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Efficacy of tigecycline for the treatment of complicated intra-abdominal infections in real-life clinical practice from five European observational studies

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Objectives: Tigecycline is a broad-spectrum antibiotic approved for the treatment of complicated intra-abdominal infections (cIAIs). The efficacy of tigecycline when administered as monotherapy or in combination with other antibacterials in the treatment of cIAIs in routine clinical practice is described.

Patients and methods: Individual patient-level data were pooled from five European observational studies (July 2006 to October 2011).

Results: A total of 785 cIAI patients who received tigecycline were included (mean age 63.1 ± 14.0 years). Of these, 56.6% were in intensive care units, 65.6% acquired their infection in hospital, 88.1% had at least one comorbidity and 65.7% had secondary peritonitis. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores at the beginning of treatment were 16.9 ± 7.6 ($n=614$) and 7.0 ± 4.2 ($n=108$), respectively, indicating high disease severity. *Escherichia coli* (41.8%), *Enterococcus faecium* (40.1%) and *Enterococcus faecalis* (21.1%) were the most frequently isolated pathogens; 49.1% of infections were polymicrobial and 17.5% were due to resistant pathogens. Overall, 54.8% ($n=430$) received tigecycline as monotherapy and 45.2% ($n=355$) as combination therapy for a mean duration of 10.6 days. Clinical response rates at the end of treatment were 77.4% for all patients (567/733), 80.6% for patients who received tigecycline as monotherapy (329/408), 75.2% for patients with a nosocomial infection (354/471), 75.8% for patients with an APACHE II score >15 (250/330) and 54.2% (32/59) for patients with a SOFA score ≥7.

Conclusions: In these real-life studies, tigecycline, alone and in combination, achieved favourable clinical response rates in patients with cIAI with a high severity of illness.

Keywords: broad-spectrum antibacterial therapy, generalized peritonitis, non-interventional studies, glycylcycline antibiotics

Introduction

Complicated intra-abdominal infections (cIAIs) are difficult to manage, often leading to substantial morbidity and mortality in affected patients.[1] Failure to initiate appropriate antimicrobial therapy early in the course of treatment can lead to an increased risk of clinical failure and increased healthcare costs.[2–4] cIAIs are commonly defined as infections that extend into the peritoneal space and are associated with either abscess formation or peritonitis.[5] From a clinical perspective, peritonitis is further categorized as primary [no loss of gastrointestinal (GI) tract integrity], secondary (loss of GI tract integrity, usually by perforation or from infected viscera such as the appendix) and tertiary (recurrent infection following a primary or secondary peritonitis).[4,6] Secondary peritonitis is the most common form of cIAI and can be further differentiated into community-acquired (~70% of all secondary peritonitis) and post-operative (~30%).[6] These

infections (post-operative and tertiary peritonitis) are usually polymicrobial and have an increasing likelihood of being due to antimicrobial-resistant strains.[4] Local epidemiology is variable, but some of the most commonly isolated pathogens in cIAIs are Gram-negative *Enterobacter* spp., *Escherichia coli, Klebsiella* spp., *Proteus* spp., *Pseudomonas aeruginosa* and the Gram-positive *Enterococcus* spp., *Staphylococcus* spp. and *Streptococcus* spp.[4]

The epidemiological shift towards drug-resistant pathogens in cIAIs, together with the limited number of currently available appropriate antimicrobial agents, presents a challenge for the successful management of this infection, especially in the population of severely ill, high-risk patients. Tigecycline is a broad-spectrum antibiotic with known activity against multiple pathogens often isolated in patients with cIAI.[7–10] The clinical efficacy and safety of tigecycline monotherapy for the treatment of cIAIs has been studied in comparison with a standard regimen of imipenem/cilastatin in several Phase III randomized clinical trials (RCTs),[11–14] and in comparison with a commonly used combination of ceftriaxone sodium plus metronidazole in a multicentre, open-label, randomized study.[15] The results of these trials demonstrated that tigecycline was as efficacious as the comparators for the treatment of cIAIs with a similar safety profile. In September 2010, the US FDA issued a warning regarding an imbalance in overall mortality in patients treated with tigecycline that was noted in the completed clinical trials.[16] A number of meta-analyses have also noted numerically higher all-cause mortality in patients treated with tigecycline versus comparators in RCTs.[17–20] The European Medicines Agency (EMA) reviewed the evidence and concluded that the benefits of tigecycline continue to outweigh its risks; however, they issued a recommendation that tigecycline should be used only when it is known or suspected that other antibiotics are not suitable.[21]

The RCTs conducted to date and included in the meta-analyses have included only a small number of intensive care unit (ICU) patients. In real-life clinical practice, tigecycline may be an option for the treatment of patients with complicated infections that are resistant to other available agents.[7] Many of these patients could be critically ill in an ICU or surgical ward, with substantial comorbidities and higher disease severity than those treated with tigecycline in the published trials.[22] Further data are needed to clarify the role of tigecycline in the treatment of cIAIs in these critically ill patients.

The objective of this analysis was to evaluate the clinical efficacy of tigecycline in patients with cIAI treated in the routine hospital care setting in five non-interventional, observational studies conducted in four European countries [Germany, Italy, France and two studies in Spain (Spain-1 and Spain-2)]. The characteristics and comorbidities of patients with cIAI and the prescription of tigecycline and concomitant use of other antibiotics were also evaluated.

Patients and methods

The analysis included data documented by hospital-based physicians on the treatment and outcomes of patients receiving tigecycline in five non-interventional, observational studies conducted in Europe from July 2006 to October 2011. The study from Germany has been published in full[23,24] and preliminary data from three of the studies (Italy, France and Spain-2) have been presented or published previously.[25–27] The design of each

study and the methodology of data acquisition, assessment of clinical efficacy and the statistical analysis of the five observational studies is provided in detail in the accompanying article by Bassetti *et al.*[28]

In brief, due to the observational nature of the studies, there were few protocol specifications or inclusion/exclusion criteria. Hospitalized patients were included if they received tigecycline for any indication during the study period. Spain-1 included only patients with a diagnosis of complicated skin and soft-tissue infection (cSSTI) or cIAI. Two studies (France and Spain-2) included only patients admitted to the ICU. The administration of tigecycline, dosage, duration of treatment and prescription of other antibiotics during or after the start of tigecycline were at the discretion of the physician. All concomitant medications were permitted. The standard approved dosage of tigecycline is an initial loading dose of 100 mg, followed by 50 mg administered intravenously every 12 h (twice daily), as recommended in the summary of product characteristics.[7]

This research was conducted in accordance with the Declaration of Helsinki and all national and institutional standards. The protocol of each study was approved by the local ethics committee or institutional review board. Due 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 from France and Spain-1.

Diagnosis of cIAI

The diagnosis and classification of cIAI was at the discretion of the physician. cIAIs are commonly defined as complicated when a patient has to be scheduled for a laparotomy or percutaneous aspiration and meets at least three of the following five criteria: (i) fever (rectal temperature 38.5°C/101.3°F); (ii) a white blood cell count of 12000 cells/mm³; (iii) symptoms referable to the abdominal cavity (e.g. anorexia, nausea, vomiting and pain); (iv) signs of intra-abdominal infection, e.g. tenderness (with or without rebound), involuntary guarding, absence of bowel sounds, or abdominal wall rigidity; and (v) radiological evidence of GI perforation or localized collections of potentially infected material.[5]

cIAIs were classified as localized or generalized peritonitis or intra-abdominal abscess. cIAIs that had spread beyond the initial local site were further classified as primary peritonitis (no loss of GI tract integrity), secondary peritonitis (loss of GI tract integrity, usually by perforation or from infected viscera such as the appendix) or tertiary peritonitis (recurrent infection) as pre-specified in the case report form.[4,6]

Data acquisition and evaluations

Data were collected on case report forms at the start of therapy with tigecycline and included patients' characteristics, infection diagnosis, disease severity score, microbiological pathogens isolated and therapy regimens. A description of the cIAI diagnosis was recorded, including the site of infection and classification of peritonitis as primary, secondary or tertiary. The severity of disease at the start of tigecycline therapy was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score in Germany, Italy, Spain-1 and Spain-2 and by the Sequential Organ Failure Assessment (SOFA) score in France and Spain-2. Reasons for tigecycline use were pre-specified in the case report form with check boxes. Local hospital laboratory and microbiology techniques were used to identify isolated pathogens in four studies (Germany, Spain-1, France and Spain-2).[29] The pathogenic species (or species groups) to be documented were pre-specified in the case report form with check boxes.

Clinical outcome

Clinical outcome was assessed by the investigator at the end of treatment (EOT) or upon discharge. For this analysis, patients who were

assessed by the investigator as 'cured' or 'improved, with no further anti-biotic required' were assigned an outcome of 'response' and patients who were assessed by the investigator as 'failure' or 'improved, with further antibiotic required' were assigned an outcome of 'non-response'. Patients whose clinical outcome could not be assessed for any reason were assigned an outcome of 'indeterminate'. Patients who died following a successful response to tigecycline at EOT were counted as 'responders' and patients who died before or at EOT were counted as 'non-responders'.

Safety

The numbers of adverse events (AEs), serious AEs (SAEs), premature dis-continuations and deaths occurring at any time during the study, includ-ing the follow-up period, were recorded. Mortality rates were examined by disease severity score at the time of tigecycline administration. A detailed description of the criteria for the assessment of safety is pro-vided in the accompanying paper by Guirao et al.[30]

Statistical analysis

Descriptive statistics included relative frequencies for categorical vari-ables and means (and standard deviations) or medians (and IQRs) for continuous variables. A pooled analysis of patient-level data from the five studies was conducted for selected characteristics. Only patients with a single diagnosis of cIAI were included; patients who were diag-nosed with cIAI plus another infection (e.g. both cIAI and cSSTI) were excluded. Data were analysed in tabulated summaries with the number of patients with available (i.e. non-missing) data as the denom-inator. Clinical response rates were calculated for patients who received the standard dose of tigecycline as recommended in the summary of product characteristics[7] and were stratified according to mean APACHE II (≤15 or >15) and SOFA (<7 or ≥7) scores documented at baseline, mode of infection acquirement (nosocomial or community-acquired) and treatment with tigecycline as monotherapy or in combination therapy, and as first-line or second-line therapy.

Results

Patient characteristics

Across the five studies, a total of 785 patients with cIAI were treated with tigecycline, representing 44.1% of all patients. Patients' characteristics at the start of tigecycline therapy, in-cluding demographics, disease severity scores and comorbidities, are shown in Table 1. Of the cIAI patients with available data, 58.2% were male, with a mean age of 63.1 ± 14.0 years and a mean body mass index (BMI) of 27.4 ± 6.7 kg/m^2; 49.2% of patients were over the age of 65 years. The cIAIs were primarily classified as nosocomial (65.6% overall), although there was a range across the studies, from 49.5% in Spain-1 to 90.6% in Spain-2. The majority of patients had a history of prior anti-bacterial therapy (76.9%) and suffered from at least one co-morbidity (88.1%). Of 689 patients with one or more comorbidities, these included hypertension (58.4%), diabetes mellitus (30.4%), arteriosclerosis/coronary heart disease (26.9%) and renal insufficiency (24.7%); 22.8% of patients were classified as obese.

There was heterogeneity between the studies with regard to the percentage of patients enrolled from the ICU, with all patients (100.0%) in France and Spain-2 in the ICU at the time of tigecycline administration, compared with 1.1% of patients in Spain-1, 46.3% in Italy and 61.7% in Germany (Table 1).

Disease severity scores

APACHE II scores were collected at baseline in four of the five studies and were documented in a total of 614 patients in Germany, Italy, Spain-1 and Spain-2 (Table 1). The overall mean APACHE II score was 16.9, with the lowest mean score (7.9) recorded for patients in Spain-1 and the highest mean score (19.5) for patients in Spain-2. A total of 357 (58.1%) patients had an APACHE II score >15, and the mean score among these patients was 21.6 (median 20.0). SOFA scores were documented for 108 patients in France and Spain-2. Mean SOFA scores in these countries were 6.8 and 7.5, respect-ively. Overall, 60 patients (55.6%) had a SOFA score ≥7, and the mean score among these patients was 10.1 (median 9.0) (Table 1). Figure 1 shows the percentage of patients across the five studies with high disease severity at the time of tigecycline administration, as evidenced by APACHE II score >15 or SOFA score ≥7.

Description of cIAI

A description of infection characteristics was available for 590 patients in three studies (Germany, Spain-1 and France) (Table 2). Diffuse (generalized) peritonitis was the most common type of cIAI infection, presenting in 51.2% of patients; 32.7% had local peritonitis and 21.6% an intra-abdominal abscess. The majority of peritonitis cases (65.7%) were classified as secondary. The most common sites of infection were the colon/rectum (41.4%), liver/pancreas (21.7%) and small intestine (19.9%).

Antibiotic treatment

Across the five studies, there were 734 cIAI patients (93.5%) who received the standard dosage of tigecycline (Table 3). The mean duration of therapy with tigecycline was 10.6 ± 6.1 days (range 1–78 days). Data on the use of tigecycline as first- or second-line therapy were available for 781 patients. There was heterogeneity across the studies in the prescription of tigecycline; however, overall tigecycline was initiated first-line in 48.7% and second-line in 51.3% of patients. Tigecycline was used as monotherapy in 54.8% of cIAI patients and in combination with other antibac-terials in 45.2% (Table 3). However, there were differences between the studies, with 81.8% of the patients in Spain-2 re-ceiving tigecycline in combination with another antibacterial compared with only 4.3% of the patients in Italy. Data on the concomitant use of antibacterials were available for 348 patients in Germany, Spain-1, France and Spain-2 (Table 4). Although there were differences between countries, the most commonly used antibiotic classes used in combination with tigecycline were third- and fourth-generation cephalosporins in Germany (45.1%), aminoglycosides in France (43.9%) and fluoroquino-lones in Spain-1 (50.0%) and Spain-2 (33.3%).

Reasons for tigecycline use

Data on the main reasons for tigecycline use in cIAI patients were available for 785 patients (Table 5). Mainly, tigecycline was used when resistant pathogens were suspected (42.9%), when the infection required a broad-spectrum antibiotic or was

Table 1. Summary of patient characteristics

	Country where study was performed					
	Germany	Italy	Spain-1	France	Spain-2	Total
Number of cIAI patients	418	162	94	78	33	785
Demographics						
male, *n* (%)	256 (61.2)	89 (54.9)	47 (50.0)	43 (55.1)	22 (66.7)	457 (58.2)
age (years), mean ± SD (range)	64.0 ± 12.9 (19–89)	63.9 ± 14.7 (18–92)	59.1 ± 16.5 (18–89)	63.0 ± 14.2 (19–86)	60.6 ± 14.6 (25–84)	63.1 ± 14.0 (18–92)
BMI (kg/m^2), mean ± SD	27.7 ± 6.9	NA	26.0 ± 5.3	27.3 ± 7.0	NA	27.4 ± 6.7
Clinical characteristics						
ICU admission, *n* (%)	258 (61.7)	75 (46.3)	1 (1.1)	78 (100.0)	32 (100.0)	444 (56.6)
missing/unknown, *n*	0	0	0	0	1	1
history of prior antibacterial, *n* (%)	358 (85.6)	127 (78.4)	15 (16.0)	73 (93.6)	31 (93.9)	604 (76.9)
presence of ≥1 comorbidity, *n* (%)	395 (94.5)	149 (92.0)	73 (80.2)	42 (53.8)	30 (90.9)	689 (88.1)
missing/unknown, *n*	0	0	3	0	0	3
Mode of infection acquirement						
nosocomial, *n* (%)	281 (67.7)	103 (64.0)	46 (49.5)	52 (66.7)	29 (90.6)	511 (65.6)
community, *n* (%)	134 (32.3)	58 (36.0)	47 (50.5)	26 (33.3)	3 (9.4)	268 (34.4)
missing/unknown, *n*	3	1	1	0	1	6
Severity/organ dysfunction scores						
APACHE II score, *n*	386	162	34	NA	32	614
mean ± SD (range)	18.5 ± 8.2 (0–59)	14.3 ± 4.3 (4–25)	7.9 ± 4.0 (2–18)	—	19.5 ± 6.0 (6–36)	16.9 ± 7.6 (0–59)
≤15, *n* (%)	131 (33.9)	84 (51.9)	33 (97.1)	—	9 (28.1)	257 (41.9)
≤15, mean (median)	10.5 (12.0)	10.9 (11.0)	7.5 (8.0)	—	12.3 (13.0)	10.3 (11.0)
>15, *n* (%)	255 (66.1)	78 (48.1)	1 (2.9)	—	23 (71.9)	357 (58.1)
>15, mean (median)	22.6 (21.0)	17.9 (17.0)	18.0 (18.0)	—	22.3 (22.0)	21.6 (20.0)
missing/unknown, *n*	32	0	60	—	1	93
SOFA score, *n*	NA	NA	NA	76	32	108
mean ± SD (range)	—	—	—	6.8 ± 4.4 (0–17)	7.5 ± 3.6 (0–14)	7.0 ± 4.2 (0–17)
<7, *n* (%)	—	—	—	36 (47.4)	12 (37.5)	48 (44.4)
<7, mean (median)	—	—	—	2.9 (3.0)	4.0 (5.0)	3.1 (3.0)
≥7, *n* (%)	—	—	—	40 (52.6)	20 (62.5)	60 (55.6)
≥7 mean (median)	—	—	—	10.4 (10.0)	9.6 (9.0)	10.1 (9.0)
missing/unknown, *n*	—	—	—	2	1	3
Patients with ≥1 comorbidity, *n*	395	149	73	42	30	689
comorbid conditions[a]						
hypertension, *n* (%)	246 (62.3)	NA	31 (42.5)	NA	13 (44.8)	290 (58.4)
diabetes mellitus, *n* (%)	108 (27.3)	67 (45.0)	15 (20.5)	13 (31.0)	6 (20.7)	209 (30.4)
arteriosclerosis/CHD, *n* (%)	119 (30.1)	NA	7 (9.6)	NA	NA	126 (26.9)
heart failure, *n* (%)	76 (19.2)	53 (35.6)	4 (5.5)	NA	4 (13.8)	137 (21.2)
COPD, *n* (%)	62 (15.7)	34 (22.8)	8 (11.0)	NA	7 (24.1)	111 (17.2)
renal insufficiency, *n* (%)	131 (33.2)	28 (18.8)	4 (5.5)	4 (9.5)	3 (10.3)	170 (24.7)
hepatic failure, *n* (%)	39 (9.9)	9 (6.0)	2 (2.7)	0	3 (10.3)	53 (7.7)
neoplasia, *n* (%)	100 (25.3)	111 (74.5)	NA	NA	13 (44.8)	224 (39.1)
immunosuppression, *n* (%)	33 (8.4)	21 (14.1)	8 (11.0)	26 (61.9)[b]	5 (17.2)	93 (13.5)
obesity, *n* (%)	107 (27.1)	19 (12.8)[c]	17 (23.3)	14 (33.3)	0[c]	157 (22.8)[c]
alcohol abuse, *n* (%)	54 (13.7)	7 (4.7)	6 (8.2)	NA	2 (6.9)	69 (10.7)
smoking, *n* (%)	79 (20.0)	NA	8 (11.0)	NA	1 (3.4)	88 (17.7)
missing/unknown, *n*	0	0	0	0	1	1

CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; NA, not available.
Percentages were calculated for patients with non-missing data only.
[a]Percentages of comorbid conditions were calculated for patients with at least one comorbidity.
[b]Includes neoplasia in France.
[c]Includes study-level data from Italy and Spain-2.

of polymicrobial origin (53.3%) and when previous therapy had failed (38.6%). Allergy or intolerance to other antibiotics was the reason given for tigecycline prescription in 14.9% of patients in Spain-1 and 27.3% in Spain-2. Renal failure was listed as a reason for 15.4% of patients in France.
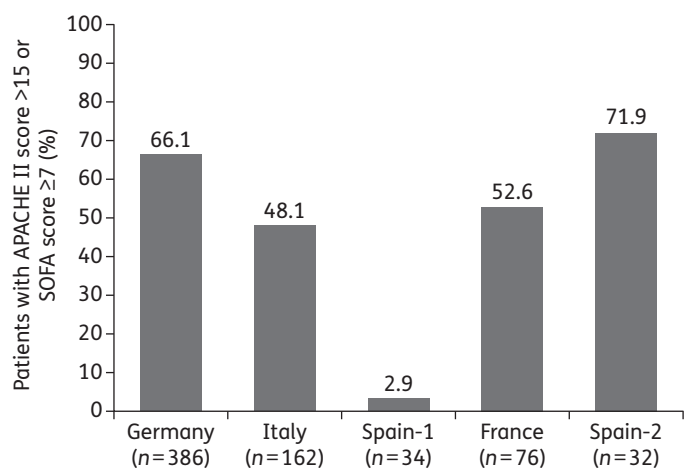
Pathogens isolated at baseline

In Germany, Spain-1, France and Spain-2, microbiological data were available for 623 patients with cIAI. Among these, 464 patients (74.5%) had at least one pathogen and 306 patients (49.1%) had more than one pathogen isolated from intra-abdominal specimens at the start of tigecycline therapy. Among patients with at least one isolate, the most frequently detected pathogens were *E. coli* (41.8%), *Enterococcus faecium* (40.1%) and *Enterococcus faecalis* (21.1%). Other notable Gram-negative pathogens included *Enterobacter* spp. [55 patients (11.9%)], *Klebsiella pneumoniae* [50 patients (10.8%)] and *P. aeruginosa* [45 patients (9.7%)]. *Staphylococcus aureus* was identified in 55 (11.9%) patients. A pooled analysis of the proportion of patients with selected resistant pathogens [including extended-spectrum β-lactamase (ESBL)-producing *E. coli*, *Klebsiella oxytoca* and *K. pneumoniae*, vancomycin-resistant *Enterococcus* (VRE) and methicillin-resistant *S. aureus* (MRSA)] showed that, overall, 17.5% of patients had at least one resistant pathogen and 2.7% had more than one resistant pathogen at baseline. Further data on the microbiological findings from these studies are provided in the accompanying article by Heizmann et al.[29]

Figure 1. Disease severity at baseline in patients with cIAI. Percentages were calculated for patients with non-missing data only. Disease severity was assessed by APACHE II score in Germany, Italy, Spain-1 and Spain-2, and by SOFA score in France.

Table 2. Description of cIAIs

| | Country where study was performed | | | | | |
	Germany	Italy	Spain-1	France	Spain-2	Total
Number of patients	418	NA	94	78	NA	590
Infection subtype[a]						
local peritonitis, n (%)	130 (32.3)	—	41 (45.6)	9 (15.3)	—	180 (32.7)
generalized peritonitis, n (%)	230 (57.2)	—	14 (15.6)	38 (64.4)	—	282 (51.2)
intra-abdominal abscess, n (%)	72 (17.9)	—	35 (38.9)	12 (20.3)	—	119 (21.6)
missing/unknown, n	16	—	4	19	—	39
Type of peritonitis[b]						
primary, n (%)	81 (21.1)	—	14 (16.3)	0	—	95 (17.5)
secondary, n (%)	285 (74.2)	—	48 (55.8)	24 (32.9)	—	357 (65.7)
tertiary, n (%)	18 (4.7)	—	24 (27.9)	49 (67.1)	—	91 (16.8)
missing/unknown, n	34	—	8	5	—	47
Infection site[a]						
appendix, n (%)	14 (3.8)	—	6 (6.4)	1 (1.3)	—	21 (3.9)
biliary tract/gall bladder, n (%)	35 (9.6)	—	15 (16.0)	8 (10.3)	—	58 (10.8)
colon/rectum/large intestine, n (%)	154 (42.1)	—	31 (33.0)	38 (48.7)	—	223 (41.4)
duodenum/stomach, n (%)	45 (12.3)	—	4 (4.3)	6 (7.7)	—	55 (10.2)
liver/pancreas, n (%)	81 (22.1)	—	25 (26.6)	11 (14.1)	—	117 (21.7)
small intestine, n (%)	80 (21.9)	—	13 (13.8)	14 (17.9)	—	107 (19.9)
other, n (%)	9 (2.5)	—	3 (3.2)	12 (15.4)	—	24 (4.5)
missing/unknown, n	52	—	0	0	—	52

NA, not available.
Percentages were calculated for patients with non-missing data only.
[a]Patients could have more than one infection subtype or site.
[b]Refers to any subtype of infection and includes patients with intra-abdominal abscess who were classified as having secondary or tertiary peritonitis according to physician reporting.

Table 3. Prescription of tigecycline, alone or in combination, in patients with cIAI

	Country where study was performed					Total
	Germany	Italy	Spain-1	France	Spain-2	
Number of patients	418	162	94	78	33	785
Standard dosage, *n* (%)	375 (89.7)	162 (100.0)	93 (98.9)	73 (93.6)	31 (93.9)	734 (93.5)
Duration (days), mean (range)[a]	10.7 (1–51)	9.5 (3–25)	11.1 (3–25)	9.8 (2–78)	16.0 (6–37)	10.6 (1–78)
Therapy regimen						
first-line, *n* (%)	188 (45.0)	116 (71.6)[b]	21 (22.3)	43 (58.1)	12 (36.4)[b]	380 (48.7)[b]
second-line, *n* (%)	230 (55.0)	46 (28.4)[b]	73 (77.7)	31 (41.9)	21 (63.6)[b]	401 (51.3)[b]
missing/unknown, *n*	0	0	0	4	0	4
monotherapy, *n* (%)	192 (45.9)	155 (95.7)	56 (59.6)	21 (26.9)	6 (18.2)	430 (54.8)
in combination with other antibacterials, *n* (%)	226 (54.1)	7 (4.3)	38 (40.4)	57 (73.1)	27 (81.8)	355 (45.2)

Percentages were calculated for patients with non-missing data only.
[a]Only patients who received a standard dosage regimen of tigecycline were included.
[b]Includes study-level data from Italy and Spain-2.

Table 4. Antibacterial agents used in combination with tigecycline for treatment of patients with cIAI

	Country where study was performed					Total
	Germany	Italy	Spain-1	France	Spain-2	
Number of patients receiving combination therapy	226	7	38	57	27	355[a]
Agent, *n* (%)[b]						
third-/fourth-generation cephalosporins	102 (45.1)	NA	11 (28.9)	5 (8.8)	3 (11.1)	121 (34.8)
ceftazidime	86 (38.1)	NA	11 (28.9)	2 (3.5)	3 (11.1)	102 (29.3)
cefepime	14 (6.2)	NA	0	0	0	14 (4.0)
aminoglycosides	4 (1.8)	NA	7 (18.4)	25 (43.9)	8 (29.6)	44 (12.6)
amikacin	1 (0.4)	NA	6 (15.8)	22 (38.6)	7 (25.9)	36 (10.3)
carbapenems	26 (11.5)	NA	4 (10.5)	7 (12.3)	7 (25.9)	44 (12.6)
imipenem	10 (4.4)	NA	3 (7.9)	5 (8.8)	2 (7.4)	20 (5.7)
meropenem	14 (6.2)	NA	1 (2.6)	1 (1.8)	5 (18.5)	21 (6.0)
fluoroquinolones	36 (15.9)	NA	19 (50.0)	3 (5.3)	9 (33.3)	67 (19.3)
ciprofloxacin	28 (12.4)	NA	12 (31.6)	3 (5.3)	7 (25.9)	50 (14.4)
glycopeptides	8 (3.5)	NA	1 (2.6)	3 (5.3)	3 (11.1)	15 (4.3)
metronidazole	18 (8.0)	NA	3 (7.9)	3 (5.3)	4 (14.8)	28 (8.0)
penicillins	24 (10.6)	NA	3 (7.9)	14 (24.6)	4 (14.8)	45 (12.9)
piperacillin/tazobactam	7 (3.1)	NA	3 (7.9)	12 (21.1)	4 (14.8)	26 (7.5)

NA, not available.
Percentages were calculated for patients with non-missing data only.
[a]Denominator for percentage calculations in the total column (*n*=348) does not include patients in Italy.
[b]Patients could receive more than one antibacterial in combination with tigecycline.

Clinical outcome

Clinical response rates for cIAI patients who received the standard dose of tigecycline are shown in Table 6 and Figures 2–4. A successful clinical response was documented for 567/733 patients (77.4%) who received tigecycline alone or in combination, and overall response rates ranged from 61.6% in France (where all of the patients were in the ICU) to 91.3% in Spain-1 (where only 1.1% were in the ICU) (Figure 2). There was a trend towards higher response rates in patients with lower versus higher APACHE II scores (Table 6). Among 330 patients with an APACHE II score >15 at the time of tigecycline administration, there were 250 (75.8%) responders, 54 non-responders (16.4%) and 26 (7.9%) with an indeterminate outcome. Among 59 patients in France and Spain-2 with a SOFA score

Table 5. Reasons for tigecycline use, alone or in combination, in patients with cIAI

	Country where study was performed					
	Germany	Italy	Spain-1	France	Spain-2	Total
Number of patients	418	162	94	78	33	785
Reason, n (%)[a]						
failure of previous therapy[b]	226 (54.1)	33 (20.4)[c]	26 (27.7)	12 (15.4)	6 (18.2)[c]	303 (38.6)[c]
suspicion of resistant pathogens	191 (45.7)	102 (63.0)[c]	14 (14.9)	23 (29.5)	7 (21.2)[c]	337 (42.9)[c]
need broad-spectrum coverage/polymicrobial infection	204 (48.8)	NA	50 (53.2)	56 (71.8)	22 (66.7)[c]	332 (53.3)[c]
allergy to/intolerance of previous antibacterial	6 (1.4)	15 (9.3)[c]	14 (14.9)	7 (9.0)	9 (27.3)[c]	51 (6.5)[c]
renal impairment	NA	NA	NA	12 (15.4)	0[c]	12 (10.8)[c]
other	NA	NA	NA	8 (10.3)	NA	8 (10.3)

NA, not available.
Percentages were calculated for patients with non-missing data only.
[a]Patients could have more than one reason.
[b]Previous therapy includes all treatments that were given prior to treatment with tigecycline.
[c]Includes study-level data from Italy and Spain-2.

Table 6. Clinical response at EOT in patients with cIAI who received the standard dose of tigecycline alone or in combination

	Country where study was performed					
	Germany	Italy	Spain-1	France	Spain-2	Total
Clinical response by disease severity						
number of patients	345	162	34	NA	30	571
APACHE II ≤15, n/n (%)	93/116 (80.2)	69/84 (82.1)	28/33 (84.8)	—	5/8 (62.5)	195/241 (80.9)
APACHE II >15, n/n (%)	171/229 (74.7)	63/78 (80.8)	0/1	—	16/22 (72.7)	250/330 (75.8)
number of patients	NA	NA	NA	71	30	101
SOFA <7, n/n (%)	—	—	—	25/32 (78.1)	8/10 (80.0)	33/42 (78.6)
SOFA ≥7, n/n (%)	—	—	—	19/39 (48.7)	13/20 (65.0)	32/59 (54.2)
Clinical response by therapy regimen						
number of patients	375	NA	92	69	NA	536
first-line therapy, n/n (%)	130/168 (77.4)	—	19/20 (95.0)	24/39 (61.5)	—	173/227 (76.2)
second-line therapy, n/n (%)	155/207 (74.9)	—	65/72 (90.3)	17/30 (56.7)	—	237/309 (76.7)

NA, not available.
Percentages were calculated for patients with non-missing data only. Response was defined as clinical cure or improvement without additional antibiotic.

≥7, there were 32 (54.2%) responders, 16 non-responders (27.1%) and 11 (18.6%) with an outcome of indeterminate. Community-acquired infections were associated with higher response rates than those acquired in the hospital (81.6% versus 75.2%, respectively; Figure 3). Seventy-nine of 471 patients (16.8%) with nosocomial infections were classified as non-responders and 38 (8.1%) had an outcome of indeterminate. The clinical response rate was 80.6% (329/408) for patients treated with tigecycline as monotherapy and 73.2% (238/325) for patients who received combination therapy (Figure 4). Forty-nine of 408 patients (12.0%) treated with monotherapy were classified as non-responders and 30 (7.4%) had an indeterminate outcome. No difference was observed in clinical response rates for patients who received tigecycline as first- or second-line therapy (76.2% versus 76.7%, respectively; Table 6).

Safety profile and patient discontinuation

Data on all-cause AEs, SAEs and reasons for discontinuation were available for 590 cIAI patients who received tigecycline alone or in combination in Germany, Spain-1 and France. A total of 499 AEs were documented in 223 patients (37.8%); 151 patients (25.6%) experienced SAEs. Tigecycline was stopped prematurely in 162 patients (27.5%); the main reasons recorded were clinical failure (31.7%) and microbiological failure (18.0%). Data on mortality were available for 785 cIAI patients in all five studies. There were 147 all-cause patient deaths recorded at any time during the study, including the follow-up period, giving a mortality rate of 18.7%. The mortality rate was higher in patients with higher (>15) versus lower (≤15) APACHE II scores (23.8% versus 16.0%, respectively), and a similar trend was seen when
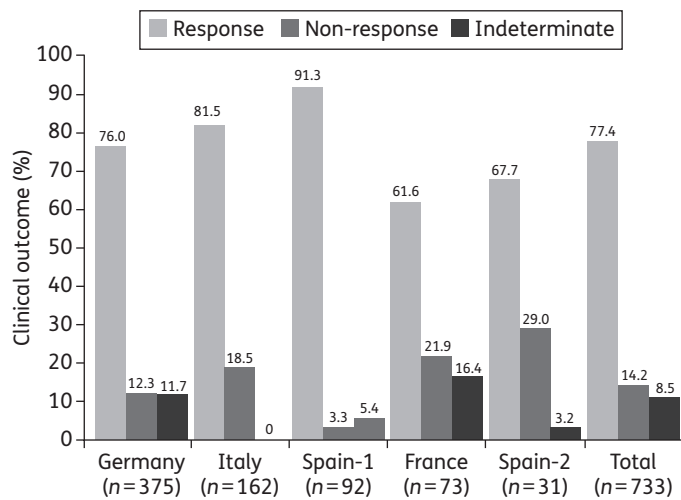
Figure 2. Clinical outcome at EOT in patients with cIAI who received the standard dose of tigecycline alone or in combination. Percentages were calculated for patients with non-missing data only. Response was defined as clinical cure or improvement without additional antibiotic. Non-response was defined as failure or improvement with additional antibiotic. Patients whose response could not be ascertained were assigned an indeterminate outcome.
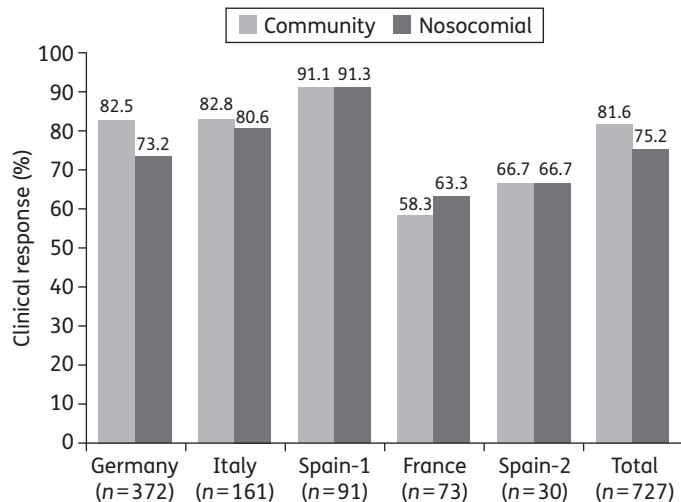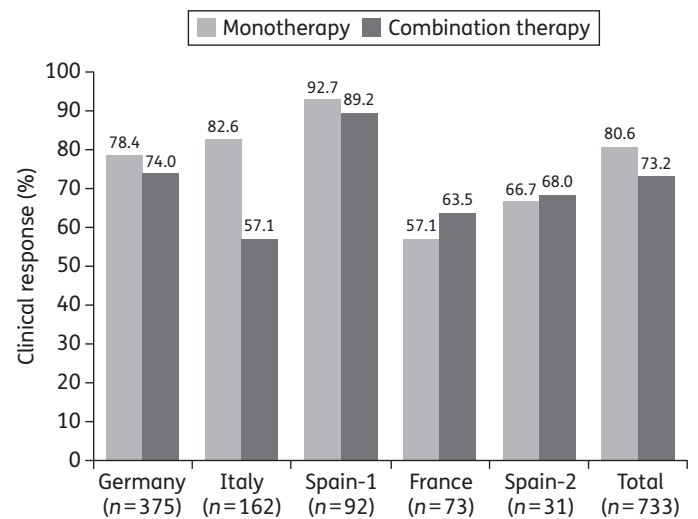

Figure 4. Clinical response in patients with cIAI who received the standard dose of tigecycline alone or in combination. Percentages were calculated for patients with non-missing data only. Response was defined as clinical cure or improvement without additional antibiotic.

Figure 3. Clinical response by mode of infection acquirement in patients with cIAI who received the standard dose of tigecycline alone or in combination. Percentages were calculated for patients with non-missing data only. Response was defined as clinical cure or improvement without additional antibiotic.

patients were stratified by SOFA score (SOFA $\geq$7, 28.3%; SOFA <7, 14.6%). Further data on the safety and tolerability profile of tigecycline in these observational studies is provided in the accompanying article by Guirao *et al.*[30]

Discussion

The treatment of cIAIs consists in general of surgical and/or interventional source control, intensive care and administration

of antibiotics.[5,6] The increasing number of infections due to resistant bacteria (e.g. ESBL producers, VRE, MRSA and carbapenem-resistant bacteria) calls for new drugs that encompass this spectrum of bacteria. Tigecycline has been investigated in RCTs and is licensed for treatment of cIAI.[12] However, the mean APACHE II score in these RCTs was 6.1—thus not representing the severity of illness in (heavily pretreated) patients with infections due to resistant bacteria, who might benefit from treatment with tigecycline.

In this analysis, we investigated the real-life clinical use of tigecycline for the treatment of hospitalized patients with cIAI in five studies from four European countries. All the studies were observational and non-interventional in nature, thus documenting the efficacy and safety of tigecycline as it is used in routine clinical practice. In particular, we were interested in the type, severity and microbiology of patients' infections, their concomitant treatment with other antibiotics, the specific reasons for tigecycline administration and the clinical outcome and safety of tigecycline.

cIAI was the main indication in these studies, accounting for 44.1% of all patients treated with tigecycline in the five studies across Europe. Prescription of tigecycline was therefore used for an approved indication and in accordance with the product charactersitics.[7] In this analysis, tigecycline when administered as monotherapy or in combination with other antibacterials has shown efficacy in cIAI patients with mild to moderate severity (Spain-1) and in high-risk and severely ill patients (Germany, Italy, France and Spain-2). Patients were severely ill from both a systemic point of view (presence of comorbid conditions and high APACHE II or SOFA scores) and a local point of view (high frequency of generalized peritonitis and infections in the colon/rectum and low frequency of appendicitis). The characteristics of patients in these observational studies are quite different from those enrolled in the registration trials, which excluded patients with a high disease severity.[12–15]

Clinicians saw the indication for tigecycline primarily in patients with locally advanced and systemically severe cIAI. The results of the observational trials support the benefit of tigecycline in terms of clinical success. The most recent (2010) guidelines of the Surgical Infection Society and the Infectious Diseases Society of America (SIS-IDSA) for the management of cIAI recommend the use of tigecycline only in patients with mild to moderate disease, based on the limited data available at the time of publishing and due to the fact that the IDSA recommends antibacterial coverage of *Pseudomonas* spp. in community-acquired cIAI in high-risk or severely ill patients.[5] A European expert group has chosen an approach where tigecycline is advocated for use in post-operative and tertiary peritonitis—i.e. forms of peritonitis where the likelihood of resistant bacteria as causative pathogens is much higher than in community-acquired IAIs of mild to moderate severity.[6,31] The new guidelines recently published by the World Society of Emergency Surgery (WSES) recommend tigecycline for the treatment of hospital-acquired IAIs in both stable non-critical patients and critically ill patients presenting with risk factors for multidrug-resistant pathogens.[32]

It is worth noting that tigecycline is the only drug approved for treatment of cIAI due to resistant Gram-positive bacteria (MRSA and VRE).[7] The newer antibiotics (daptomycin and linezolid) are not approved for this indication.[33,34] Studies on the treatment of infections caused by ESBL-producing bacteria have shown that through an individualized strategy of prescribing with a harmonized use of different antibiotic classes, the percentage of resistant Gram-negative bacilli decreased significantly.[35,36] Therefore, the antibiotic-selective pressure on carbapenems may be reduced by using other classes for the treatment of infections caused by ESBL producers (a 'carbapenem-sparing strategy'). On the other hand, most of the studies included patients with pulmonary infections; therefore the results cannot be extrapolated to patients with cIAI.

As expected, the main reasons for use of tigecycline in patients with cIAI were its broad-spectrum coverage, failure of previous antibacterial therapy and suspicion of resistant pathogens. This clinical practice is consistent with current international guidelines recommending tigecycline as single-agent therapy for the empirical treatment of cIAI.[5] There was wide heterogeneity in clinical practice across the four countries, with 95.7% of cIAI patients in Italy receiving tigecycline as monotherapy compared with 18.2% in Spain-2. The high use of combination therapy in Spain-2 may relate to the high severity of illness and proportion of nosocomial infections (>90%) among the patients treated with tigecycline in this study. When used in combination, tigecycline was often paired with third- or fourth-generation cephalosporins. This may indicate that the clinicians intended to cover *Pseudomonas* spp. The pathogenetic role of *Pseudomonas* in cIAI still needs to be clarified, but in the four studies where patients were investigated microbiologically, the proportion of isolated *P. aeruginosa* was in the range of 0%–21%, showing a large variability across the studies.[29] Considering the high selection of critically ill patients in these studies, coverage of non-fermenting Gram-negative pathogens, including *Pseudomonas*, appears to be necessary in some institutions.[37]

Despite the fact that many of the patients in these five studies were critically ill and requiring ICU care at the time of tigecycline administration, and had clinical factors known to be associated with failure of treatment for cIAIs (including high APACHE II scores, advanced age, comorbidity involving organ dysfunction, peritoneal involvement or diffuse peritonitis and healthcare-related infection),[32] the overall clinical outcomes were good, and largely in the range of previously reported results with tigecycline in Phase III trials with populations showing substantially lower mean APACHE II scores.[12] A successful clinical response was observed in 77.4% of all cIAI patients pooled across the five European studies compared with 80% in the pooled tigecycline patients of the two pivotal cIAI trials, in which the mean APACHE II score of tigecycline-treated patients was 6.3 versus 16.9 in the present analysis.[12] In the present analysis, clinical response rates in cIAI patients receiving tigecycline ranged from approximately 62% and 68% in France and Spain-2 to 91% in Spain-1. The difference in response rates may reflect the heterogeneity in patient populations treated with tigecycline across the studies and the finding that all (100.0%) patients in the studies from France and Spain-2 were critically ill in the ICU, compared with only 1.1% of patients in Spain-1. These findings are also consistent with the trend towards lower response rates observed in patients with higher disease severity, as evidenced by clinical response rates stratified by APACHE II and SOFA scores. The numerically higher clinical response rates observed in patients who received tigecycline as monotherapy compared with those who received combination regimens may be a bias related to the preferred use of combination regimens in patients with poor risk profiles and higher disease severity. Consistent with this finding is that the highest percentage of combination therapy use was observed in the studies from France and Spain-2, in which all of the patients were in the ICU.

Recent warnings from both the FDA and EMA have highlighted the numerically higher mortality rate observed in all randomized trials comparing tigecycline and comparators.[16,38] In all Phase III and IV (cSSTI and cIAI) studies, death occurred in 2.4% (54/2216) of patients receiving tigecycline and in 1.7% (37/2206) of patients receiving comparator drugs.[7] Taking into account those findings, the EMA Committee for Medicinal Products for Human Use (CHMP) recommended changes to the product information to ensure that it is used appropriately, by making prescribers aware that the medicine has been associated with an increased mortality in clinical studies.[21]

In accordance with previous literature, our analysis showed that severity of illness, as defined by APACHE II or SOFA score at baseline, was a predictor of mortality in the group of patients for whom these data were collected.[39,40] Additionally, assuming that the probability of the occurrence of a fatal outcome is around 26.2% for a cIAI patient having a disease severity score close to the mean values found in our observational studies (estimated APACHE II score of 17),[41] the observed actual all-cause hospital mortality rate (18.7%) was lower than expected in this group of tigecycline-treated patients.

This analysis has several limitations, and the results should be viewed as descriptive due to the observational, non-interventional and non-comparative design of each study. By definition, observational studies are not allowed to include randomization and control groups. This is one of the limitations of the mentioned studies and does not allow comparison of treatment results with those of another regimen. The data can be complex to interpret, particularly given the heterogeneity across the countries in terms of sites, hospitals and patient

care. Two studies included primarily critically ill patients in the ICU, whereas three studies also included patients from surgical wards with a broader range of disease severity scores. The modality of treatment with tigecycline also varied across studies, as shown by the variation in use of tigecycline as monotherapy or in combination with other antibiotics. Another source of heterogeneity is the epidemiology of multidrug-resistant pathogens that varies across Europe, leading to differences in the clinical approach to empirical treatment. Nevertheless, the clinical success rates in this observational analysis were similar across the different countries, healthcare systems, local microbiological environments, treatment modalities and prescription behaviours, indicating a robust clinical value of tigecycline in real-life scenarios.

In summary, these real-life observational studies in Europe included a high proportion of seriously ill patients who were not captured in the Phase III registration trials of tigecycline. In these patients tigecycline, alone and in combination, achieved favourable clinical response rates. We believe that this analysis adds important information to guide the antibacterial management of this group of patients, who have a substantial morbidity and mortality.

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