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ORIGINAL RESEARCH ARTICLE

An Evaluation of the Effectiveness of Risk Minimization Measures for Tigecycline in the European Union

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Abstract

Background Risk minimization measures (RMM) were implemented from February 2011 in the European Union to address risks of superinfection, off-label use and lack of efficacy associated with tigecycline. The objective of this study was to evaluate RMM effectiveness by describing prescription patterns among adults and children treated with any dose of tigecycline for any indication pre- and post-RMM implementation; incidence proportions of superinfection and lack of efficacy among adults treated with approved doses of tigecycline for complicated intra-abdominal infection and complicated skin and soft tissue infection were also evaluated.

Methods This was an observational, retrospective chart-abstraction study, including charts from 777 patients (399 pre-RMM, 378 post-RMM) at 13 sites across Austria, Germany, Italy, Greece and the United Kingdom (UK). Potential superinfection and lack of efficacy cases among those using tigecycline for on-label indication, age, dose, and duration were adjudicated. The distribution of indications for tigecycline was analyzed overall (i.e. across both study periods) and stratified by study period. Numbers and incidence proportions of superinfection and lack of efficacy cases (potential and adjudicated) were calculated overall and by study period.

Results Off-label use (indication or age) decreased from 54.2% [95% confidence interval (95% CI): 49.0, 59.3%] pre-RMM to 35.7% (95% CI 30.4, 41.2%) post-RMM. Overall, 45.7% (95% CI 41.9, 49.5%) of patients were prescribed tigecycline off-label; the most commonly reported off-label indications were characterized as "other" (25.5%), hospital acquired pneumonia (8.2%), other pneumonia (6.3%), bacteremia (5.2%) and diabetic foot infection (1.5%). Across study periods, incidence proportions of definite or probable superinfection and lack of efficacy in adults treated for approved indications, authorized treatment doses and duration were 4.5% (95% CI 2.1, 8.4%) and 5.5% (95% CI 2.8, 9.7%), respectively.

Conclusions Off-label use of tigecycline decreased following RMM implementation. Overall incidence proportions of definite or probable superinfection and lack of efficacy were low. EU PAS register number: EUPAS3674

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Key Points

The proportion of off-label tigecycline use decreased across five EU countries following implementation of a healthcare provider educational program

Proportions of definite and probable superinfection and lack of efficacy were low across both study periods

1 Introduction

Tigecycline is an intravenously administered broad-spectrum glycylcycline antibiotic, indicated in both the USA and the European Union (EU) for treatment of complicated intra-abdominal infection (cIAI) and complicated skin and soft tissue infection (cSSTI) excluding diabetic foot infection, and for community-acquired pneumonia in the USA. It has broad-spectrum coverage, demonstrating in vitro activity against both gram-positive and gram-negative pathogens [1]. Tigecycline is not affected by the two, major tetracycline-resistance mechanisms as well as resistance mechanisms such as beta-lactamases, target-site modifications, macrolide efflux pumps or enzyme target changes [2].

An increase in all-cause mortality has been observed across Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator-treated patients [3]. In all 13 controlled trials, death occurred in 4.0% (150/3788) of patients receiving tigecycline and 3.0% (110/3646) of patients receiving comparator drugs. In a pooled analysis of these trials, the adjusted risk difference of all-cause mortality was 0.6% [95% confidence interval (CI) 0.1, 1.2] between tigecycline and comparator-treated patients [3]. The cause of the imbalance has not been established. One independent meta-analysis of clinical trial data suggested decreased clinical and microbiological efficacy of tigecycline combined with higher rates of superinfections as explanations [4], while others [5, 6] were not able to identify any significant differences in efficacy or microbiologic eradication to account for the results.

In order to reduce off-label prescribing of tigecycline, and raise awareness of the risk of superinfection and lack of efficacy, the marketing authorization holder (MAH) agreed with the European Medicines Agency (EMA) to develop and disseminate risk minimization measures (RMMs) for tigecycline. RMMs are public health interventions intended to prevent the occurrence of adverse drug reactions associated with exposure to a drug, or to reduce its severity should the event occur [7]. The RMMs for tigecycline included changes to the Summary of Product Characteristics (SmPC) [8], a Direct to Healthcare Professional Communication (DHPC), and a healthcare provider educational program. Changes to the SmPC highlighted approved uses of tigecycline in the EU, the mortality imbalance observed in clinical trials and the risks of superinfection and lack of efficacy, and emphasized that tigecycline should be used only in situations where it is known or suspected that other alternatives are not suitable. The accompanying educational program was rolled out in each country in the EU through pre-recorded webcast sessions in local languages to which infectious disease physicians, clinical microbiologists, intensive care physicians, and surgeons were invited.

With the primary objective of assessing the effectiveness of the modified SmPC and corresponding communication activities, and in accordance with EU legislation requiring the evaluation of RMM effectiveness [9], the MAH undertook a retrospective chart abstraction study in the EU comparing prescription patterns among patients treated with any dose of tigecycline for any indication (on- or off-label), prior to and following implementation of the RMM in February 2011. The study also evaluated the incidence of adjudicated superinfection and lack of efficacy among adult patients treated with tigecycline for the approved duration of time and dosage for cIAI and cSSTI, overall (i.e. across both study periods) and in each study period separately.

2 Methods

A retrospective chart abstraction study was the optimal design for this real-world evaluation of the effectiveness of mandatory RMMs. Where the value of RMMs is deemed clear, it is not ethical to withhold the RMM from a control group [10]. Accordingly, the tigecycline RMMs were not implemented using a phased approach: DHPCs were disseminated to all countries in March 2011, while invitations to participate in the educational program were issued in June 2011. It was therefore not possible to compare in parallel sites or regions exposed to the RMM to control sites or regions unexposed to the RMM. A chart abstraction design was selected due to lack of electronic healthcare databases with available inpatient prescription data in European countries with high tigecycline prescription volume.

A total of 127 healthcare professionals (HCPs) at 121 hospitals and medical centers in Austria, Greece, Germany, Italy, the United Kingdon (UK) and Spain were contacted and asked to complete a site qualification questionnaire if they were interested in participating in the study. The questionnaire included questions about the number of patients administered tigecycline during the two time-periods of interest (pre- and post-RMM implementation), and the availability of human resources at the hospital or ward for conducting such a study. Thirty-five HCPs responded to the questionnaire. Twenty-two sites were initially selected, of which 13 were ultimately included. For most of the sites selected but not included, failure to initiate was due to inability to meet study timelines. The two sites selected in Spain were excluded because informed consent is required from deceased and living patients in Spain, and including only consenting patients would likely bias study results. Similarly, since informed consent is required in Italy from

all living patients, data from the three Italian sites were included in sensitivity analyses only. All of the sites included were academic centers.

Independent ethics committee (IEC) and/or institutional review board (IRB) approval was obtained for each participating site. In Austria, IEC approval was obtained from the Ethics Committee of the Medical University of Vienna (Ethik-Kommission der Medizinschen Universität Wien und des Allgemeinen Krankenhauses der Stadt Wien—AKH). In Germany, approval was obtained from the Ethics Committee of the University of Freiburg (Ethik-Kommission der Universität Freiburg) and the Ethics Committee of the Charité Medical School Berlin Ethikkommission der Charité—Universitätsmedizin Berlin. In Greece, approval was obtained from the Scientific Committees of Attikon Hospital and the General Hospital of Athens Georgios Gennimatas. In Italy, approvals were obtained from the Central Ethics Committee of the University Hospital of Bologna (Comitato Etico Indipendente dell 'Azienda Ospedaliero-Universitaria di Bologna Policlinico S.Orsola-Malpighi), the Ethics Committee of the University Hospital of Verona (Comitato Etico Indipendente dell 'Azienda Ospedaliera Universitaria Integrate Verona), and the Ethics Committee of the University Hospital of Udine (Comitato Etico Indipendente dell 'Azienda Ospedaliera Universitaria di Udine). Finally, approval in the UK was obtained from the NRES Committee Yorkshire & The Humber-Leeds West.

All patients treated with at least one dose of tigecycline for any indication within selected hospitals or wards between 01 February 2010 and 01 February 2011 (pre-RMM implementation period) and between 01 February 2012 and 01 February 2013 (post-RMM implementation period) were retrospectively identified through review of electronic medication databases or paper registries as eligible for inclusion. Treatment with tigecycline during either of the two study periods was the only inclusion criterion for the study; there were no exclusion criteria. Eligible patients either commenced or completed treatment with tigecycline within the above-specified periods. Trained nurses or physicians were instructed to abstract patient charts and record data onto an electronic case report form in a random order to avoid introduction of bias. Data were "key-coded" in order to preserve patient anonymity: only the site investigator was able to link the patient identification number to any personally identifying information. Medical record data prepared as part of the adjudication package were anonymized prior to leaving the study site.

For the primary objective of assessing prescription patterns, and particularly, the proportion of on-label use, among patients treated with tigecycline prior to and following implementation of the RMM in February 2011, on-label use was defined as use for an on-label indication and in patients aged $\geq$18 years. Potential cases of superinfection and lack of efficacy were adjudicated for subjects with a narrower definition of on-label use, namely, dosing regimens consistent with tigecycline approved labeling (i.e. 100 mg loading dose; 25 or 50 mg BID maintenance dosing), age $\geq$18 years and duration of tigecycline treatment $\geq$48 h. Consideration of appropriate dosage and duration of treatment were deemed necessary for the accurate evaluation of efficacy and superinfection.

Potential superinfection cases were those where patient charts revealed emergence of a new infection (evidence of clinical diagnosis or microbiological results) not present at baseline >2 days following initiation of tigecycline therapy. New infection included either a new isolate at the site of the primary infection or the development of an infection distant to the site of primary infection. Potential lack of efficacy cases, were those where additional intervention and/or antibiotic therapy was provided in the absence of clinical improvement to treat the infection, or death due to the infection occurred >2 days following initiation of tigecycline therapy.

Two external adjudicators reviewed all relevant medical record data from potential superinfection and lack of efficacy cases (among on-label users) to classify potential cases as either definite-, probable- or non-cases, or as having insufficient information for adjudication; where there was lack of consensus, a third adjudicator served as tie-breaker. Classification of definite superinfection required clinically significant positive culture of microorganism >48 h after tigecycline therapy initiation in addition to clinical signs and symptoms of infection. If the culture was from the same site, the microorganism was required to be different than that isolated within the first 48 h, and if the culture was from a different site, the microorganism could be any clinically significant microorganism. Cases with inadequate surgical control were not considered to be definite superinfection. Probable superinfections met the criteria above but lacked culture evidence for definite superinfection, while non-cases lacked clinical signs or symptoms of superinfection.

Classification of definite lack of efficacy required a clinically significant positive culture of a tigecycline-susceptible organism both before and after >48 h of tigecycline therapy in addition to information on progression of infection (absence of clinical improvement); breakthrough infections with this level of evidence were considered definite cases of lack of efficacy. In the case of death, the event needed to be due to infection treated with tigecycline to be considered a definite case of lack of efficacy. Cases with inadequate surgical control were not considered definite lack of efficacy. Probable lack of efficacy was defined as above, but lacked culture evidence, and a non-case exhibited clinical improvement after tigecycline therapy or a clinically significant positive culture of an organism not susceptible to tigecycline at baseline, or in the case of death, death not due to the infection treated with tigecycline.

2.1 Statistical Analysis

Characteristics of the sample including demographics, comorbidities and disposition at discharge are summarized with counts and percentages. Frequencies of indications for which tigecycline was prescribed and the proportion of these characterized as off-label use were calculated overall (irrespective of study period) and for the periods before and after RMM implementation. Counts and incidence proportions of superinfection and lack of efficacy were similarly calculated overall and pre- and post-RMM implementation, for potential cases as well as adjudicated cases. Reasons for adjudication as "non-cases" are also summarized with counts and percentages.

An exploratory logistic regression analysis was conducted to evaluate factors associated with off-label use (off-label indication and pediatric use) throughout the entire study period. The analysis was performed using backward elimination and a p value criterion of 0.05. Covariates included study period (pre-RMM or post-RMM), age (<65 or ≥65 years), gender, previous antibiotic therapy (yes vs. no), country, previous surgical procedures (yes vs. no), and number of co-morbidities (0, 1–3, ≥4).

3 Results

3.1 Patient and Site Characteristics

The primary analyses excluded the 90 patients enrolled in three Italian sites for a total patient number of 687; sensitivity analyses were conducted using all 777 patients. The distribution of patients by country, site, and study period is shown in Table 1.

Patient characteristics by indication and study period are shown in Table 2. Irrespective of study period or indication, 52% of the study participants were male and mean age on admission was 61.4 years (SD 16.40). Patients treated with tigecycline before the RMM (for any indication) were slightly older compared with those treated after the RMM (mean 63.2, SD 15.98 vs. mean 59.2, SD 16.66).

At admission, over one-third of patients (36.7%) had one or more forms of cardiovascular or cerebrovascular disease. Almost one-third of patients (30.3%) had a history of malignancy, and an immunocompromised state was reported for 19.9%. Diabetes with (7.4%) or without (17.6%) end-organ damage and moderate/severe renal disease (24.6%) were also commonly reported. Liver disease was reported in 18.6% of patients, with most cases characterized as moderate/severe. While inconsistently recorded in patient charts, where recorded, 83.8% of patients had baseline APACHE II scores ≥15 at baseline.

The burden of co-morbidities as assessed by the presence of relevant medical history appeared to be higher for patients treated after the RMM compared to patients treated before. For instance, higher proportions of patients treated after the RMM had a history of malignancy (33.1 vs. 27.9% pre-RMM), were in an immunocompromised state (21.7 vs. 18.5% pre-RMM), and had liver disease (22.9 vs. 15.0% pre-RMM) or moderate/severe renal disease (28.0 vs. 21.7% pre-RMM). A higher proportion of prior antibiotic use was seen following the RMM compared to before (87.1

Table 1 Distribution of patients by country and site

Site number	Country	Type of site	Site of patient recruitment	Number of patients enrolled		
				Before RMM	After RMM	Overall sample
1016	Austria	University	Hospital as a whole	38	51	89
1020	Austria	University	Infectious disease ward/department	5	7	12
1023	UK	University	Hospital as a whole	167	67	234
1030	UK	University	Intensive care unit	2	8	10
1015	Germany	University	Hospital as a whole	62	36	98
1024	Germany	University	Intensive care unit	39	43	82
1027	Germany	University	General and transplant surgery	26	57	83
1001	Germany	University	Intensive care unit	19	33	52
1004	Greece	University	Internal medicine	1	0	1
1006	Greece	Public	Hospital as a whole	14	12	26
1002	Italy	University	Hospital as a whole	12	0	12
1017	Italy	University	Hospital as a whole	11	19	30
1018	Italy	University	Hospital as a whole	3	45	48
Total no. patients				399	378	777
Total no. patients excluding Italy				373	314	687

RMM risk minimization measures

Table 2 Patient characteristics, primary analysis

	Pre-RMM				Post-RMM				Overall
	Any indication* *n* (%)	cIAI *n* (%)	cSSTI *n* (%)	Off-label *n* (%)	Any Indication* *n* (%)	cIAI *n* (%)	cSSTI *n* (%)	Off-label *n* (%)	*n* (%)
Total	373	129	42	202	314	142	60	112	687
Age on admission (years)									
Mean (SD)	63.2 (15.98)	62.0 (14.46)	63.4 (16.48)	64.0 (16.81)	59.2 (16.66)	59.0 (15.01)	60.2 (16.04)	58.8 (18.94)	61.4 (16.40)
<18 years	2 (0.5)	0 (0.0)	0 (0.0)	2 (1.0)	5 (1.6)	0 (0.0)	0 (0.0)	5 (4.5)	7 (1.0)
18–44 years	49 (13.1)	14 (10.9)	7 (16.7)	28 (13.9)	50 (15.9)	23 (16.2)	10 (16.7)	17 (15.2)	99 (14.4)
45–64 years	141 (37.8)	59 (45.7)	15 (35.7)	67 (33.2)	130 (41.4)	65 (45.8)	26 (43.3)	39 (34.8)	271 (39.4)
65+ years	181 (48.5)	56 (43.4)	20 (47.6)	105 (52.0)	129 (41.1)	54 (38.0)	24 (40.0)	51 (45.5)	310 (45.1)
Female gender	196 (52.5)	67 (51.9)	22 (52.4)	107 (53.0)	134 (42.7)	52 (36.6)	31 (51.7)	51 (45.5)	330 (48.0)
Immunocompromised	69 (18.5)	32 (24.8)	4 (9.5)	33 (16.3)	68 (21.7)	39 (27.5)	6 (10.0)	23 (20.5)	137 (19.9)
Malignancy	104 (27.9)	46 (35.7)	9 (21.4)	49 (24.3)	104 (33.1)	64 (45.1)	11 (18.3)	29 (25.9)	208 (30.3)
Liver disease	56 (15.0)	33 (25.6)	6 (14.3)	17 (8.4)	72 (22.9)	54 (38.0)	4 (6.7)	14 (12.5)	128 (18.6)
Renal disease									
Severe	50 (13.4)	17 (13.2)	5 (11.9)	28 (13.9)	47 (15.0)	16 (11.3)	6 (10.0)	25 (22.3)	97 (14.1)
Moderate	31 (8.3)	13 (10.1)	4 (9.5)	14 (6.9)	41 (13.1)	28 (19.7)	5 (8.3)	8 (7.1)	72 (10.5)
Diabetes									
With end organ damage	29 (7.8)	5 (3.9)	2 (4.8)	22 (10.9)	22 (7.0)	6 (4.2)	7 (11.7)	9 (8.0)	51 (7.4)
Without end organ damage	63 (16.9)	28 (21.7)	5 (11.9)	30 (14.9)	58 (18.5)	31 (21.8)	8 (13.3)	19 (17.0)	121 (17.6)
Cardiovascular disease	138 (37.0)	43 (33.3)	22 (52.4)	73 (36.1)	114 (36.3)	33 (23.2)	32 (53.3)	49 (43.8)	252 (36.7)
Peptic ulcer disease	6 (1.6)	4 (3.1)	0 (0.0)	2 (1.0)	13 (4.1)	7 (4.9)	3 (5.0)	3 (2.7)	19 (2.8)
Chronic pulmonary disease	50 (13.4)	17 (13.2)	7 (16.7)	26 (12.9)	34 (10.8)	8 (5.6)	6 (10.0)	20 (17.9)	84 (12.2)
Connective tissue disease	6 (1.6)	1 (0.8)	1 (2.4)	4 (2.0)	1 (0.3)	0 (0.0)	1 (1.7)	0 (0.0)	7 (1.0)
Dementia	8 (2.1)	2 (1.6)	2 (4.8)	4 (2.0)	5 (1.6)	2 (1.4)	1 (1.7)	2 (1.8)	13 (1.9)
Hemiplegia	5 (1.3)	1 (0.8)	1 (2.4)	3 (1.5)	7 (2.2)	5 (3.5)	2 (3.3)	0 (0.0)	12 (1.7)
Recent neutropenia**	11 (2.9)	5 (3.9)	0 (0.0)	6 (3.0)	10 (3.2)	4 (2.8)	1 (1.7)	5 (4.5)	21 (3.1)
Other antibiotic use 7 days pre-tigecycline	255 (69.1)	97 (75.2)	37 (88.1)	121 (61.1)	264 (87.1)	122 (86.5)	43 (75.4)	99 (94.3)	519 (77.2)
Deceased at discharge	105 (28.2)	39 (30.2)	10 (23.8)	56 (27.7)	113 (36.0)	55 (38.7)	11 (18.3)	47 (42.0)	218 (31.7)
APACHE II score									
N	116	47	15	54	124	75	16	33	240
<15	15 (12.9)	10 (21.3)	2 (13.3)	3 (5.6)	24 (19.4)	17 (22.7)	3 (18.8)	4 (12.1)	39 (16.3)
≥15	101 (87.1)	37 (78.7)	13 (86.7)	51 (94.4)	100 (80.6)	58 (77.3)	13 (81.3)	29 (87.9)	201 (83.8)

RMM risk minimization measures, *cIAI* complicated intra-abdominal infection, *cSSTI* complicated skin and soft tissue infection

* cIAI, cSSTI, or off label use

** Recent – within 6 months of hospital admission

vs. 69.1%); the difference was particularly notable among off-label users (94.3 vs. 61.1%).

Across both study periods, all-cause mortality (31.7%) was higher among patients with cIAI and off-label indications (34.7 and 32.5%, respectively) than patients with cSSTI (20.6%). The all-cause mortality rate was lower before the RMM (28.2%) compared to after (36.0%). While this trend was consistent across all indications (cIAI, cSSTI, off-label), the increase was particularly notable in the cIAI (30.2 vs. 38.7%) and off-label (27.7 vs. 42.0%) population subgroups. All pediatric patients were discharged alive (data not shown in Table).

3.2 Off-Label Use of Tigecycline

Overall, 45.7% of patients treated with tigecycline (95% CI 41.9, 49.5%) were treated for an off-label indication or pediatric use (Table 3). Prior to RMM implementation, 54.2% of the indications were off-label or pediatric use (95% CI 49.0, 59.3%) compared to 35.7% (95% CI 30.4, 41.2%) after RMM implementation. Sensitivity analyses including data from Italy were consistent with these findings. A decrease in off-label use post-RMM was seen across all countries. The lowest proportion of overall off-label use was observed in Italy (25.4%) and the highest was observed in Austria (60.4%).

The most commonly reported off-label indications were characterized as "other" (25.5%), hospital-acquired pneumonia (8.2%), other pneumonia (6.3%), bacteremia (5.2%) and diabetic foot infection (1.5%). Prior to implementation of the RMM, 62.8% of those with off-label indications were treated for "other" off-label indications (i.e. off-label indications other than hospital acquired pneumonia, other pneumonia, diabetic foot

Table 3 Indications for use and off-label use, primary analysis

	Pre-RMM *n* (%)	Post-RMM *n* (%)	Overall *n* (%)
Indications for use among adult patients[#]	$n = 370$	$n = 309$	$n = 679$
cIAI	129 (34.9)	142 (46.0)	271 (39.9)
cSSTI	42 (11.4)	60 (19.4)	102 (15.0)
Off-label indications	199 (53.8)	107 (34.6)	306 (45.1)
Hospital acquired pneumonia	31 (8.4)	25 (8.1)	56 (8.2)
Pneumonia (other)	23 (6.2)	20 (6.5)	43 (6.3)
Diabetic foot infection	7 (1.9)	3 (1.0)	10 (1.5)
Bacteremia	19 (5.1)	16 (5.2)	35 (5.2)
Other	125 (33.8)	48 (15.5)	173 (25.5)
Off-label use (indication and pediatric use*) in total and by country			
Total	$n = 373$	$n = 314$	$n = 687$
On-label use	171 (45.8)	202 (64.3)	373 (54.3)
Off-label use	202 (54.2)	112 (35.7)	314 (45.7)
Germany	$n = 146$	$n = 169$	$n = 315$
On-label use	82 (56.2)	126 (74.6)	208 (66.0)
Off-label use	64 (43.8)	43 (25.4)	107 (34.0)
Austria	$n = 43$	$n = 58$	$n = 101$
On-label use	15 (34.9)	25 (43.1)	40 (39.6)
Off-label use	28 (65.1)	33 (56.9)	61 (60.4)
Greece	$n = 15$	$n = 12$	$n = 27$
On-label use	9 (60.0)	9 (75.0)	18 (66.7)
Off-label use	6 (40.0)	3 (25.0)	9 (33.3)
UK	$n = 169$	$n = 75$	$n = 244$
On-label use	65 (38.5)	42 (56.0)	107 (43.9)
Off-label use	104 (61.5)	33 (44.0)	137 (56.1)

RMM risk minimization measures, *cIAI* complicated intra-abdominal infection, *cSSTI* complicated skin and soft tissue infection

One adult patient prescribed tigecycline for cIAI was excluded from these analyses due to an inappropriate dosing sequence

* The patient receiving an inappropriate dosing sequence is considered an off-label user (despite cIAI indication and adult age)

Table 4 Predictors of off-label use (off-label indication and pediatric use), primary analysis

	Adjusted odds ratio (95% CI)*
Study period	
Pre-RMM	Reference
Post-RMM	0.657 (0.460, 0.938)
Age	
<65	Reference
≥65	1.094 (0.769, 1.556)
Gender	
Male	Reference
Female	0.834 (0.589, 1.180)
Previous antibiotic therapy	
Yes	Reference
No	0.837 (0.535, 1.310)
Country	
Germany	Reference
Austria	2.463 (1.476, 4.110)
Greece	0.452 (0.182, 1.123)
UK	1.585 (1.042, 2.413)
Number of co-morbidities	
0	Reference
1–3	1.094 (0.681, 1.758)
4 or more	1.056 (0.512, 2.177)
Previous surgical procedures	
Yes	Reference
No	4.521 (3.101, 6.590)

The prescription of tigecycline for one patient was considered to be off-label because of the dosing sequence, despite this patient being prescribed tigecycline for cIAI and being over 18 years of age

RMM risk minimization measures, *cIAI* complicated intra-abdominal infection, *CI* confidence interval

* $P\ (y|x) = 1/(1 + e^{-\alpha-\beta x})$, where y = the probability of disease, x = a given risk factor, and e is the exponential function. In the case of multiple adjustments, βx is replaced by a linear term involving factors representing each risk x (e.g. $\beta_1 x_1 + \beta_2 x_2$, etc.). The reference category is the level of the categorical variable against which other levels of that variable are compared

infection or bacteremia), versus 44.9% after implementation of the RMM.

In the exploratory logistic regression analysis performed to evaluate factors associated with off-label use (Table 4), treatment in the post-RMM period was associated with significantly decreased odds of off-label use compared with treatment in the pre-RMM period [adjusted odds ratio (OR) 0.66, 95% CI 0.46, 0.94]. Patients in Austria (OR 2.46, 95% CI 1.48, 4.11) and the UK (OR 1.59, 95% CI 1.04, 2.41) were significantly more likely to be treated off-label compared with patients in Germany. No history of previous surgical procedures was associated with increased likelihood of off-label use (OR 4.52, 95% CI 3.10, 6.59). No other variables reached statistical significance.

3.3 Superinfection

The overall incidence of definite and probable superinfection across approved indications, ages, doses and treatment durations ($n = 199$) was 4.5% (95% CI 2.1, 8.4%), with 3.8% pre-RMM (95% CI 1.1, 9.5%) and 5.3% post-RMM (95% CI 1.8, 12.0%) (Table 5). Sensitivity analyses including data from Italy were consistent with the primary analysis results.

Sixty potential superinfection cases were reported. Potential superinfection was reported in 32.5 and 22.9% of cIAI and cSSTI cases, respectively, in total (pre- and post-RMM). Amongst the 49 cIAI potential superinfection cases, 6 (12.2%) were adjudicated as probable or definite cases. Associated pathogens were *Enteroccocus spp.* ($n = 4$), *Klebsiella spp.* ($n = 3$), *Escherichia coli* ($n = 2$), *Proteus spp.* ($n = 1$) and *Pseudomonas aeruginosa* ($n = 1$). For 4 cases, the information available was considered insufficient for adjudication, and 39 were determined not to be a superinfection. Amongst the 11 cSSTI potential superinfection cases, 3 (27.2%) were adjudicated to be probable or definite cases. Associated pathogens were one report each of *Enteroccocus spp.*, *Proteus spp.*, *Enterobacter spp.* and *Citrobacter spp.* For two cases, the information available was considered insufficient for adjudication, and six were determined not to be a superinfection. For the cases that were determined not to be a superinfection, reasons are detailed in Table 5.

3.4 Lack of Efficacy

The overall incidence proportion of definite and probable lack of efficacy among patients treated with tigecycline for on-label indications, ages, doses and treatment durations was 5.5% (95% CI 2.8, 9.7%), with 2.9% pre-RMM (95% CI 0.6, 8.1%) and 8.5% after (95% CI 3.8, 16.1%) (Table 6). Sensitivity analyses including data from the Italian sites found similar results.

Among the 199 patients using tigecycline for approved indications, ages, doses and treatment durations, 107 potential lack of efficacy cases were reported (54.3% of cIAI cases and 52.1% of cSSTI cases). Amongst the 82 cIAI potential lack of efficacy cases, 8 (9.8%) were adjudicated as either probable or definite cases (6 probable, 2 definite). For 7 cIAI cases, the information available was considered insufficient for adjudication, and 67 were determined not to be lack of efficacy. Amongst the 25 cSSTI potential lack of efficacy cases, 3 cases (12.0%) were adjudicated as probable cases and none were adjudicated as definite. For 3 cases, the information available was considered insufficient for adjudication, and 19 were determined not lack of efficacy. Reasons for which cases

Table 5 Incidence of potential and adjudicated superinfection by approved indication* (primary analysis)

	Pre-RMM ($n = 105$)		Post-RMM ($n = 94$)		All patients ($n = 199$)	
	cIAI *n* (%)	cSSTI *n* (%)	cIAI *n* (%)	cSSTI *n* (%)	cIAI *n* (%)	cSSTI *n* (%)
No. patients treated for approved indications	82 (78.1)	23 (21.9)	69 (73.4)	25 (26.6)	151 (75.9)	48 (24.1)
No. patients with potential superinfection	23 (28.0)	3 (13.0)	26 (37.7)	8 (32.0)	49 (32.5)	11 (22.9)
Adjudicated case status	$n = 23$	$n = 3$	$n = 26$	$n = 8$	$n = 49$	$n = 11$
Definite	2 (8.7)	1 (33.3)	0 (0.0)	1 (12.5)	2 (4.1)	2 (18.2)
Probable	1 (4.3)	0 (0.0)	3 (11.5)	1 (12.5)	4 (8.2)	1 (9.1)
Not a case	17 (73.9)	1 (33.3)	22 (84.6)	5 (62.5)	39 (79.6)	6 (54.5)
Insufficient information	3 (13.0)	1 (33.3)	1 (3.8)	1 (12.5)	4 (8.2)	2 (18.2)
If status = 'Not a case'	$n = 17$	$n = 1$	$n = 22$	$n = 5$	$n = 39$	$n = 6$
A. Lacking clinical signs and symptoms of superinfection	2 (11.8)	0 (0.0)	2 (9.1)	0 (0.0)	4 (10.3)	0 (0.0)
B. Same organism is cultured from the same site as initial infection	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	0 (0.0)
C. Inadequate surgical control	1 (5.9)	0 (0.0)	4 (18.2)	0 (0.0)	5 (12.8)	0 (0.0)
Other reason (as combination of above)±						
A and B	2 (11.8)	0 (0.0)	0 (0.0)	1 (20.0)	2 (5.1)	1 (16.7)
A and C	3 (17.6)	0 (0.0)	6 (27.3)	2 (40.0)	9 (23.1)	2 (33.3)
B and C	1 (5.9)	0 (0.0)	6 (27.3)	0 (0.0)	7 (17.9)	0 (0.0)
A, B and C	1 (5.9)	0 (0.0)	1 (4.5)	0 (0.0)	2 (5.1)	0 (0.0)
Other reasons (not included in above)	6 (35.3)	1 (100.0)	3 (13.6)	2 (40.0)	9 (23.1)	3 (50.0)
Pathogen associated with superinfection (definite and probable) **#^	$n = 3$	$n = 1$	$n = 3$	$n = 2$	$n = 6$	$n = 3$
Enterococcus spp.	3 (100.0)	0 (0.0)	1 (33.3)	1 (50.0)	4 (66.7)	1 (33.3)
E. coli	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	2 (33.3)	0 (0.0)
Proteus spp.	1 (33.3)	0 (0.0)	0 (0.0)	1 (50.0)	1 (16.7)	1 (33.3)
Klebsiella spp.	2 (66.7)	0 (0.0)	1 (33.3)	0 (0.0)	3 (50.0)	0 (0.0)
Enterobacter spp.	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
Citrobacter spp.	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (33.3)
P. aeruginosa	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)

RMM risk minimization measures, *cIAI* complicated intra-abdominal infection, *cSSTI* complicated skin and soft tissue infection

* Among those with dosing regimens consistent with tigecycline approved labeling, age ≥18 years and duration of tigecycline treatment >48 h

** For definite and probable superinfection

Percentages may not add to 100% as one superinfection case can be associated with multiple pathogens

^ Percentages use the sub-total of definite and probable superinfections as the denominator

were determined not to indicate lack of efficacy are detailed in Table 6.

4 Discussion

This observational study suggests an important role of RMM in decreasing off-label use of tigecycline and reveals low overall incidence proportions of definite and probable superinfection and lack of efficacy in five European countries.

Less than one-half of patients were administered tigecycline for an off-label indication. A 2012 systematic review of off-label prescribing of antibiotics found off-label prescribing of antibiotics to vary from 19 to 43% in adult critical-care settings, with 31–78% of tigecycline prescriptions for off-label uses [11]. Physicians may use therapeutic agents for non-approved indications out of medical necessity. For instance, tigecycline, as a broad-spectrum antibiotic, is often used to treat multidrug-resistant infections, sometimes for off-label indications, where other antibiotics are unavailable/ineffective [12, 13], or otherwise unsuitable. Physicians must understand the proper on-label use of a product in order to make informed decisions regarding when the product should and should not be used.

Notably, off-label use of tigecycline decreased after implementation of the RMM, and the post-RMM period

Table 6 Incidence of potential and adjudicated lack of efficacy by approved indication* (primary analysis)

	Pre-RMM($n = 105$)		Post-RMM($n = 94$)		All patients($n = 199$)	
	cIAI *n* (%)	cSSTI *n* (%)	cIAI *n* (%)	cSSTI *n* (%)	cIAI *n* (%)	cSSTI *n* (%)
No. patients treated for approved indications	82 (78.1)	23 (21.9)	69 (73.4)	25 (26.6)	151 (75.9)	48 (24.1)
No. patients with potential lack of efficacy	38 (46.3)	9 (39.1)	44 (63.8)	16 (64.0)	82 (54.3)	25 (52.1)
Adjudicated case status	$n = 38$	$n = 9$	$n = 44$	$n = 16$	$n = 82$	$n = 25$
Definite	1 (2.6)	0 (0.0)	1 (2.3)	0 (0.0)	2 (2.4)	0 (0.0)
Probable	0 (0.0)	2 (22.2)	6 (13.6)	1 (6.3)	6 (7.3)	3 (12.0)
Not a case	31 (81.6)	6 (66.7)	36 (81.8)	13 (81.3)	67 (81.7)	19 (76.0)
Insufficient information	6 (15.8)	1 (11.1)	1 (2.3)	2 (12.5)	7 (8.5)	3 (12.0)
If status = 'Not a case'	$n = 31$	$n = 6$	$n = 36$	$N = 13$	$n = 67$	$n = 19$
A. Evidence of clinical improvement after Tigecycline therapy	8 (25.8)	1 (16.7)	3 (8.3)	2 (15.4)	11 (16.4)	3 (15.8)
B. Clinically significant positive culture of an organism not susceptible to tigecycline at baseline	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
C. Death not due to the infection treated with Tigecycline	1 (3.2)	0 (0.0)	0 (0.0)	2 (15.4)	1 (1.5)	2 (10.5)
D. Inadequate surgical control	5 (16.1)	0 (0.0)	7 (19.4)	1 (7.7)	12 (17.9)	1 (5.3)
Other reasons (as combination of above)#						
A and B	1 (3.2)	0 (0.0)	0 (0.0)	2 (15.4)	1 (1.5)	2 (10.5)
A and C	1 (3.2)	2 (33.3)	1 (2.8)	0 (0.0)	2 (3.0)	2 (10.5)
A and D	4 (12.9)	0 (0.0)	7 (19.4)	4 (30.8)	11 (16.4)	4 (21.1)
B and D	5 (16.1)	1 (16.7)	3 (8.3)	1 (7.7)	8 (11.9)	2 (10.5)
C and D	0 (0.0)	1 (16.7)	6 (16.7)	0 (0.0)	6 (9.0)	1 (5.3)
A and C and D	1 (3.2)	0 (0.0)	1 (2.8)	0 (0.0)	2 (3.0)	0 (0.0)
B and C and D	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.5)	0 (0.0)
Other reasons (not included in above)	4 (12.9)	1 (16.7)	7 (19.4)	1 (7.7)	11 (16.4)	2 (10.5)

RMM, risk minimization measures, *cIAI* complicated intra-abdominal infection, *cSSTI* complicated skin and soft tissue infection

* Among those with dosing regimens consistent with tigecycline approved labeling, age greater than or equal to 18 years and duration of tigecycline treatment >48 h

was found to be significantly protective of off-label use in exploratory multivariate analyses (OR 0.66, 95% CI 0.46, 0.94). We explored whether unmeasured factors may have influenced the relationship between the RMM and off-label use. Sites were queried regarding the occurrence of any event that could have affected prescribing of tigecycline during the study periods. The reported circumstances (two sites) did not provide support for a pattern of decreased off-label use in the post-RMM period: one site reported an increase in carbapenemase-producing *Klebsiella pneumoniae* in both study periods, resulting in several cases where colistin and tigecycline were the only active antibiotics; the other reported an increase in tigecycline use across both study periods due to supply problems with aztreonam (pre-RMM) and an outbreak of vancomycin-resistant enterococcus (post-RMM).

Incidence proportions of definite or probable superinfection observed among on-label users of tigecycline in the pre-RMM and post-RMM periods were low (3.8 and 5.3%, respectively) compared to published estimates. Interpretation of differences in definite and probable superinfection between pre- and post-RMM periods within our study is difficult due to wide confidence intervals around these estimates. With regard to overall proportions of superinfection, in a single-site study of patients in Turkey, superinfection (defined as the eradication of the microorganism that was present at the beginning of the treatment and the isolation of a new causative pathogen after ≥48 h of treatment) was detected in 14.9% of the cSSTI and 7.5% of cIAI patients [14]. Reasons for differences between rates in that study and our own are unclear but may be related to differences in adjudication criteria or underlying differences in the treated population.

Similar to superinfection, low incidence of definite or probable lack of efficacy among on-label users was also seen in both study periods (2.9 and 8.5% in the pre- and post-RMM periods, respectively). As above, interpretation of differences by study period is difficult due to wide confidence intervals. Though our estimates may be unstable, lack of efficacy estimates irrespective of study period among on-label users in our study appear somewhat lower than those found in a multi-country European observational

study. Montravers and colleagues, in one publication based on that study, found 11.7% definite non-response among cSSTI patients [15], while Eckmann and colleagues reported a non-response frequency of 14.2% among cIAI patients in the same population as that reported on by Montravers et al. [16]. Where differences in lack of efficacy across patient populations exist, these could be due to differences in patient illness severity or other factors (e.g. timing of treatment) that lead to failure of anti-infective drugs in general. Indeed, baseline APACHE II scores were higher in our study: 83.8% in the present study versus 16.6% in the above-mentioned multi-country study had scores >15 at baseline [17]. Thus, baseline disease severity may be a contributing factor.

Overall, the mortality rate among tigecycline-treated patients in this study was 31.7%. Patients treated for cIAIs and off-label indications had higher mortality rates (34.7 and 32.5%, respectively) than patients with cSSTI (20.6%). Notably, the mortality rate appeared to be higher after the RMM, most notably in the cIAI and off-label population subgroups. There were important differences noted in the populations after the RMM compared with before the RMM, which may have contributed to differences in mortality. These include increased proportions of surgical intervention and prior antibiotic use preceding tigecycline use, an increased burden of comorbidities, and an increase in the proportion of patients with resistant organisms after the RMM relative to before the RMM, particularly among cIAI and off-label indication patients. Indeed, it is likely that the risk minimization measures (particularly SmPC text stating that tigecycline should be used only in situations where it is known or suspected that other alternatives are not suitable) influenced prescribers to channel tigecycline to more severely ill patients (frequently those patients who have failed other therapies, or have resistant organisms not sensitive to other therapies).

This study has several strengths. It is a relatively rare example of an RMM program evaluation employing a pre- versus post-intervention comparison study design, relying on site-level chart review data and including clinical endpoints as study outcomes [18]. The collection of site-level data allowed linkage among inpatient diagnosis, procedure, medication, and microbiology (when available) data for EU patients, a linkage not accommodated by currently available databases in these countries. Adjudication of potential cases of superinfection and lack of efficacy allowed for objective assessments of these endpoints. Moreover, compared with clinical trials, this study provides an estimate of superinfection and lack of efficacy rates in a patient population with a greater number of comorbidities, higher illness severity scores, and a higher proportion of resistant organisms [19], more closely mirroring the population using tigecycline in clinical practice.

This study also had some limitations. The ability to directly attribute the change in off-label use to the RMM is limited. While we evaluated the role of changes in antimicrobial resistance and local circumstances, other unmeasured factors independent of the RMM (e.g. a shift in prescribing practices unrelated to the RMM or increased availability of other treatments) may also have influenced tigecycline prescribing. The study also did not examine the role of exposure to individual components of the RMM on study endpoints. It is not possible to determine to which (if any) component of the RMM the treating physicians had been exposed, or if tigecycline was prescribed only in a situation where it was known or suspected that other alternatives were not suitable. However, the increased mortality in the post-RMM period suggests increased use of tigecycline in patients who have failed other therapies, or have resistant organisms not sensitive to other therapies, consistent with the SmPC. In addition, lack of sufficient data on microbiology and clinical assessments in the medical record data made case classification difficult in some cases.

Finally, the generalizability of study results is unknown. Participating sites may not be comparable to those that did not participate in the study. However, the geographical distribution of the study still included four high-prescribing tigecycline countries in the EU, and sensitivity analyses including Italy exhibited results consistent with the primary analyses. These five countries represented almost three-quarters of tigecycline usage in the EU according to 2009 sales data. It should be noted, however, that the majority of patients were enrolled by sites in Germany (315/687, 45.9%) and the UK (244/687, 35.5%), which may limit somewhat the external validity of the results beyond these two countries. Generalizability of the results to RMM programs targeting drugs that have lower baseline levels of off-label use is also unknown.

5 Conclusions

In conclusion, this study found a decreased proportion of off-label use following the implementation of RMM, a notable finding which must be interpreted in light of the study limitations above. Importantly, the study also found low proportions of definite and probable superinfection and lack of efficacy among on-label users across both study periods and in a real-life treatment setting, providing further evidence that tigecycline may be an important alternative when other anti-infective agents are not suitable.

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Compliance with Ethical Standards

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Conflict of interest Vera Frajzyngier, Alvaro Quintana, Hal Tucker, Michele Wible, Anne Hickman, Nathalie Baillon-Plot, Rebecca Lundin and Scott Rottinghaus are or have been employees at Pfizer, Inc. Philippe Montravers, Matteo Bassetti, Christian Eckmann have been paid consultants for Pfizer, Inc., and received remuneration from Pfizer for their services in connection with this study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this study, formal consent was not required in the countries included as part of the primary analysis.

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