=16	Total, *n* (%); *N*=52
Macrolides, lincosamides and streptogramins	27 (75.0)	11 (68.8)	38 (73.1)
azithromycin	7 (19.4)	4 (25.0)	11 (21.2)
clarithromycin	24 (66.7)	7 (43.8)	31 (59.6)
Aminoglycosides	21 (58.3)	8 (50.0)	29 (55.8)
amikacin	20 (55.6)	6 (37.5)	26 (50.0)
tobramycin	2 (5.6)	2 (12.5)	4 (7.7)
Non-penicillin β-lactams	15 (41.7)	4 (25.0)	19 (36.5)
cefoxitin	10 (27.8)	4 (25.0)	14 (26.9)
imipenem	4 (11.1)	1 (6.3)	5 (9.6)
meropenem	3 (8.3)	1 (6.3)	4 (7.7)
Quinolones	8 (22.2)	1 (6.3)	9 (17.3)
ciprofloxacin	4 (11.1)	1 (6.3)	5 (9.6)
moxifloxacin	4 (11.1)	1 (6.3)	5 (9.6)
Sulphonamides and trimethoprim	4 (11.1)	2 (12.5)	6 (11.5)
trimethoprim/sulfamethoxazole	4 (11.1)	2 (12.5)	6 (11.5)
Drugs for treatment of tuberculosis	5 (13.9)	1 (6.3)	6 (11.5)
ethambutol	4 (11.1)	1 (6.3)	5 (9.6)
Other antibacterials	18 (50.0)	5 (31.3)	23 (44.2)
linezolid	16 (44.4)	5 (31.3)	21 (40.4)

Table 3. Summary of treatment duration by diagnosis site and treatment duration

Site of infection	Mean ± SD duration of therapy (days)	Median duration of therapy (days)
Lung		
<1 month (*n*=10)	14.1±8.5	13.5
≥1 month (*n*=26)	255.0±265.7	161.0
Extrapulmonary		
<1 month (*n*=4)	19.3±6.0	20.5
≥1 month (*n*=12)	142.7±123.3	87.5

Twenty-nine patients (55.8%) were considered to have discontinued tigecycline use prematurely. Adverse events were the most common reason for discontinuation, occurring in 16 patients (30.8%). Other reasons for discontinuation were lack of efficacy in 10 patients (19.2%), a requested withdrawal of treatment for 1 patient (1.9%) and other reasons in 2 patients (3.8%).

Concomitant antibiotics for the treatment of RGM infection were used during the course of tigecycline therapy in 49 patients (94.2%) (Table 3). The most commonly used antibiotics were macrolides in 38 patients (73.1%), aminoglycosides in 29 patients (55.8%), linezolid in 21 patients (40.4%) and non-penicillin β-lactam antibacterials (cefoxitin, imipenem, meropenem) in 19 patients (36.5%).

Efficacy

Overall, 25 patients (48.1%) were considered clinically improved, 16 (30.8%) were categorized as clinical failures and 11 (21.2%) were deemed indeterminate (Table 4). Among the 36 patients with lung infection, 16 (44.4%) were clinically improved, with 11 (30.6%) failures and 9 (25.0%) considered indeterminate. Of those patients with cystic fibrosis and non-cystic fibrosis pulmonary infection, duration of therapy appeared to influence treatment outcome (Table 5). No patients were assessed as clinically improved with treatment duration of <1 month. Results in patients with extrapulmonary infection were similar (Table 6). Among the patients treated for ≥1 month, 10/15 (66.7%) of patients with lung infection and underlying cystic fibrosis were considered improved and only 3/15 (20.0%) were considered failures; for those without cystic fibrosis, 6/11 (54.5%) were considered improved and 4/11 (36.4%) were considered failures. Among the 12 patients with extrapulmonary infections treated for ≥1 month, 9 (75.0%) were considered improved and 3 (25.0%) were considered failures.

Safety

The most frequently reported adverse events were nausea, vomiting, fever, diarrhoea, asthenia and anorexia (Table 7). Serious adverse events were reported in 29 patients. The most common of these were exacerbation of the underlying condition, nausea, vomiting, sepsis/multiorgan failure, respiratory failure and pneumonia/respiratory infection. Twelve patients had serious adverse

Table 4. Patients with clinical improvement, failure or indeterminate response by infection site and pathogen (based on intent to treat)[a]

Infection site/organism	Improved, *n*	Failed, *n*	Indeterminate, *n*
All sites, total	25	16	11
M. abscessus complex	18	12	8
M. chelonae	5	3	1
M. abscessus complex/ *M. chelonae*	2	1	2
Lung, total	16	11	9
M. abscessus complex	13	9	8
M. chelonae	1	1	0
M. abscessus complex/ *M. chelonae*	2	1	1
Extrapulmonary, total	9	5	2
skin/soft tissue			
M. abscessus complex	2	0	0
M. chelonae	3	1	1
bone			
M. abscessus complex	1	0	0
multiple			
M. abscessus complex	0	1	0
M. chelonae	1	1	0
blood			
M. abscessus complex	1	0	0
M. abscessus complex/ *M. chelonae*	0	0	1
CNS			
M. abscessus complex	0	1	0
prosthesis			
M. abscessus complex	0	1	0
prophylaxis			
M. abscessus complex	1	0	0

[a]Patients in this table were not separated into treatment groups of <1 or ≥1 month as in Table 3.

Table 5. Summary of final clinical evaluation of 36 lung infections by the presence or absence of cystic fibrosis and tigecycline therapy duration

Therapy duration	Improved, *n* (%)	Failed, *n* (%)	Indeterminate, *n* (%)
<1 month			
cystic fibrosis, *n*=6	—	3 (50.0)	3 (50.0)
no cystic fibrosis, *n*=4	—	1 (25.0)	3 (75.0)
≥1 month			
cystic fibrosis, *n*=15	10 (66.7)	3 (20.0)	2 (13.3)
no cystic fibrosis, *n*=11	6 (54.5)	4 (36.4)	1 (9.1)

Table 6. Summary of final clinical evaluation of 16 extrapulmonary infections by tigecycline therapy duration

Therapy duration	Improved, *n* (%)	Failed, *n* (%)	Indeterminate, *n* (%)
<1 month			
cystic fibrosis, *n*=0	—	—	—
no cystic fibrosis, *n*=4	—	2 (50.0)	2 (50.0)
≥1 month			
cystic fibrosis, *n*=1	1 (100.0)	—	—
no cystic fibrosis, *n*=11	8 (72.7)	3 (27.3)	—

Table 7. Adverse events reported in five or more patients[a]

Adverse event	Patients, *n* (%); *N*=52
Any adverse event	49 (94.2)
Most common adverse events	
nausea	33 (63.5)
vomiting	18 (34.6)
fever	13 (25.0)
diarrhoea	12 (23.1)
anorexia	11 (21.2)
asthenia	11 (21.2)
abdominal pain	9 (17.3)
respiratory disorder	8 (15.4)
pain	6 (11.5)
insomnia	6 (11.5)
chest pain	5 (9.6)
peripheral oedema	5 (9.6)
weight loss	5 (9.6)
tinnitus	5 (9.6)
Serious adverse events	29 (55.8)
related to study drug (see the text for details)	12 (23.1)

[a]Includes all patients with either lung or extrapulmonary infection.

events considered by the investigator to be related to tigecycline. They included vomiting with or without nausea and/or epigastric pain (four patients, resolved; resolution not reported in one patient), nausea and anorexia (one patient, resolved), ileus and acute pancreatitis (one patient, resolved), hypoglycaemia and acute pancreatitis (one patient, resolved), liver dysfunction (one patient, resolved), junctional arrhythmia (one patient, resolved), facial oedema (one patient, partially resolved) and venous thrombosis (one patient, present at the time of death). Eight deaths were reported and were considered related to the subject's underlying disease/infections. None of the deaths was considered related to tigecycline therapy.

It should be noted that use of antiemetics such as ondansetron prior to tigecycline infusion or when necessary for nausea became a routine part of therapy in Study 205 (reported by R. J. W., B. A. B.-E. and D. E. G.).

Discussion

In this combined clinical experience with tigecycline-containing regimens for salvage treatment of RGM infections, clinical improvement was evident in 48.1% of patients. This improvement occurred in spite of a history of prior drug therapy in ∼90% of these patients, many of whom were enrolled in a compassionate-use setting. As expected, slightly lower improvement rates were demonstrated for RGM lung infections compared with extrapulmonary sites of infection in the current analysis (44.4% versus 56.3%, respectively). The relatively high mortality rate (*n*=8, 15.4%) was consistent with severe illness associated with these RGM infections.

The most frequent presentation of RGM infection in our patients was pulmonary disease due to *M. abscessus* complex or *M. abscessus*/*M. chelonae*. In the USA, *M. abscessus* is the third most frequently recovered NTM respiratory pathogen and usually accounts for >80% of RGM respiratory disease isolates,[2] as was the case in our study. Lung infection with *M. abscessus* complex is generally considered incurable, although resection of localized disease may be successful in appropriate patients.[4] This study antedated the recognition of the difference in clinical response between *M. abscessus* subsp. *abscessus* and the former *M. massiliense*.[16] Nevertheless, given that no currently available treatment regimen has been shown to achieve the goal of long-term conversion of sputum cultures,[2] the 61.5% clinical improvement demonstrated in patients with *M. abscessus* complex or *M. abscessus*/*M. chelonae* pulmonary infection in this population treated for ≥1 month is a meaningful indication of therapeutic success achieved with tigecycline-containing treatment regimens.

There was considerable interindividual variability in tigecycline dosing and it was clear that target doses were not achieved in most patients. Approximately half of the patients had dose reductions due to nausea, vomiting or anorexia. In the investigator-initiated study, adjustments to dosages were based on the level of tolerability. Slow dose titration and the use of antiemetics, such as ondansetron, in the latter part of the study improved patient tolerability. In addition, because tigecycline is given intravenously and is generally required over extended periods of time in these patients, practical considerations frequently resulted in the use of once-daily dosing after hospital discharge. Thus, it is worth noting that the improvements observed with tigecycline treatment occurred in spite of the lower dosages achievable in this group of patients. Although it may seem reasonable in certain situations, once-daily dosing of tigecycline is unproven clinically.

The incidences of nausea and vomiting observed in this study population were higher than those reported in controlled trials (nausea, 24%–43%; vomiting, 12%–27%[23–27]). The reasons for the higher incidence of these events in this population are unclear, but may in part be the effects of concomitant medications, the underlying disease severity and/or the longer duration of tigecycline treatment (>3 months in 46.2% of patients), which far exceeded the recommended duration of treatment for approved indications. It is not currently known whether patients with infections due to RGM are less able to tolerate tigecycline than those infected with other organisms, but the duration of tigecycline treatment in these patients (mean, 164.6 days; maximum, 3.5 years) may suggest otherwise.

Although tigecycline has consistently demonstrated excellent activity *in vitro* against clinical isolates of both tetracycline-

susceptible and tetracycline-resistant *M. abscessus* and *M. chelonae*,[9,28–30] few reports of clinical experience with tigecycline for the treatment of RGM infections are found in the medical literature.[29,31–38] Garrison *et al.*[33] reported three cases of *M. abscessus* surgical wound-site infections associated with solid organ transplants. In two cases, tigecycline was included in the initial treatment regimen and complete resolution was observed after treatment courses of 8 weeks and 8.5 months, respectively. In the third case, a 4 week regimen of tigecycline monotherapy following *in vitro* susceptibility testing resulted in successful resolution of the signs and symptoms. Regnier *et al.*[34] reported 16 patients with RGM cutaneous infections after mesotherapy injections (the majority were *M. chelonae*), of which 6 received triple therapy with tigecycline, tobramycin and clarithromycin as first-line treatment. The median duration of tigecycline therapy was 52 days and all patients fully recovered. Schneider *et al.*[35] described two immunosuppressed patients with nodular lymphangitis related to *M. chelonae*, which resolved after treatment with antibiotic therapy that included oral clarithromycin, iv tigecycline and iv tobramycin. Huang *et al.*[29] reported one patient with *M. abscessus* infection cured with tigecycline for 2 weeks plus clarithromycin for 8 months. The combination of clarithromycin and tigecycline was later reported to demonstrate synergism but, interestingly, antagonism was demonstrated with the combination of amikacin and tigecycline.[36]

Another successful treatment in an elderly woman with an unusual RGM species, *Mycobacterium alvei*, in a prosthetic joint infection, was recently reported by Lee *et al.*[37] The tigecycline MIC for this isolate of *M. alvei* was found to be ≤0.03 mg/L (presumptively susceptible based on previously published data). The patient received iv amikacin and tigecycline for 4 weeks followed by oral ciprofloxacin and trimethoprim/sulfamethoxazole for the following 6 months. She remained culture negative at a 6 month follow-up.[37]

To our knowledge, our study is the largest reported clinical experience with tigecycline-containing regimens for the treatment of RGM infections to date. Our efficacy and safety results, along with the observed duration of tigecycline treatment in these patients (mean, 164.6 days; maximum, 3.5 years), may suggest a potential role for tigecycline use in the management of RGM infections, but further clinical evaluation is needed before a definite role in therapy can be established.

The clinical and microbiological outcomes in this analysis and experiences in Study 205 indicate that the use of alternative dosing strategies might be evaluated to improve tolerability in patients with RGM infections, especially given the need for prolonged treatment regimens in these patients. For example, although a loading dose of tigecycline is recommended for treatment regimens that typically are limited to 14 days,[19] it may be less useful for a more prolonged course of treatment. Tolerability improvement was observed by one investigator in the patients included in Study 205 with the use of slow up-titration after initiation of treatment at 25 mg once daily for the first 2 weeks. Finally, post-prandial administration of iv tigecycline or the ready availability of antiemetic medications such as sublingual ondansetron should be considered.[39] The usefulness of these suggestions would need to be tested in a clinical study.

In addition to those limitations applicable to any uncontrolled open-label treatment study, this report has limitations imposed by the inclusion of patients from a compassionate-use programme. Criteria for success or failure of treatment in these patients could only be applied based on the descriptive information provided by the treating primary physicians. Therefore, microbiological data, such as clearance of RGM from culture and MICs, were not provided in most cases. Classification of pathogen species/subspecies also was often limited by laboratory capabilities in each geographic region. Another limitation of the present study is the relatively small number of patients treated. A large cooperative study would likely be required to recruit sufficient numbers of patients. However, even though the number of patients involved in this study was small, the results suggest that tigecycline could be clinically beneficial as part of a multidrug treatment strategy, especially against RGM species causing serious disease, before susceptibilities are available. Validation of the study findings in a controlled clinical trial setting would be useful, although conducting such a trial would be complicated by the limited patient population, the chronic nature of these infections, the lack of standard criteria for evaluating efficacy and the need to treat these patients with multiple antibiotics. Compared with a clinical trial of selected patients, the current analysis may better reflect treatment outcomes in a real-world setting.

In summary, this analysis provides information on the efficacy of tigecycline as part of an antibiotic regimen for salvage treatment of *M. abscessus* and *M. chelonae* infections and suggests that tigecycline has an acceptable safety profile in patients treated for ≤3.5 years. In the analysed population, tigecycline appears to be a useful addition to other currently available antibiotics in patients with these difficult-to-treat infections.

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Transparency declarations

G. D., E. G. S. and B. M. are former employees of Pfizer Inc.; G. D. and B. M. hold stock in Pfizer Inc. R. J. W., B. A. B.-E. and D. E. G.: none to declare.

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