Journal of Global Antimicrobial Resistance 18 (2019) 199–206

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Influence of age on the clinical efficacy of tigecycline in severely ill patients

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ARTICLE INFO

Article history:
Received 28 September 2018
Received in revised form 7 February 2019
Accepted 28 March 2019
Available online 3 April 2019

Keywords:
Elderly
Glycylcycline
Tetracycline
Tigecycline
Complicated skin and soft-tissue infection
Complicated intra-abdominal infection

ABSTRACT

Objectives: The aim of this study was to define the relationship between age and response to tigecycline among patients treated for complicated skin and soft-tissue infections (cSSTIs) and complicated intra-abdominal infections (cIAIs).
Methods: Pooled data derived from five European observational studies on the use of tigecycline (July 2006–October 2011), either as monotherapy or in combination with other antibiotics, for the treatment of cSSTI or cIAI were used in the analysis.
Results: The total population ($N = 1782$ patients) was divided into three age categories: <65 years (804 patients); 65–80 years (836 patients) and >80 years (139 patients) (data unknown/missing for 3 patients). The overall mean Acute Physiology and Chronic Health Evaluation (APACHE) II score for patients with cSSTI and cIAI was 15.0 ± 7.9 and 16.9 ± 7.6, respectively, and the overall mean Sequential Organ Failure Assessment (SOFA) score was 5.8 ± 3.9 and 7.0 ± 4.2, respectively. Overall, patients with cSSTI and cIAI in the three age groups showed a good response to tigecycline treatment (76.2–80.0% and 69.2–81.1%, respectively) with patients aged ≤80 years showing higher response rates. Patients with cIAI appeared to be at greater risk for all types of adverse events compared with those with cSSTI, particularly in the older age groups.
Conclusion: In these real-life studies, tigecycline, either alone or in combination, achieved favourable clinical response rates in all age categories of patients with cSSTIs and cIAIs with a high severity of illness.

1. Introduction

Accounting for approximately 19.2% of the total population in Europe according to data from 2016, elderly people (aged ≥65 years) have relatively high use of healthcare resources, and age is a risk factor for poor outcome [1–3]. Several factors may contribute to poor outcomes in the elderly population with infections such as complicated skin and soft-tissue infection (cSSTI) and complicated intra-abdominal infection (cIAI). Challenges in antibiotic treatment of infections in the elderly include increased risk of infection owing to age-related immune degeneration [4], more frequent exposure to the healthcare system and residence in chronic healthcare institutions leading to an increased risk of multidrug-resistant infections [5,6], increased vulnerability to antibiotic adverse drug reactions, heightened risk of *Clostridioides* (formerly *Clostridium*) *difficile* infection [6] and different pharmacokinetics/pharmacodynamics [7].

cSSTIs are among the most commonly encountered infections in the hospital setting and encompass a heterogeneous group of infections affecting the deep soft tissue [8,9]. Some of the most common pathogens implicated in cIAI and cSSTI are multidrug-resistant, including extended-spectrum β-lactamase-producing *Escherichia coli* in cIAI and methicillin-resistant *Staphylococcus aureus* (MRSA) in cSSTI [10,11].

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https://doi.org/10.1016/j.jgar.2019.03.018

Tigecycline is a broad-spectrum antibiotic that has been approved for the treatment of cSSTI (with the exception of diabetic foot infection) and cIAI [12,13]. In the USA, tigecycline is also approved for the treatment of community-acquired bacterial pneumonia [12]. The efficacy of tigecycline versus other antimicrobials for the treatment of cSSTIs and cIAIs has been demonstrated in double-blind, randomised, phase III randomised clinical trials [14,15]. Real-world data on the use of tigecycline obtained through five non-interventional, observational studies conducted in four European countries [Germany, Italy, France and Spain (two studies, Spain-1 and Spain-2)] from July 2006 to October 2011 were pooled and analysed to describe the prescribing patterns for tigecycline [16], its efficacy in the treatment of cSSTIs [8], its efficacy in the treatment of cIAIs [17], its safety and tolerability in the treatment of cSSTIs and cIAIs [18], and the resistance mechanisms and epidemiology of multidrug-resistant pathogens in Europe [19].

The analysis reported here utilises data collected from the aforementioned observational studies to define the relationship between age and response to tigecycline among patients treated for cSSTI and cIAI.

2. Materials and methods

2.1. Patients

This analysis included data collected by hospital-based physicians in five non-interventional, observational studies conducted in Europe (July 2006–October 2011). The study designs, together with inclusion and exclusion criteria for each study, are described in Table 1 of Bassetti et al. [16]. Owing to the observational nature of the studies, there were few inclusion/exclusion criteria or protocol specifications, except for the receipt of tigecycline. Diagnosis of cSSTI and cIAI was at the discretion of the physician with no independent adjudication or external safety committee. SSTIs are commonly defined as complicated when surgical intervention is required and/or the infectious process is suspected or confirmed to involve deeper soft tissue such as the fascia and/or muscle layers. cIAIs are commonly defined as infections that extend into the peritoneal space and are associated with either abscess formation or peritonitis [8,17]. For further information about the definition of cSSTI and cIAI, refer to Montravers et al. [8] and Eckmann et al. [17], respectively. Hospitalised patients were included if they received tigecycline for any indication during the study period, with the exception of the Spain-1 study that included only patients with a diagnosis of cSSTI or cIAI. Two studies (France and Spain-2) included only patients admitted to the intensive care unit (ICU) [8,17]. Administration of tigecycline, dosage, duration of treatment and prescription of other antibiotics during or after the initiation of tigecycline were at the physician's discretion. All concomitant medications were permitted [8,17]. The total population was divided into three age categories for the purpose of this analysis: <65 years; 65–80 years; and >80 years.

This research was conducted in accordance with the Declaration of Helsinki as well as all national and institutional standards. The protocol of each study was approved by the local ethics committee or institutional review board. Owing to the non-interventional observational nature of the studies, written informed consent was not required for enrolment in the studies in Germany, Italy and Spain-2. Written informed consent was obtained from patients prior to participation in the studies in France and Spain-1.

Table 1
Baseline characteristics of patients included in the analysis.

Characteristic	cSSTI (N = 254)			cIAI (N = 785)		
	<65 years (n = 117)	65–80 years (n = 114)	>80 years (n = 23)	<65 years (n = 370)	65–80 years (n = 358)	>80 years (n = 54)
Male sex [n (%)]	83 (70.9)	62 (54.4)	12 (52.2)	219 (59.2)	209 (58.4)	28 (51.9)
Mean BMI (kg/m^2)	28.4	28.2	25.7	26.9	27.9	27.1
Clinical characteristics						
ICU admission [n (%)]	42 (36.2)	38 (33.3)	7 (34.4)	201 (54.3)	213 (59.7)	27 (50.0)
Missing/unknown (n)	0	1	0	0	1	1
APACHE II score ≤15 [n (%)]	45 (52.9)	53 (54.1)	16 (72.7)	138 (48.6)	100 (35.7)	18 (37.5)
Missing/unknown (n)	19	12	1	49	41	2
SOFA score (only France and Spain-2) <7 [n (%)]	14 (60.9)	5 (55.6)	0	25 (45.5)	19 (39.6)	4 (80.0)
Missing/unknown (n)	0	0	0	0	2	0
Co-morbidities						
≥1 co-morbidity [n (%)]	99 (84.6)	109 (95.6)	23 (100)	314 (84.9)	325 (90.8)	47 (87.0)
Co-morbid conditions [n/N (%)]						
COPD	22/94 (23.4)	30/107 (28.0)	6/23 (26.1)	36/294 (12.2)	65/303 (21.5)	10/46 (21.7)
Diabetes mellitus	44/99 (44.4)	69/109 (63.3)	13/23 (56.5)	74/314 (23.6)	116/324 (35.8)	18/47 (38.3)
Heart failure	27/94 (28.7)	49/107 (45.8)	13/23 (56.5)	41/294 (13.9)	79/303 (26.1)	17/46 (37.0)
Hypertension	50/80 (62.5)	80/90 (88.9)	15/16 (93.8)	94/228 (41.2)	169/234 (72.2)	25/32 (78.1)
Obesity	32/78 (41.0)	22/87 (25.3)	2/16 (12.5)	53/233 (22.7)	74/242 (30.6)	10/32 (31.3)
Renal failure	32/99 (32.3)	57/109 (52.3)	13/23 (56.5)	55/314 (17.5)	95/324 (29.3)	20/47 (42.6)
Smoker	29/80 (36.3)	12/90 (13.3)	0/0	66/228 (28.9)	21/234 (9.0)	0/0
Baseline pathogens [n/N (%)]						
Polymicrobial infection	35/102 (34.3)	29/95 (30.5)	6/16 (37.5)	145/297 (48.8)	142/285 (49.8)	17/38 (44.7)
Anaerobes	13/78 (16.7)	8/77 (10.4)	4/12 (33.3)	56/216 (25.9)	55/217 (25.3)	2/28 (7.1)
Gram-negative bacilli	32/78 (41.0)	28/ (36.4)	5/12 (41.7)	137/216 (63.4)	137/217 (63.1)	21/28 (75.0)
Gram-positive cocci	60/78 (76.9)	65/77 (84.4)	9/12 (75.0)	161/216 (74.5)	161/217 (74.2)	19/28 (67.9)
Site of infection acquisition [n (%)]						
Nosocomial infection[a]	58 (50.0)	67 (58.8)	13 (56.5)	232 (63.2)	240 (67.6)	37 (68.5)
Community-acquired infection[a]	58 (50.0)	47 (41.2)	10 (43.5)	135 (36.8)	115 (32.4)	17 (31.5)
Previous antibiotic therapy [n (%)]	87 (75.0)	81 (71.1)	16 (69.6)	291 (78.6)	272 (76.0)	38 (70.4)

cSSTI, complicated skin and soft-tissue infection; cIAI, complicated intra-abdominal infection; BMI, body mass index; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; COPD, chronic obstructive pulmonary disease.

[a] Includes non-cSSTI and non-cIAI indications such as pneumonia and bacteraemia.

2.2. Data acquisition and evaluation

Data were collected and evaluated as described in Bassetti et al. [16].

2.3. Clinical outcome

Clinical outcome was assessed by the investigator at the end of treatment or on discharge. Definitions of clinical outcome are as described in Bassetti et al. [16].

2.4. Safety

The number of adverse events (AEs), serious AEs and premature discontinuations as well as all-causality mortality occurring at any time during the study, including the follow-up period, were recorded. A detailed description of the criteria for assessment of safety is available in Guirao et al. [18].

2.5. Statistical analysis

Statistical differences in the distribution of baseline characteristics among the three age groups were assessed using one-way analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables. Descriptive statistics included relative frequencies for categorical variables, and mean ± standard deviation or median (interquartile range) for continuous variables. A pooled analysis of patient-level data from the five studies was conducted for selected characteristics. The χ^2 test was used to determine whether an association existed between age group and response to treatment. Data were analysed in tabulated summaries with the number of patients with available (i.e. non-missing) data as the denominator. Diagnoses of cSSTI and cIAI were mutually exclusive for inclusion, although patients could have other simultaneous infections. AEs were tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. All-causality mortality was analysed by indication and by disease severity score using the Acute Physiology and Chronic Health Evaluation (APACHE) II and/or Sequential Organ Failure Assessment (SOFA) scores at the beginning of tigecycline treatment.

3. Results

3.1. Patient characteristics

3.1.1. Age

A total of 1782 patients received at least one dose of tigecycline at 191 geographic sites across the five observational studies. The results of the five studies were pooled and the total population was divided into three age categories: <65 years (804 patients); 65–80 years (836 patients); and >80 years (139 patients). Data were unknown/missing from 3 patients (0.2%) in the overall population; all of these patients were in the cIAI population (0.4%). Over one-half of the total patient population from these pooled studies was aged ≥65 years [975/1779 (non-missing data only); 54.8%].

Males represented 61.4% of the total population; however, males accounted for a smaller proportion of the total as the age group increased (63.4% of the <65 years age group, 62.0% of the 65–80 years age group and 48.2% of the >80 years age group), probably due to lower life expectancy. Mean body mass index (BMI) in the total pooled population was 27.5 ± 6.5 kg/m^2 (range 14–90 kg/m^2) [16]. BMI was highest in the 65–80 years group (28.0 kg/m^2) and lowest in the >80 years group (26.7 kg/m^2).

3.1.2. Indications

Within each age group, the population was divided into three categories based on infection type, namely cIAI, cSSTI and total, the latter including patients who received tigecycline for any indication (Table 1; data for the total population are not shown). The most frequent indications for prescription of tigecycline were cIAI (785 patients) and cSSTI (254 patients), together representing 58.3% of the total pooled population. Other diagnoses for which patients received tigecycline included pneumonia, bloodstream infection and sepsis-related conditions [16]. Of the cIAI patients, the most common diagnosis was generalised peritonitis (51.2%) and the most common type among these patients was secondary peritonitis (65.7%). Many infections were secondary to perforation of the colon or rectum (41.4%), and 94.8% required surgery [17]. For the cSSTI patients, the most common diagnosis was necrotizing infection (43.8%) and the majority had deep soft-tissue infections (75.5%), with 69.0% requiring surgical intervention [10]. The age distribution of patients was similar in the cIAI and cSSTI groups (Table 1).

3.1.3. Severity of illness

For cIAI, ICU admission was highest in the 65–80 years age group (59.7%) and lowest in the >80 years age group (50.0%); for cSSTI, ICU admission was highest in those aged <65 years (36.2%) and lowest in those aged 65–80 (33.3%). The APACHE II and SOFA scores documented before tigecycline treatment in this patient cohort confirmed a particularly high level of disease severity [16]. APACHE II scores were collected in 205 cSSTI and 614 cIAI patients in the studies from Germany, Italy, Spain-1 and Spain-2. Overall mean scores in these patients were 15.0 ± 7.9 and 16.9 ± 7.6, respectively. SOFA scores were documented for 32 cSSTI and 108 cIAI patients in France and Spain-2, and the overall mean scores in these patients were 5.8 ± 3.9 and 7.0 ± 4.2, respectively [18].

3.1.4. Co-morbidities

Co-morbidities were present in 90.9% of cSSTI patients (the most common being hypertension, diabetes mellitus and arteriosclerosis) [8]. Co-morbidities were present in a similar proportion of cIAI patients (87.4%; the most common being hypertension, diabetes mellitus and neoplasia) [17]. There was a trend for a higher proportion of patients aged ≥65 years having at least one co-morbidity compared with those aged <65 years (86.8% vs. 93.5% vs. 93.5% for those aged <65, 65–80 and >80 years, respectively). The most common co-morbid conditions in each age group are shown in Table 1.

3.1.5. Baseline pathogens

Pathogens identified at baseline are shown in Table 1. No clear association was identified between age group and the likelihood of having a polymicrobial infection. Patients in the >80 years age group with cIAI were somewhat less likely to have an anaerobe identified at baseline (7.1% for >80 years vs. 25.9% for <65 years), whilst in the overall population patients in the 65–80 years age group were somewhat more likely to have a resistant pathogen (46.1% for 65–80 years vs. 39.3% and 39.8% for <65 years and >80 years age groups, respectively).

3.1.6. Site of infection acquisition

For cSSTI, an equal proportion of patients in the <65 years age group had nosocomial and community-acquired infection (both 50.0%) (Table 1). However, both in the 65–80 years and >80 years age groups there was a bias towards nosocomial acquisition (58.8% nosocomial vs. 41.2% community-acquired infection for 65–80 years and 56.5% nosocomial vs. 43.5% community-acquired infection for >80 years). By contrast, in the cIAI group, among those patients aged <65 years a larger proportion had a nosocomial

infection (63.2% nosocomial vs. 36.8% community-acquired). This trend became more pronounced in advanced age (67.6% nosocomial vs. 32.4% community-acquired for 65–80 years and 68.5% nosocomial vs. 31.5% community for >80 years age groups).

3.1.7. Previous antibiotic therapy

The majority of patients in these studies had a history of prior antibacterial therapy (80.2%). The likelihood of having received previous antibiotic therapy decreased with increasing age (81.3% vs. 79.8% vs. 76.3% for those aged <65, 65–80 and >80 years, respectively), as shown in Table 1.

Further details on baseline demographic and clinical characteristics are provided in Montravers et al. [8] and Eckmann et al. [17].

3.1.8. Use of tigecycline: dosing

The majority (>90%) of cSSTI and cIAI patients in the observational studies received the standard dosage of tigecycline, and the mean duration of tigecycline treatment was 12.0 ± 7.0 days and 10.6 ± 6.1 days for cSSTI and cIAI, respectively [18]. In the current analysis, no clear association was noted between age group and decision to prescribe the standard dose of tigecycline in the total pooled population or in the cSSTI group. However, in the cIAI group standard-dose prescription was higher than average among patients aged >80 years (89.2%). There was a slight trend towards shorter duration of therapy with increased age in the total pooled population: 11.3 days for <65 years vs. 10.6 days for >80 years.

Tigecycline was administered first-line to 44.4% of cSSTI patients and 48.7% of cIAI patients [18]. There was no clear association between line of therapy (first- versus second-line) and age when all infection types were considered. However, for cIAI a greater percentage of patients received first-line tigecycline therapy in the older age category (54.1% for >80 years vs. 38.0% for <65 years). More patients received tigecycline monotherapy compared with combination therapy overall, and monotherapy was more widely used with increasing age. Combination therapy was more prevalent among patients treated for cIAI than for cSSTI; cIAI patients aged <65 years were most likely to receive combination therapy (49.2%), whilst cSSTI patients aged 65–80 years were least likely to receive combination therapy (24.6%).

3.1.9. Reasons for tigecycline use

The most frequently cited reasons for prescription of tigecycline in all age groups were as follows.

- Broad pathogen spectrum: cSSTI, 50.6%, 43.0% and 62.5% for <65, 65–80 and >80% years, respectively; and cIAI, 45.9%, 54.3% and 48.5% for <65, 65–80 and >80% years, respectively.
- Failure of previous therapy: cSSTI, 43.5%, 54.4% and 56.3% for <65, 65–80 and >80% years, respectively; and cIAI, 48.0%, 41.7% and 37.8% for <65, 65–80 and >80% years, respectively.
- Polymicrobial infection: cSSTI, 38.5%, 75.0% and 0% for <65, 65–80 and >80% years, respectively; and cIAI, 73.0%, 67.6% and 100.0% for <65, 65–80 and >80% years, respectively.
- Suspected or identified resistant pathogen: cSSTI, 43.5%, 51.1% and 37.5% for <65, 65–80 and >80% years, respectively; and cIAI, 38.4%,40.6% and 29.7% for <65, 65–80 and >80% years, respectively.

3.2. Clinical response

3.2.1. Overall

In the cSSTI group, patients aged ≤80 years showed higher response rates (79.8% and 80.0% for <65 years and 65–80 years age groups, respectively, vs. 76.2% for >80 years). Similar results were seen in the cIAI group (81.1% and 75.2% for <65 years and 65–80 years age groups, respectively, vs. 69.2% for >80 years). In the cSSTI group there was a particularly high proportion of responders among the >80 years group (76.2%) (Table 2). Overall, the youngest patients (<65 years) showed the best response to treatment; however, almost 70% of the >80 age group were classified as responders to tigecycline at the end of treatment (74.7% for <65 years, 73.6% for 65–80 years and 69.7% for >80% years; data not shown). Marginally more patients in the oldest age group (>80 years) were classified as having an indeterminate response (9.2% for <65 years, 10.7% for 65–80 years and 11.5% for >80% years). Analysis of the response rates in the different age groups showed no statistical association between age group and response (χ^2 *P*-value = 0.706).

Among those patients with an APACHE II score >15, response rates declined slightly with increasing age in the cIAI group (80.2% for <65 years, 73.2% for 65–80 years and 73.3% for >80 years), and decreased in the cSSTI group between the <65 years and 65–80 years age groups (80.0% vs. 70.7%, respectively).

3.2.2. Clinical response by site of infection acquisition

Community-acquired infections were associated with better clinical response across all age groups compared with nosocomial

Table 2
Clinical response of patients included in the analysis.

Response	cSSTI (*N* = 254)						cIAI (*N* = 785)					
	<65 years (*n* = 117)		65–80 years (n = 114)		>80 years (n = 23)		<65 years (n = 370)		65–80 years (n = 358)		>80 years (*n* = 54)	
	n (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*
Overall response												
Non-responder	9 (8.7)	104	15 (14.3)	105	3 (14.3)	21	44 (13.0)	339	51 (15.0)	339	9 (17.3)	52
Responder	83 (79.8)		84 (80.0)		16 (76.2)		275 (81.1)		255 (75.2)		36 (69.2)	
Indeterminate	12 (11.5)		6 (5.7)		2 (9.5)		20 (5.9)		33 (9.7)		7 (13.5)	
By severity of disease												
APACHE II score >15 (responder)	28 (80.0)	35	29 (70.7)	41	4 (80.0)	5	105 (80.2)	131	123 (73.2)	168	22 (73.3)	30
By site of infection acquisition												
Nosocomial (responder)	38 (73.1)	52	49 (77.8)	63	9 (69.2)	13	164 (78.8)	208	164 (73.2)	224	25 (67.6)	37
Community (responder)	44 (86.3)	51	35 (83.3)	42	7 (87.5)	8	109 (85.2)	128	89 (79.5)	112	11 (73.3)	15
By therapy type												
Combination (responder)	21 (67.7)	31	15 (57.7)	26	4 (66.7)	6	125 (76.7)	163	102 (70.8)	144	11 (68.8)	16
Monotherapy (responder)	62 (84.9)	73	69 (89.6)	77	12 (80.0)	15	150 (85.2)	176	153 (78.5)	195	25 (69.4)	36
Empirical (responder)	21 (87.5)	24	28 (87.5)	32	7 (77.8)	9	86 (80.4)	107	73 (69.5)	105	8 (61.5)	13
Targeted (responder)	25 (75.8)	33	31 (77.5)	40	4 (100.0)	4	44 (77.2)	57	62 (82.7)	75	10 (71.4)	14
First-line (responder)	27 (79.4)	34	32 (88.9)	36	6 (100.0)	6	74 (83.1)	89	86 (72.3)	119	13 (68.4)	19

cSSTI, complicated skin and soft-tissue infection; cIAI, complicated intra-abdominal infection; APACHE, Acute Physiology and Chronic Health Evaluation.

infections, with the most marked difference in the >80 years age group of the total pooled population (64.0% nosocomial responders vs. 82.4% community responders) (Fig. 1). The relationship between site of infection acquisition and clinical response was similar in the cIAI and cSSTI groups, with the difference between nosocomial and community-acquired infection being most pronounced in the cSSTI group (Table 2).

3.2.3. Tigecycline therapy

Tigecycline was prescribed as monotherapy in 181 (71.8%) cSSTI patients and 430 (54.8%) cIAI patients [18]. The likelihood of being prescribed tigecycline monotherapy increased with age in the total pooled population (41.6% for <65 years, 52.9% for 65–80 years and 59.0% for >80 years), a trend that was reflected both in the cSSTI and cIAI groups (see Table 2). Tigecycline monotherapy was associated with a better response rate compared with combination therapy for all age groups (Fig. 2). Monotherapy also appeared to be related to improved clinical response compared with combination therapy both in the cIAI and cSSTI groups, with a more pronounced difference observed in the cSSTI group (Fig. 2). There was no clear association between empirical versus targeted therapy in terms of clinical response across the age groups (Table 2).

3.3. Adverse events and mortality

Patients with cIAI appeared to be at greater risk for all types of AE compared with those with cSSTI, particularly in the 65–80 years and >80 years age groups (Table 3). Discontinuation due to an AE did not show any clear association with any age group. Total discontinuations were higher in the >80 age group compared with the younger age groups (cSSTI, 25.0% for >80 years vs. 18.7% and 18.0% for <65 years and 65–80 years, respectively; and cIAI, 45.9% for >80 years vs. 22.9% and 29.6% for <65 years and 65–80 years, respectively).

All-cause mortality observed in the total pooled population treated with tigecycline alone or in combination with other therapies was 9.4% for those with cSSTI and 18.6% for those with cIAI [18]. Overall, there was a trend towards higher mortality with increasing age, which was more pronounced in the cIAI group (13.8% for <65 years, 21.8% for 65–80 years and 31.5% for >80 years) than in the cSSTI group (9.4% for <65 years, 9.6% for 65–80 years and 8.7% for >80 years). Rates of overall mortality and mortality due to an AE were higher for patients with cIAI than those with cSSTI (Table 3).

4. Discussion

In this analysis, use of tigecycline was investigated in different age groups ($N = 1782$ patients) in real-life clinical practice in five observational studies in four European countries.

Overall, the patient population in these observational studies was representative of that seen in clinical practice; many had an APACHE II or SOFA score indicative of severe disease, most had previously been treated with other antibiotics, and the majority suffered from co-morbidities.

Over one-half of the total patient population from these pooled studies was ≥65 years of age, meaning that this study represents an older population than is typically included in clinical trials and more closely resembles the patients likely to receive tigecycline for cIAI or cSSTI in clinical practice. The relatively small number ($n = 139$) of patients in the >80 years age group limits interpretation of the observations from this analysis but is to be expected based on general population demographics. Likewise, the lower representation of males in the higher age groups is equally unsurprising considering the typically lower life expectancy for males [20].

The higher frequency of co-morbidities observed among patients aged ≥65 years reflects the frequency of co-morbidities in the elderly reported widely in the literature [21]. The lower rate of smoking with increasing age may be related to the lower life expectancy of people who smoke, who may therefore be less likely to reach 80 years of age [22]. The equal split between nosocomial and community-acquired infections in the cSSTI group is in accordance with other reports in the literature [11].

Overall, this analysis indicates that tigecycline is a rational therapy choice in very elderly patients for the treatment both of cIAIs and cSSTIs despite the previously mentioned challenges of immune degradation, increased risk of drug-resistant infection, atypical signs of infection, co-morbidities and vulnerability to AEs. As a greater percentage of patients received first-line tigecycline therapy in the older age category (for cIAI), it is possible that tigecycline was the drug of choice in these patients to reduce the risk of treatment failure due to resistance. Clinical response rates in those aged >80 years, although slightly lower than in younger patients, perhaps due to the higher rate of polymicrobial infection in the older group, remain high with no statistically significant differences from the other age groups. This finding differs from experience elsewhere in the literature where a clear relationship between older age and persistence of infection has been shown [23]. Those patients receiving monotherapy as opposed to combination therapy achieved better clinical response rates;

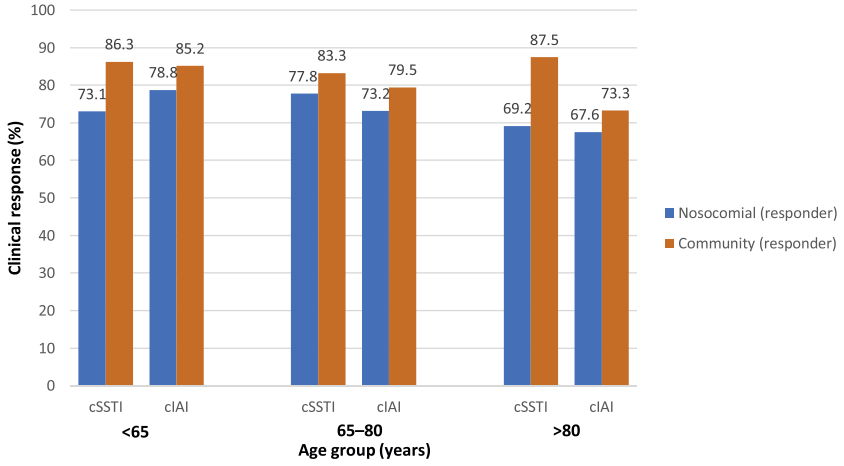

Fig. 1. Tigecycline age analysis by site of infection acquisition (nosocomial versus community-acquired). cSSTI, complicated skin and soft-tissue infection; cIAI, complicated intra-abdominal infection.

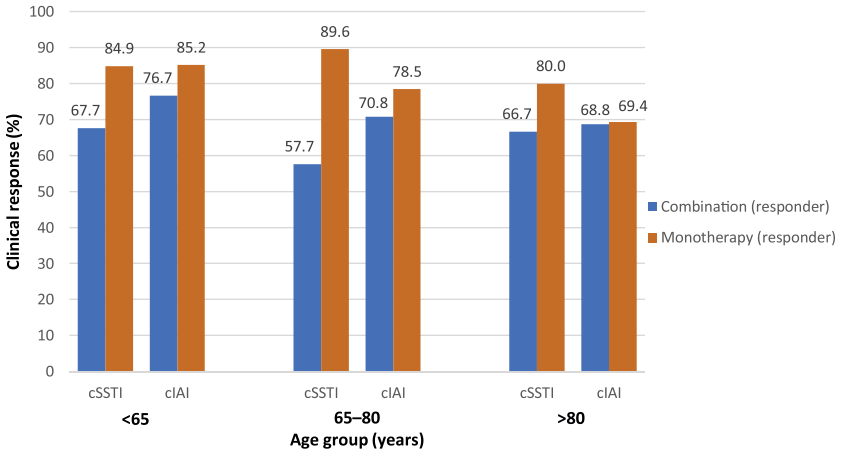

Fig. 2. Tigecycline age analysis by type of therapy (monotherapy versus combination therapy). cSSTI, complicated skin and soft-tissue infection; cIAI, complicated intra-abdominal infection.

Table 3
Adverse events of patients included in the analysis.

	cSSTI (*N* = 254)						cIAI (*N* = 785)					
	<65 years (*n* = 117)		65–80 years (*n* = 114)		>80 years (*n* = 23)		<65 years (*n* = 370)		65–80 years (*n* = 358)		>80 years (*n* = 54)	
	n (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*N*
Adverse events (AEs)												
Total no. of AEs	46	92	37	90	7	16	208	279	240	271	46	37
Patients with AEs	27 (29.3)		17 (18.9)		5 (31.3)		89 (31.9)		113 (41.7)		19 (51.4)	
Patients with serious AEs	15 (16.3)		12 (13.3)		2 (12.5)		58 (20.8)		77 (28.4)		15 (40.5)	
Patients with severe AEs	14 (15.2)		4 (4.4)		1 (6.3)		36 (12.9)		45 (16.6)		13 (35.1)	
Deaths due to AEs	10 (10.9)		7 (7.8)		2 (12.5)		36 (12.9)		59 (21.8)		12 (32.4)	
Discontinuation due to AE	7 (7.6)		3 (3.3)		1 (6.3)		24 (8.6)		22 (8.1)		6 (16.2)	
Overall mortality												
Total no. of deaths	11 (9.4)	117	11 (9.6)	115	2 (8.7)	23	51 (13.8)	370	78 (21.8)	358	17 (31.5)	54
Total discontinuations	17 (18.7)	91	16 (18.0)	89	4 (25.0)	16	64 (22.9)	279	80 (29.6)	270	17 (45.9)	37
AE	3 (17.6)	17	2 (12.5)	16	1 (25.0)	4	3 (4.7)	64	7 (8.9)	80	3 (17.6)	17
Treatment failure	6 (35.3)		8 (50.0)		0		28 (43.8)		18 (22.8)		4 (23.5)	
Death	6 (35.3)		2 (12.5)		1 (25.0)		13 (20.3)		27 (34.2)		5 (29.4)	
Microbiological failure	1 (5.9)		0		0		9 (14.1)		17 (21.5)		3 (17.6)	
Others	1 (5.9)		4 (25.0)		2 (50.0)		16 (25.0)		18 (22.8)		2 (11.8)	

cSSTI, complicated skin and soft-tissue infection; cIAI, complicated intra-abdominal infection.

however, this could be due to patients with cIAI being more severely ill than those with cSSTI rather than a direct result of the combination therapy. In this study, nosocomial infections were associated with a lower clinical response, which may be related to a host who has severe health concerns. Overall, responses with tigecycline in the elderly were better for those patients who had cSSTI compared with those who had cIAI (76.2% responders in the >80 years group for cSSTI vs. 69.2% for cIAI).

The rates of all classes of AEs and mortality increased with advancing age. The main serious AEs leading to death in cSSTI and cIAI patients were multiorgan failure and progression to sepsis and septic shock. More AEs were seen among patients with cIAI; this may be due to differences in the severity of infection or may reflect the fact that more patients with cSSTI received monotherapy. The non-comparative, non-controlled nature of these observational studies makes it unfeasible to infer causality for the drug regimen used. Nevertheless, it seems clear that an unfavourable outcome of multiorgan failure or sepsis might be related to variables that are independent of treatment; indeed, the delayed management of elderly patients is also a well-known cause of multiorgan failure and septic shock [24]. For example, pre-treatment APACHE II and SOFA scores were closely correlated with mortality, and many patients in these studies had co-morbid conditions and severe infections and/or were critically ill in the ICU. For details about the AEs recorded during these studies and further data on mortality, refer to Guirao et al. [18].

The observational nature of this analysis limits interpretation and the results should be viewed as descriptive only as there was no control group of patients not treated with tigecycline in this assessment. Furthermore, the data can be complex to interpret, particularly given the heterogeneity of patient populations and the differences across the studies in the prescription of tigecycline. Treatment decisions were at the discretion of the treating physician and were non-adjudicated. The patient population was heterogeneous, with different hospital settings and different inclusion/exclusion terms for the five separate studies. Stratification of the total population into three age groups meant that the >80 years age group was small and the conclusions relating to this age group should therefore be viewed with caution. A further limitation is that no pharmacokinetic/pharmacodynamic (PK/PD) data could be provided for this analysis owing to the observational nature of the study; these data are warranted in future trials to accurately define the PK/PD changes in the elderly.

In summary, when tigecycline is used for the treatment of cSSTIs and cIAIs, and at the correct dosage, the results reported in this analysis were associated with a favourable outcome considering the characteristics of the patient population included. This

analysis provides useful data to support clinical decision-making around the use of antibiotics in elderly populations.

Funding

The studies from Germany (NCT00488488), France (NCT00799591) and Spain-1 (NCT00827541) were supported by Wyeth Pharma (now Pfizer). The study from Spain-2 (performed by the Spanish ICU Tigecycline Study Group) and the study from Italy were conducted independently and received no financial support. Editorial support was funded by Pfizer PFE France.

Competing interests

MB serves on scientific advisory boards for AstraZeneca, Bayer, Cubist, Pfizer Inc., MSD, Tetraphase and Astellas Pharma Inc. and has received funding for travel or speaker honoraria from Algorithm, Angelini, Astellas Pharma Inc., AstraZeneca, Cubist, Pfizer, MSD, Gilead Sciences, Novartis, Ranbaxy and Teva; XG has received personal compensation for academic and scientific activities from Pfizer; PM has served as speaker for Astellas, AstraZeneca, Basilea, Cubist, Gilead, MSD, The Medicines Company and Pfizer and has advisory board membership for Astellas, AstraZeneca, Cubist, MSD, Parexel, Tetraphase, The Medicines Company and Pfizer; GMR has served on scientific advisory boards or acted as consultant for Pfizer, AstraZeneca, Merck, Angelini, Menarini, Achaogen, Rempex/The Medicines Company, Basilea, bioMérieux, Biotest, Zambon, Accelerate, Elitech, Nordic Pharma and Thermo Fisher and has received speaker honoraria, travel grants or research grants to the laboratory from Pfizer, AstraZeneca, Novartis, Merck, Angelini, Rempex/The Medicines Company, Basilea, bioMérieux, Becton Dickinson, Estor, Biotest, Zambon, Alifax, Accelerate, Elitech, Nordic Pharma, Liofilchem, Arrow, Seegene and Checkpoints; MSG has received research grants, speaker honoraria or served on scientific advisory board for Pfizer, MSD, Achaogen, GSK, Theravance, Gilead, Novartis, Fresenius Kabi, Fresenius Healthcare, Astellas, Basilea, Thermo Fisher Scientific, Cepheid, Masimo and the European Union (IMI-COMBACTE. H2020-SEPCELL); CE has received research grants, speaker honoraria and served as advisor/consultant for Angelini, Astellas, AstraZeneca, Bayer Healthcare, Durata, MSD, Novartis and Pfizer. GS declares no competing interests.

Ethical approval

The Italian study was approved by a local ethics committee in Italy (Comitato Etico Azienda Ospedaliera Universitaria San Martino di Genova). The observational study from Spain (Spain-1) followed the Declaration of Helsinki on human rights regarding clinical research; the Committee of Ethics and Research of Hospital San Carlos also approved this observational study. Spain-2 was an anonymised retrospective chart review, therefore no approval was required from the Ethics Review Board. In accordance with French law, approval of an ethics committee for the French study was not required. However, the protocol was submitted for advice to the Comité Consultatif pour le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS) and was approved by the institutional review board (Comité d'Evaluation de l'Ethique des Projets de Recherche Biomédicale Groupement Hospitalier Universitaire Nord). All patients gave written informed consent to participate. Approval of the Commission Nationale de l'Informatique et des Libertés (CNIL) was obtained, ensuring that patient data were kept confidential according to French regulations. A Scientific Committee (the authors) independently designed the study and reviewed all of the collected data.

Acknowledgments

The authors thank all of the investigators who documented the patients in these observational studies. Statistical support for the pooled analyses was provided by Michele Wible (Pfizer). Editorial support for this manuscript was provided by Emily Reeve and Yvonne McNamara (Synergy Medical Communications Ltd., London, UK).

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