



Tigecycline in the treatment of multidrug-resistant *Acinetobacter baumannii* meningitis: Results of the Ege study



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ABSTRACT

Objectives: In this study we retrospectively reviewed *A. baumannii* meningitis cases treated with tigecycline including regimens and evaluated the efficacy of tigecycline in the therapy.

Patients and Methods: Study was performed in seven tertiary-care educational hospitals from five cities of Turkey and one center from France. We extracted data and outcomes of all adult (aged > 18) patients with culture proven *A. baumannii* meningitis treated with tigecycline including antibiotic therapy until April 2016. **Results:** A total of 23 patients (15 male and eight female) fulfilled our inclusion criteria. All *Acinetobacter* strains were carbapenem-resistant and susceptible to tigecycline. Six cases received tigecycline monotherapy while 17 received tigecycline including combination therapy (10 with colistin, 4 with netilmicin, 3 with amikacin, 4 with meropenem). Seven of 23 cases (30%) died during the tigecycline including therapy (1 in monotherapy, 4 in colistin, 2 in netilmicin, 1 amikacin, one case received tigecycline + netilmicin followed by tigecycline + colistin). Hence, overall end of treatment (EOT) success was 70%. However, since further 27% died due to additional nosocomial infections, overall clinical success (relieved symptoms at the EOT and one-month post-therapy survival without any relapse or reinfection) decreased to 43%.

Conclusion: We conclude that tigecycline may be an alternative in the salvage treatment of nosocomial multidrug-resistant *Acinetobacter* spp. meningitis. *Acinetobacter* spp. Meningitis.

1. Introduction

In spite of developments in neurosurgery, antimicrobial agents, medicine and intensive care, meningitis, as well as nosocomial or healthcare-associated meningitis (HCAM), are still associated with

significant mortality and morbidity [1–11]. Multidrug-resistant (MDR) as well as carbapenem-resistant *Acinetobacter baumannii* (CRAB) is an important global problem in any kind of nosocomial infection [4,12–16]. *Acinetobacter* spp is also one of the most common bacterial agents in the etiology of HCAM and the most common one in Turkey

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Table 1
Clinical and laboratory findings at the start of tigecycline including therapy.

Case N	Gender/Age	Fever/Disturbances in level of consciousness/convulsions	Nausea-vomiting/ neck stiffness	CSF leukocyte/mm ³	CSF protein (mg/dl)	CSF glucose (mg/dl)	Blood leukocyte/mm ³ (Blood PNL%)
1	F/39	+ / + / -	+ / +	300	135	40	17000 (85%)
2	M/48	+ / + / -	+ / +	500	132	42	20700 (70%)
3	M/74	+ / + / -	+ / +	280	143	47	16100 (68%)
4	F/53	- / + / -	- / +	280	148	51	10300 (66%)
5	M/79	+ / + / +	+ / +	460	123	54	14700 (69%)
6	F/60	+ / + / +	+ / +	450	103	35	13200 (75%)
7	M/75	+ / + / +	- / -	> 1000	201	50	9140 (82%)
8	M/43	+ / + / -	- / -	3450	2055	32	24100 (94%)
9	M/26	+ / + / +	+ / +	350	110	1	10600 (83%)
10	F/21	- / - / -	- / -	> 1000	167	43	20800 (85.4%)
11	M/55	+ / + / -	- / +	> 1000	104	58	11800 (91.2%)
12	M/23	+ / + / -	- / -	280	397	24	32000 (94.1%)
13	F/58	- / + / -	- / -	> 1000	382	29	15530 (86%)
14	F/46	- / + / -	+ / -	> 1000	38	60	16250(79%)
15	M/43	+ / + / -	- / -	> 1000	82	38	13670 (76%)
16	F/70	+ / + / +	+ / +	> 1000	517	58	10990 (86%)
17	M/68	+ / + / -	+ / +	500	289	27	10800 (74%)
18	M/?	+ / + / -	- / -	> 1000	308	55	19600 (88%)
19	F/48	+ / - / -	+ / -	> 1000	317	59	8400 (82%)
20	M/25	+ / + / -	- / -	300	281	23	11900 (75%)
21	M/47	+ / + / -	+ / -	> 1000	182	41	10300 (70%)
22	M/59	+ / + / -	- / -	> 1000	411	26	7460 (71%)
23	M/37	+ / + / +	+ / +	350	250	40	22000 (75%)

[1,3]. Treatment options are limited and depend on the susceptibility pattern of the infecting isolate [1]. Tigecycline is a glycylcycline antimicrobial agent, active in vitro against a variety of Gram-positive and Gram-negative organisms including CRAB [1,4,17–19]. The United States Food and Drug Administration (FDA) approved tigecycline for the treatment of complicated intra-abdominal infections, complicated skin and skin structure infections and community-acquired pneumonia. However, its off-label use in other CRAB infections such as nosocomial pneumonia, bacteremia or meningitis is common due to its pharmacological profile and bacterial spectrum [5–10]. In this multicenter study, we retrospectively reviewed *A. baumannii* meningitis cases treated with tigecycline including regimens and evaluated the efficacy of tigecycline in the therapy.

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

2. Materials and methods

This study was performed in seven tertiary-care educational hospitals from five cities of Turkey (Izmir, Ankara, Adana, Çanakkale, Diyarbakir) and one hospital from Rennes-France. We extracted data and outcomes of all adult (aged > 18) patients with culture-proven *A. baumannii* meningitis treated with tigecycline including therapy between January 2007–April 2016. Demographic, clinical and laboratory findings, predisposing factors, as well as information on response to treatment and outcome were obtained retrospectively by the study site authors. Ege University Institutional Review Board approved the study.

A definite diagnosis of meningitis was based on the isolation of *A. baumannii* in at least one CSF culture. Typical CSF findings included a leukocytosis with a predominance of polymorphonuclear cells (≥ 250 leukocytes/ml), and classical clinical manifestations of meningitis. Nosocomial meningitis was defined as bacterial infection not present when the patient was admitted to the hospital or clinical evidence of infection within a short period of time after discharge from the hospital where the patient had received an invasive procedure. Patients developing meningitis after neurosurgical procedures were defined as having post-neurosurgical infection [11,20]. Accordingly, all cases had nosocomial post neurosurgical meningitis.

CSF samples were obtained by lumbar puncture or percutaneous aspiration of shunt reservoir or puncture of extra ventricular drainage tubing. Samples were routinely centrifuged and the pellet was Gram stained.

Identification of *A. baumannii* and determination of antimicrobial susceptibility were performed using the VITEK 2 automated system (BioMerieux Inc, Mercy L'etoil, France) and conventional methods. For tigecycline susceptibility, the FDA clinical minimum inhibitory concentration (MIC) breakpoints for *Enterobacteriaceae* (2 mg/l-sensitive) were used. Other antibacterial susceptibility tests were evaluated according to Clinical Laboratory Standards Institute (CLSI) criteria until 2014 and EUCAST in 2015 and 2016 [21,22].

Microbiological success was defined as clearance of *A. baumannii* in repeated CSF cultures on day 3–5 and/or at the end of tigecycline including treatment (EOT). EOT success was defined as relieved symptoms (which were present at the beginning) at the end of treatment accompanied by microbiological success. Overall success was defined as EOT success and one-month post-therapy survival without any relapse or reinfection.

Fisher exact test was used for comparison of major treatment groups.

3. Results

A total of 23 patients (15 male and eight female) fulfilled our inclusion criteria. All cases were in intensive care units at the beginning of the tigecycline including therapy. Gender, age, underlying diseases and other characteristics of the cases, are shown in Tables 1 and 2.

3.1. Clinical presentation and diagnosis

Five cases had shunt infection (2/6 in tigecycline monotherapy group vs 3/17 in others, p:0.57), 12 were on lumbar drainage (6/6 in tigecycline monotherapy group vs 6/17 in others, p:0.013) whereas seven were on external ventricular drainage on the day of CRAB meningitis diagnosis (0/6 in tigecycline monotherapy group vs 7/17 in others-p:0.12- lumbar drainage or external ventricular drainage 6/6 vs 13/17 p:0.53).

Twenty-one cases had disturbances in the level of consciousness (6/

Table 2
Susceptibility data of infecting strains, underlying diseases, treatment details and outcome data of the *A. baumannii* meningitis cases.

Patient no	Bacteria	Antibacterial sensitivity pattern of the infecting <i>A. baumannii</i> strain	Antibiotherapy in the previous 30 days	Underlying condition	Treatment (IV)&duration (day)	Day 3-5 CSF microbiologic response	End of treatment CSF leukocyte/ Culture result	One month follow up result	Glasgow coma score at the start and end of tigeicycline therapy
1	<i>A. baumannii</i>	Tigecycline, colistin	No antibiotic	Cranial mass, lumbar drainage	Tigecycline 2x50 mg (16 days)	Bacterial eradication	Bacterial eradication	No relapse or reinfection	7/14
2	<i>A. baumannii</i>	Tigecycline, colistin	No antibiotic	Intracerebral hemorrhage, lumbar drainage	Tigecycline 2x50 mg (13 days)	Bacterial eradication	Bacterial eradication	No relapse or reinfection	9/14
3	<i>A. baumannii</i>	Tigecycline, colistin	No antibiotic	Intracerebral hemorrhage, lumbar drainage	Tigecycline 2x50 mg (21 days)	Bacterial eradication	Bacterial eradication	Exitus during follow up due to nosocomial pneumonia	9/14
4	<i>A. baumannii</i>	Tigecycline, colistin	Ceftriaxone	Traumatic brain injury, lumbar drainage	Tigecycline 2x50 mg (12 days)	Bacterial eradication	Bacterial eradication	Exitus during follow up due to nosocomial pneumonia	7/9
5	<i>A. baumannii</i>	Tigecycline, colistin	Ampicillin/sulbactam	Subarachnoid bleeding, shunt infection, lumbar drainage,	Tigecycline 2x50 mg (5 days)	No data	No data	Exitus on day 5 of treatment due to meningitis/sepsis.	6/exitus
6	<i>A. baumannii</i>	Tigecycline, colistin	No antibiotic	Traumatic brain injury, shunt infection, lumbar drainage	Tigecycline 2x50 mg (11 days)	Bacterial eradication	Bacterial eradication	Exitus during follow up due to nosocomial pneumonia	7/8
7	<i>A. baumannii</i>	Tigecycline, colistin, tetracycline, doxycycline	Piperacillin/tazobactam	Subdural hematoma	Tigecycline 2x50 mg (54 days) + colistin 3 x 150 mg (13 days)	No data	No data	No relapse or reinfection	9/14
8	<i>A. baumannii</i>	Tigecycline	Ceftriaxone, metronidazole, chloramphenicol	Subacute hematoma, lumbar drainage	Tigecycline 2x50 mg (23 days) + colistin 2 x 150 mg (23 days)	2800 leukocytes/mm ³ / <i>A. baumannii</i>	2800 leukocytes/mm ³ / <i>A. baumannii</i>	Exitus on day 23 of treatment due to meningitis and possible catheter infection	4/exitus
9	<i>A. baumannii</i>	Tigecycline, colistin	No antibiotic	V-P shunt revision, shunt infection,	Tigecycline 2x50 mg (24 days) + colistin 3 x 150 mg (29 days) + colistin 2x5 mg IT (20 days) + vancomycin 2 x 1 gr (19 days)	80 leukocytes/mm ³ / Bacterial eradication	No leukocyte /mm ³ / Bacterial eradication	Exitus at the end of treatment	7/exitus
10	<i>A. baumannii</i>	Tigecycline, amikacin, colistin	Cefazolin, meropenem, linezolid	Nasal encephalocoele, lumbar drainage	Tigecycline 2x50 mg (26 days) + colistin 2 x 150 mg (26 days)	10 leukocytes/mm ³ / Bacterial eradication	Bacterial eradication	No relapse or reinfection	15/15
11	<i>A. baumannii</i>	Tigecycline, colistin, ciprofloxacin, netilmicin, tetracycline, levofloxacin; amikacin (I), imipenem (I), meropenem (II)	Piperacillin/tazobactam, colistin (nephrotoxicity)	Gun shot injury, extraventricular drainage	Tigecycline 2x50 mg (7 days), colistin 2 x 150 mg followed by meropenem 3 x 2 gr (12 days), vancomycin 2 x 1 gr (3 days),	No data	No data	Exitus during treatment possibly due to meningitis.	6/exitus
12	<i>A. baumannii</i> E. faecium	Tigecycline, colistin, amikacin, netilmicin, levofloxacin (I)	Cefazolin, ceftriaxone, metronidazole	Epidural and subdural hematoma	Tigecycline 2x50 mg (16 days) + meropenem 3 x 2 gr (14 days) + vancomycin 2 x 1 gr (18 days), colistin 2 x 150 mg (24 days)	50 leukocytes/mm ³ Bacterial eradication	No data	No relapse or reinfection	10/11
13	<i>A. baumannii</i>	Tigecycline (MIC:0.5 mg/L), gentamicin, tobramycin, netilmicin; cotrimoxazole (I)	Ceftriaxone, vancomycin	Aneurysm; subarachnoid bleeding, extraventricular drainage	Tigecycline 2x50 mg (67 days) + colistin 2 x 150 mg (63 days) + colistin 2x5 mg intrathecal (19 days)	800 leukocytes/mm ³ / <i>A. baumannii</i>	No leukocyte / Bacterial eradication	No relapse or reinfection, reshunting	13/13

(continued on next page)

Table 2 (continued)

Patient no	Bacteria	Antibacterial sensitivity pattern of the infecting <i>A. baumannii</i> strain	Antibiotherapy in the previous 30 days	Underlying condition	Treatment (IV)&duration (day)	Day 3-5 CSF microbiologic response	End of treatment CSF leukocyte/ Culture result	One month follow up result	Glasgow coma score at the start and end of tigecycline therapy
14	<i>A. baumannii</i>	Tigecycline (MIC:0.5 mg/L), colistin gentamicin, netilmicin, amikacin (I)	Cefazolin, meropenem, vancomycin, cefepime, linezolid	Aneurysm, subarachnoid bleeding, extraventricular drainage	Tigecycline 2x50 mg (68 days) + colistin 2x150 mg (14 days) + rifampin 1x600 mg (54 days)	300 leukocytes/mm ³ / Bacterial eradication	No leukocyte / Bacterial eradication	No relapse or reinfection	12/11
15	<i>A. baumannii</i>	Tigecycline, colistin, gentamicin, netilmicin ; doxycycline (I), amikacin (I), levofloxacin (I)	Meropenem, vancomycin	Subdural hemorrhage, shunt infection	Tigecycline 2x50 mg (24 days) + colistin 2x150 mg (24 days) + colistin 2x5 mg intrathecal (22 days)	120 leukocytes/mm ³ / <i>A. baumannii</i>	No leukocyte / Bacterial eradication	Relapse <i>A. baumannii</i> meningitis on day 22	10/10
16	<i>A. baumannii</i>	Tigecycline, cotrimoxazole, netilmicin, doxycycline (I)	Ceftazidime, vancomycin	Lumbar spinal stenosis	Tigecycline 2x50 mg (18 days) + netilmicin 1x150 mg it (3 days) followed by 1x400 mg IV (6 days) followed by colistin 2x150 mg (9 days)	> 1000 leukocytes/mm ³ / <i>A. baumannii</i>	No leukocyte / Bacterial eradication	Exitus on day 18 of treatment possibly due to <i>P. stuartii</i> sepsis.	9/Exitus
17	<i>A. baumannii</i>	Tigecycline, ceftazidime, doxycycline, netilmicin, cefoperazone/sulbactam (I), amikacin (I)	Meropenem, vancomycin	Subarachnoid bleeding, hydrocephalus, extraventricular drainage	Tigecycline 2x50 mg (14 days) + netilmicin (14 days) + linezolid 2x600 mg (14 days)	No leukocyte / Bacterial eradication	No data	Exitus on day 14 of treatment possibly due to meningitis.	13/Exitus
18	<i>A. baumannii</i>	Tigecycline	Cefazolin, cefoperazone/sulbactam, meropenem, vancomycin	Intracerebral hemorrhage, lumbar drainage	Tigecycline 2x50 mg, (18 days) + netilmicin 1x400 mg (18 days)	240 leukocytes/mm ³ / Bacterial eradication	No leukocyte / Bacterial eradication	Reinfection (MRSA)	6/7
19	<i>A. baumannii</i>	Colistin, tigecycline, netilmicin	Cefazolin, meropenem, vancomycin	Pituitary gland adenoma adenoma, rhinorrhea	Tigecycline 2x50 mg (8 days) + netilmicin 1x150 mg intrathecal (3 days) + netilmicin 1x400 mg iv (5 days) netilmicin total 8 days	No data	No data	No relapse or reinfection	15/15
20	<i>A. baumannii</i>	Tigecycline, amikacin, doxycycline	Vancomycin	Hydrocephalus + VP shunt dysfunction, extraventricular drainage	Tigecycline 2x50 mg (25 days) + amikacin 2x500 mg (25 days)	80 leukocytes/mm ³ / <i>A. baumannii</i>	No leukocyte / Bacterial eradication	No relapse or reinfection	10/9
21	<i>A. baumannii</i>	Tigecycline, netilmicin, cefoperazone/sulbactam	Piperacillin/tazobactam, ciprofloxacin, linezolid, teicoplanin	Intracerebral hemorrhage, hydrocephalus, VP shunt infection	Tigecycline 2x50 mg (14 days) + amikacin 2x500 mg (14 days) + rifampin 2x300 mg (14 days)	No data	> 1000 leukocytes/mm ³ / <i>P. aeruginosa</i>	Reinfection (<i>P. aeruginosa</i> meningitis)	5/5
22	<i>A. baumannii</i>	Tigecycline, colistin, amikacin (I), imipenem (I), meropenem (I)	Ceftazidime, vancomycin, meropenem, linezolid	Cerebral abscess, extraventricular drainage	Tigecycline (26 days) + meropenem (33 days) + amikacin (23 days, IT)	> 1000 leukocytes/mm ³ / Bacterial eradication	300 leukocytes/mm ³ / Bacterial eradication	Exitus on day 26 of treatment	7/Exitus
23	<i>A. baumannii</i>	Tigecycline, colistin	Ciprofloxacin	Subdural hematoma, cervical 3-4 fracture, hydrocephalus, extraventricular drainage	Tigecycline 2x50 mg (21 days) + meropenem 3x2 gr (21 days)	80 leukocytes/mm ³ / Bacterial eradication	10 leukocytes/mm ³ / Bacterial eradication	No relapse or reinfection	8/12

6 in tigecycline monotherapy group vs 15/17 in others, $p:1$) and 11 had neck stiffness (6/6 in tigecycline monotherapy group vs 5/17 in others, $p:0.0048$). Nineteen cases had a fever (5/6 in tigecycline monotherapy group vs 14/17 in others, $p:1$). Six cases had convulsions (2/6 in tigecycline monotherapy group vs 4/17 in others, $p:0.63$) and twelve had nausea and vomiting (5/6 in tigecycline monotherapy group vs 7/17 in others, $p:0.155$) (Table 1).

Twenty patients had leukocytosis ($> 10,000/\text{mm}^3$). Three cases did not have leukocytosis but had polymorphonuclear leukocyte predominance (Table 1). Glasgow coma scale results of all cases at the start of tigecycline including therapy are in Table 2.

All cases had CSF pleocytosis (median $500/\text{mm}^3$, range 280–3450/ mm^3 , Table 1). Mean CSF protein level was 299 mg/dl (range 38–2055 mg/dl, Table 1), Mean CSF glucose level was 41 mg/dl (range 1–60 mg/dl, Table 1). All cases had culture-proven *A. baumannii* meningitis. Case 12 had mixed infection with *E. faecium*. All *A. baumannii* strains were carbapenem-resistant (only two intermediately-resistant). All strains were susceptible to tigecycline. Seventeen strains were susceptible to colistin while colistin susceptibility was unknown in six strains. Nine and three strains were susceptible to netilmicin and amikacin, respectively. Tigecycline MIC was available in two cases and was 0.5 mg/l in both (Table 2).

3.2. Previous antibacterial treatment

When we evaluated the antibiotic therapy history of the cases during the one-month time period before the *A. baumannii* meningitis episode, all but five received at least one antibiotic (2/6 in tigecycline monotherapy group vs 16/17 in others, $p:0.15$). The most commonly used antibiotic was vancomycin (8 cases). Seven cases received meropenem while five cases received cefazoline. Others are detailed in Table 2. Eleven cases had received empirical meningitis therapy (Case 10-13-14-15-16-17-18-19-20-21-22; 0/6 in tigecycline monotherapy group vs 11/17 in others, $p:0.07$) before tigecycline including regimens.

3.3. Tigecycline including CRAB meningitis treatment

Data related to the duration of treatment regimens are summarized in Table 2. Tigecycline dosage was 50 mg q12h in all cases. Six cases received tigecycline monotherapy (Case 1-6), while 17 received tigecycline including combination therapy (10 with colistin, 4 with netilmicin, 3 with amikacin, 4 with meropenem- Table 2). Tigecycline level in cerebrospinal fluid or sera was not measured in any case.

Ten cases received tigecycline + colistin (Case 7-16). Of these ten, three received concomitant intrathecal colistin (case 9-13 and 15). In case 16 tigecycline and netilmicin (3 days intrathecal and 6 days intravenous) combination was started. Afterwards, netilmicin was switched to colistin due to microbiological failure. In case 11 colistin was switched to meropenem after nephrotoxicity on day 5. Case 14 received additional rifampin as the third antibacterial agent. Case 12 received additional vancomycin also for *E. faecium* meningitis.

Four cases were given tigecycline and netilmicin combination (Case 16-19). In case 16 tigecycline and netilmicin (3 days intrathecal and 6 days intravenous) combination was started. Afterwards, netilmicin was switched to colistin due to microbiological failure. In case 17 linezolid was also added to antibiotic therapy empirically. In case 18 tigecycline and netilmicin were started after failure with cefoperazone/sulbactam and meropenem. Case 19 received netilmicin for three days intrathecally and five days intravenously.

Three cases received tigecycline and amikacin including therapy (Case 20-21-22). Case 22 received amikacin only intrathecally in combination with meropenem and case 21 received additional rifampin as the third antibacterial agent.

Finally, four cases (Case 11, 12, 22 and 23) were given tigecycline and meropenem including therapy. Case 11 received meropenem after colistin nephrotoxicity. Case 12 received additional colistin while case

22 received additional intrathecal amikacin. In case 11 and 22 the infecting strains were intermediately resistant to meropenem. Case 12 and 23 received meropenem despite the infecting strain was resistant to it.

3.4. Microbiological response on day 3–5

Repeated CSF culture on day 3–5 was available for 18 cases and overall efficacy was 72% (13/18, Table 2). Among these 18 cases, microbiological efficacy on day 3–5 was evident in 5 of 5 cases in monotherapy group, 4 of 8 in tigecycline + colistin group, 1 of 3 in tigecycline + netilmicin group, 2 of 2 tigecycline + amikacin group and in 2/2 in cases received tigecycline + meropenem combination. There was no significant difference between the monotherapy vs any combination therapy ($p:0.128$).

Tigecycline monotherapy (Case 1-6): Microbiological response data on day 3–5 were available for five cases all of whom had CSF clearance at both time points. Case 5 did not have repeated CSF culture and died on day 5 possibly due to meningitis.

Tigecycline and colistin including therapy (Case 7-16): Eight of 10 cases had repeated CSF culture on day 3–5 and four had bacteriological eradication (Case 9, 10, 12, 14). Two cases (Case 7 and 11) did not have repeated CSF culture. However, case 7 had clinical response at the end of therapy and had one-month survival without any relapse. Case 11 died during therapy.

Tigecycline and netilmicin including therapy (Case 16-19): Three of four cases had repeated CSF culture on day 3–5 and two (Case 17 and 18) had bacteriological eradication. Case 16 had bacteriologic failure with tigecycline and netilmicin combination and netilmicin was switched to colistin. Case 19 did not have repeated CSF culture but had clinical response at the end of therapy and had one-month survival without any relapse.

Tigecycline and amikacin including therapy (Case 20-22): Two of three cases had repeated CSF culture on day 3–5 and one (Case 22) had bacteriological eradication. Case 21 did not have repeated CSF culture on day 3–5.

Tigecycline and meropenem including therapy (Case 11, 12, 22 and 23): Case 11 did not have repeated CSF culture on day 3–5. Other cases had bacterial eradication on day 3–5.

3.5. End of therapy microbiological response

EOT microbiological efficacy data were available in 17 cases and overall efficacy was 88% (15/17). Microbiological efficacy at the end of the treatment was evident in 5 of 5 in monotherapy group, 6 of 7 tigecycline + colistin group, 1 of 3 tigecycline + netilmicin group, 2 of 3 tigecycline + amikacin group and 2/2 of cases who received tigecycline + meropenem group.

Tigecycline monotherapy (Case 1-6): Microbiological response data at the EOT were available for five cases all of whom had CSF clearance. The only case who had not microbiological response data died on day 5 of tigecycline monotherapy.

Tigecycline and colistin including therapy (Case 7-16): Seven cases had EOT CSF culture and six had bacteriological eradication (Case 9, 10, 13, 14, 15, 16). The case with bacteriological failure (case 8) died. Among three cases without EOT CSF culture data one (Case 11) died during therapy whereas two had EOT as well as one-month survival without any relapse (Case 7 and 12).

Tigecycline and netilmicin including therapy (Case 16-19): Only one case (Case 18) had EOT CSF culture and had bacteriological eradication. Case 17 had bacteriological cure on day 3–5 but died during treatment. Case 19 did not have EOT CSF culture but had EOT clinical response as well as one-month survival without any relapse. In case 16 was netilmicin was switched to colistin after failure.

Tigecycline and amikacin including therapy (Case 20-22): Three cases had EOT CSF culture. Two (Case 20 and 22) had bacteriologic cure whereas one (Case 21) had developed *P. aeruginosa* meningitis

during the tigecycline including therapy.

Tigecycline and meropenem including therapy (Case 11, 12, 22 and 23): Case 22 and 23 had EOT CSF culture data and both had bacterial cure. Case 11 died during therapy whereas case 12 had EOT as well as one-month survival without any relapse or reinfection.

3.6. Clinical success and mortality

Seven of 23 cases (30%) died during the tigecycline including therapy (1 in monotherapy, 4 in colistin, 2 in netilmicin, 1 amikacin, case 16 received tigecycline + netilmicin followed by tigecycline + colistin). Hence, EOT clinical success was 70%.

Among the remaining 16 cases, one had relapsing *A. baumannii* meningitis, one case had reinfection with *P. aeruginosa*, one case had reinfection with MRSA and three cases died due to nosocomial pneumonia during one-month follow-up. Hence, overall clinical success (relieved symptoms at the end of treatment and one-month post-therapy survival without any relapse or reinfection) was 43% (10/23). There was no difference in terms of EOT clinical success (5/6 vs 11/17, p : 0.62) and clinical success at the end of one-month follow-up (2/6 vs 8/17, p : 1) in monotherapy vs any combination group. Glasgow coma scale at the EOT was 15 in two cases, 14 in four and 13 in one case. Others' EOT Glasgow coma score was 12 or less (Table 2). When tigecycline monotherapy was compared with tigecycline + aminoglycoside combination or tigecycline + colistin there was no significant difference ($p > 0.05$).

Tigecycline monotherapy (Case 1-6): The five cases with bacterial clearance in CSF had EOT clinical success. However, three of them died due to nosocomial pneumonia during follow-up. The only case without EOT clinical success had died on day 5 of tigecycline possibly due to meningitis.

Tigecycline and colistin including therapy (Case 7-16): Five cases had EOT clinical success and did not have relapse/reinfection during one-month follow-up (Case 7, 10, 12, 13, 14). In contrast, four cases died (two possibly due to CRAB meningitis episode (Case 9 and 11), one nosocomial *Providencia stuartii* sepsis (Case 16) and one nosocomial meningitis and/or central catheter infection (Case 8). One case (Case 15) had EOT clinical response but had relapse on day 22 was retreated with tigecycline and colistin combination successfully and had no relapse during follow-up.

Tigecycline and netilmicin including therapy (Case 16-19): Two cases (Case 18 and 19) had EOT clinical response. Case 19 had no relapse/reinfection during one-month follow-up. However, case 18 had reinfection with MRSA meningitis. Case 16 who was switched to tigecycline + colistin, died possibly due to *P. stuartii* sepsis (Case 16) and case 17 died secondary to meningitis episode.

Tigecycline and amikacin including therapy (Case 20-22): Case 20 had EOT clinical success and no relapse/reinfection during one-month follow-up. Case 22 who received tigecycline, amikacin and meropenem combination during treatment died on day 26 possibly due to meningitis episode. Case 21 who received tigecycline, amikacin and rifampin combination had clearance of *A. baumannii* but developed *P. aeruginosa* meningitis on follow-up.

Tigecycline and meropenem including therapy (Case 11, 12, 22 and 23): Case 12 and 23 had EOT clinical response and no relapse/reinfection during one-month follow-up. Although case 22 had bacterial clearance in CSF culture, he died probably due to nosocomial sepsis and possibly meningitis. Case 11 died during the treatment possibly due to meningitis.

Microbiological response, as well as clinical response at the end of therapy and after one-month follow-up, are summarized in Table 3.

3.7. Adverse events

There was increase in creatinine levels in two cases who received tigecycline-colistin combination in one of whom colistin was switched

to meropenem. Two cases had mild hepatotoxicity ($\times 2$ AST-ALT) levels which also did not result in change in antibiotic therapy. There was no severe hematological, nephrological or hepatological toxicity during the tigecycline treatment of other cases.

4. Discussion

Nosocomial *Acinetobacter* infections including meningitis are becoming an increasingly common problem in intensive care units. In a recent systematic review regarding HCAM in Turkey [3], *Acinetobacter* spp. caused 30.7% of cerebrospinal fluid culture positive 689 nosocomial meningitis episodes. Pooled carbapenem resistance rate was 37.5%. CRAB is endemic in many Turkish hospitals. According to pooled national nosocomial infection surveillance data, 50 percentile of the carbapenem-resistance rate of *A. baumannii* in tertiary-care university hospitals was 93.66% in 2014 [12]. Carbapenem resistance rate in *Acinetobacter* is reported to be over $> 50\%$ in several countries including Italy, England, Saudi Arabia, China, India, Brazil and Argentina and United States [13].

There are several options in the treatment of CRAB meningitis cases according to susceptibility pattern of the relevant strain such as colistin, sulbactam, aminoglycosides and tigecycline [1–3,14,15]. In the presented study all strains were susceptible to tigecycline. Data regarding tigecycline in meningitis or *A. baumannii* meningitis is rare [6,7,16,23–28]. To our knowledge, there are a few reports in which tigecycline is used to treat *A. baumannii* meningitis. Wadi et al. [6] treated a case of *A. baumannii* meningitis with tigecycline monotherapy successfully. Tutuncu et al. [7] reported two cases of *A. baumannii* meningitis treated with tigecycline + netilmicin. Kooli et al. reported successful treatment of an *A. baumannii* meningitis case with tigecycline and colistin combination [16]. Recently there have been cases reported to be treated with intrathecal tigecycline regimens [26,24–28]. Data related to animal models are also scarce about tigecycline. Wang et al. compared tigecycline with tigecycline + vancomycin in *Streptococcus pneumoniae* meningitis of rabbits and reported that combination therapy was associated with greater clearance. However, the significance of the results obtained with the combination is limited by the absence of statistical analysis comparing the different arms [9,10]. Fang et al. [17] analyzed the effects of tigecycline at different doses with or without vancomycin on penicillin-resistant *S. pneumoniae* induced meningitis model. In their study, when used at a concentration above 20 mg/kg, tigecycline was reported to be bactericidal and was at concentration above 1 mg/ml in CSF after three h of treatment. In case of *A. baumannii* meningitis, to our knowledge there is no animal study comparing tigecycline with any antibacterial agent.

Herein we presented 23 CRAB meningitis cases treated with tigecycline including regimens. Six cases received monotherapy. Several meta-analysis regarding tigecycline in randomized-controlled studies concluded excess mortality in tigecycline arm [18,19]. Colistin entered Turkish market in 2011. Most cases but not all received colistin including combination. Hence, some of the cases were combined with non-colistin options whereas some others were treated with monotherapy.

Data regarding penetration of tigecycline into CSF is rare. Ray et al. [23] reported a serial, steady-state, serum and CSF concentrations of tigecycline when administered in the Food and Drug Administration-approved dose of 50 mg every 12 h. CSF concentrations remained relatively stable, suggesting that tigecycline did not accumulate in the CSF. Tigecycline concentrations in the CSF were between 0.035 and 0.048 mg/L, while corresponding serum concentrations were 0.097–0.566 mg/L. The calculated tigecycline penetration ratio in this patient ranged from 0% to 52%, depending on the calculation methodology utilized. In another case with shunt infection regarding penetration of tigecycline [24], the deep concentration of tigecycline (before the following expected administration, t_0) was 49 ng/ml in serum and 5.2 ng/ml in the CSF at steady-state. At 1 h after the end of the infusion, the

Table 3

Summary of microbiological response as well as clinical response at the end of therapy and one month follow up data.

	Tigecycline monotherapy (n:6)	Colistin including therapy (n:10)	Netilmicin including therapy (n:4)	Amikacin including therapy (n:3)	Meropenem including therapy (n:4)
Day 3-5 bacteriological response	5/5	4/8	2/3	1/2	3/3
End of treatment bacteriological response	5/5	6/7	1/1	2/3	2/2
End of treatment clinical success	5/6	6/10	2/4	2/3	2/4
Post treatment one month survival without relapse or reinfection	2/6	5/10	1/4	1/3	2/4

drug serum concentration was 203 ng/ml and the CSF concentration was 13.4 ng/ml. The average ratio of CSF-to-serum concentration was 0.079 (0.059–0.106 interval). Lengerke et al. [25] reported higher tigecycline level in inflamed CSF vs non-inflamed CSF and suggested that higher tigecycline levels may cause higher CSF levels. Interestingly, in recently published three case reports [26–28] tigecycline was administered by intraventricular route possibly because of the severity of these infections (2 *A. baumannii* and 1 *K. pneumoniae* meningitis/ventriculitis) and the limited treatments available. Wu et al. also analysed the pharmacokinetics of tigecycline and measured tigecycline concentrations by liquid chromatography-mass spectrometry. The trough concentrations of tigecycline in CSF for the three different dosages of tigecycline IV–intra ventricular (ICV) combined administration were 0.313, 1.290 and 2.886 mg/l for 40 mg IV/10 mg ICV, 45 mg IV/5 mg ICV and 50 mg IV /1 mg ICV tigecycline, respectively. In terms of outcome, in the case reported by Wu et al, [27] clinical success but microbiological success is not mentioned, while Lauretti et al. [26] and Fang et al. [28] reported both clinical and microbiological success. In our series none of the cases received intrathecal or intravenous high dose tigecycline probably due to the fact that all strains were susceptible to tigecycline and/or reimbursement problems. Additionally since the presented study was on retrospective design, tigecycline levels could not be measured in any case.

Seven of 23 cases (30%) died during the tigecycline including therapy. Hence, overall EOT success was 70%. However, since further 27% died due to other/further nosocomial infections, overall clinical success (relieved symptoms at the EOT and one-month post-therapy survival without any relapse or reinfection) decreased to 43%. Mortality was the least in monotherapy arm (17%) whereas it was 40% in cases who received tigecycline + colistin ($p > 0.05$) and only three received intrathecal colistin (one of these three cases survived after one-month follow-up). In the systematic review by Falagas et al., [29] which comprised 11 *A. baumannii* meningitis cases, treated with intrathecal colistin including therapy, intrathecal colistin was found to be successful in 10 cases. The difference between the outcomes of the studies may be due to the differences in the time lap between the *A. baumannii* oriented therapies or relatively low number of cases receiving intrathecal colistin which is reported to be associated with a better clinical response in some series [30,31]. Another speculative reason may be the antibacterial effect of the antibiotic combination on the infecting strain. Combination therapy for CRAB infections is mostly recommended to cause synergy. However, the results of synergy tests are rarely known at the start of therapy. In fact, as in the presented study, it is usually not performed. In the real life scenario, a combination may be synergic in one strain whereas antagonistic in other [32]. In the previously mentioned systematic review regarding nosocomial meningitis in Turkey, pathogen-specific mortality was reported to be 55.5% (30/54) for *A. baumannii* [3]. Finally, overall one-month survival was 46% in another paper regarding tigecycline therapy in 72 *Acinetobacter* nosocomial pneumonia cases [5]. Hence, although EOT clinical success of 70% is comparable, one month survival without reinfection or relapse was a bit less than general *A. baumannii* meningitis outcomes (55.5%) and comparable to MDR *A. baumannii* pneumonia results in our setting.

Our study has several limitations. It was not a formal therapeutic

trial but rather a retrospective review of cases treated with tigecycline including regimens. Besides, we did not make a sample size analysis for detecting the power of therapeutic efficacy comparison. We did not perform multiple logistic regression analysis for mortality since total number of cases was low and we did not have 10–20 events per covariate [33]. The relatively low number of cases probably resulted in not to achieve statistical significance in other comparisons, too. There was no pharmacokinetic and pharmacodynamic data, as CSF/blood levels of tigecycline were not measured in any case. Besides, molecular genetic analysis of the infecting strains could not be performed since strains were not available. In addition, since autopsy could not be performed, definite reasons for mortality could not be delineated. Only six cases were treated with monotherapy. Some of the cases received additional intrathecal therapy. Hence, success or failure in 17 cases was not due to tigecycline alone but also the effects of combination and/or intrathecal therapy. However, as mentioned before, tigecycline was reported to be associated with excess mortality suggesting not to use it as monotherapy [18,19]. Nevertheless, any study which would evaluate the efficacy of tigecycline in combination therapy regimens will have the same major disadvantage. The facts that most of the cases were from Turkey and there were mortality, relapse and reinfection after the end of successful CRAB meningitis therapy, suggest problems in infection control. Despite the above-mentioned limitations, to our knowledge, this is the largest series and dataset evaluating the microbiological and clinical efficacy of tigecycline in CRAB meningitis and comparing tigecycline monotherapy with combination therapy.

5. Conclusion

Our experience with tigecycline including therapy modalities resulted in an EOT success of 70% but since further 27% died due to other nosocomial infections, overall clinical success (relieved symptoms at the end of treatment and one-month post-therapy survival without any relapse or reinfection) decreased to 43%. These data suggest that similar to colistin [34], tigecycline can be an alternative in the salvage therapy of nosocomial CRAB meningitis. The medical community should seek easily implementable-very fastly resulting synergy testing methods in the contemporary age of antibiotic therapy, which includes only a few alternatives for CRAB. In addition, the Turkish medical community should seek effective infection control measures regarding CRAB meningitis and other nosocomial infections. We recommend physicians treating any patient with tigecycline to determine actual CSF levels of the drug (wherever the measurement of tigecycline is available), along with CSF data which could allow them to correlate CSF levels with penetration across an inflamed blood-brain barrier and maintenance of levels as therapy progresses.

Author contributions

Concept/design: ORS, Data analysis/interpretation: ORS, SM, HS, Drafting article: ORS, SM, Critical revision of article: ORS, TY, HS, SU, TD, YC, ACU Approval of article: All authors, Statistics: HS, Data collection: All authors

Competing financial interests

SU, BA, MT, HP and TD received speaker's honorarium from Pfizer. Others have no conflict of interest to declare.

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