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Comparative Study of Prescribing Patterns of Tigecycline for Trial Patients *versus* Non-trial Patients

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Abstract. *Background: Comparing published trial patients and non-trial patients in clinical practice, clinicians often doubt whether critically ill patients are sufficiently represented in randomised clinical trials. Patients and Methods: This study evaluated the extent of infection with multidrug-resistant (MDR) pathogens, anti-microbial combination therapy, off-label use and targeted-treatment in trial patients versus non-trial patients. Results: Tigecycline therapy was prescribed for off-label use in more than half of the non-trial patients; 77% of trial patients received study medication as first-line therapy in contrast to 25% of non-trial patients (p<0.001). Tigecycline therapy was targeted for 27% of trial patients versus 73% of non-trial patients (p<0.001). Ninety-six percent of non-trial patients were treated for nosocomial infections compared to 23% of trial patients (p<0.001). In one out of 22 (4.5%) trial patients an ESKAPE pathogen was found, whereas rates of vancomycin- resistant Enterococcus faecium, methicillin-resistant Staphylococcus aureus and extended spectrum-β lactamase- producing Enterobacteriaceae ranged between 13/165 (8%) and 23/165 (14%) for non-trial patients. Conclusion: Tigecycline was used for less critical populations in clinical trials than in clinical practice. Our findings confirm the particular need of potent substances such as tigecycline for critically ill patients.*

Last-resort antibiotics are crucial for antimicrobial therapy of critically ill patients with multidrug-resistant (MDR) pathogens. In the current post-antibiotic era, the pipelines for new substances have dried up (1). It is, therefore, essential to use the antimicrobials at hand wisely, thus preventing overuse and development of multiresistant bacteria (2, 3), namely vancomycin resistant *Enterococcus faecium* (VRE), methicillin resistant *Staphylococcus aureus* (MRSA) and MDR Gram-negative organisms referred to as ESKAPE bacteria (4). The best way to ensure this is to restrict the use of new substances to critical infections only. Randomised clinical trials (RCTs) should, therefore, focus on this special group of patients and infections with MDR bacteria in the early stages of the authorisation process. For tigecycline, most trials against MDR microorganisms were carried out too late for consideration in the process of approval of the drug (5, 6).

Tigecycline is an important treatment option when considering last-resort antibiotics. This fairly recently developed anti-microbial substance is the first agent in the group of glycylcyclines, and is a classical tetracycline analogue. Unlike other related anti-microbials it is active against Gram-positive as well as Gram-negative bacteria and is not affected by acquired efflux and other targeted resistance mechanisms (7). In Europe, it has been approved for treatment of complicated intra-abdominal infections (cIAI) and complicated skin and soft tissue infections (cSSSI) since May 2006.

It is being increasingly recognised by clinicians and scientists that patients in RCTs of antibiotics of last resort do not represent those patients who will later be treated with these drugs (8, 9). Moreover, the study setting may not reflect the normal place of treatment for the majority of patients. Thus, the generalizability and external validity of RCTs can be unclear (10). Fallagas *et al*. found that the use of extensive and stringent exclusion criteria in RCTs may lead to the enrolment of patients who are considerably different from those encountered in clinical practice (9). Thus, the conclusions generated from RCTs may not apply to a considerable proportion of patients viewed in real-life clinical situations (9).

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Key Words: Tigecycline, critically ill patients, multidrug-resistant bacteria, clinical trials, prescribing patterns.

As our Hospital is a centre for pivotal trials, as well as having patients in the clinical practice setting, the aim of our comparative study was to further examine this discrepancy systematically and quantify it, with focus on prescribing patterns of tigecycline and microbiology-based indication for tigecycline treatment.

Patients and Methods

A literature search was conducted before the evaluation to identify inclusion and important exclusion criteria of clinical trials relevant for marketing authorisation of tigecycline. Data were collected retrospectively from patient charts and electronic patient records for epidemiological evaluation in the current study (11). Microbiologically-relevant parameters were analysed: primary site of infection; course of treatment; prescribing patterns of tigecycline therapy such as off-label use, first-line/second-line, monotherapy/combination-therapy, targeted/empirical; isolated bacteria; MDR pathogens. Microbiological data including antimicrobial susceptibility testing was obtained from the Hospital's microbiology laboratory reports as part of standard procedures. Identification and susceptibility testing of bacterial isolates were performed by standard techniques with the use of an automated system (Phoenix, BD Diagnostic Systems, Heidelberg, Germany). Empirical use of antibiotics was defined as administration of anti-infective therapy to a patient with signs and symptoms of infection without an identified source or a specific microbiological isolate. Targeted therapy was defined as the antibiotic administration in the presence of an identified isolate. Second-line treatment was defined as treatment starting six hours or more after the initial antibiotic treatment, referring to the definition of Kumar *et al.* (12). As a special case of second-line therapy, previous antibiotic use for more than 72 h was considered as a failure of therapy. The protocol was approved by the Ethics Committee of the University of Heidelberg (reference number S 355/2007).

Patients. We included all patients who received tigecycline at the University Hospital Heidelberg, Germany, between March 2003 and December 2008 in this study. In detail, we included all patients in pivotal trials, as well as all patients consecutively treated with tigecycline during this time period, regardless of indication or ward. There was no exclusion of patients treated with tigecycline during that time.

Patients were treated after European Medicines Agency drug approval in 2006 (referred to as 'non-trial patients'), or were patients in one of three clinical trials conducted for marketing authorisation (referred to as 'trial patients'): i) tigecycline *versus* imipenem in adults with complicated intra-abdominal infections (Sponsor-ID 3074A1-306-WW not registered on www.clinicaltrials.gov) n=10; ii) emergency use of tigecycline for treatment of infections with resistant pathogens (3074A1-310-WW/NCT00205816) n=2; iii) tigecycline *versus* ceftriaxone sodium plus metronidazole complicated intra-abdominal infections (3074A1-315-WW/NCT00230971) n=10.

This setting allows direct comparison between trial patients and non-trial patients at the same hospital.

Statistical methods. All parameters were statistically analyzed with IBM® SPSS® Statistics Version 19.0.0 software (IBM®, Chicago, Illinois, USA). Independence between the two groups was determined by Pearson's Chi square test (exact two-sided) for categorical data. *p*-Values of 0.05 or less were considered statistically significant.

Results

During the defined study period, data from 187 patients who received therapy with tigecycline, predominantely in the surgical intensive care unit, were analyzed. As the University Hospital Heidelberg was one of the study centres of the pivotal trials of tigecycline, this drug-use evaluation includes 22 trial patients who were included in the multi-centre RCTs and 165 non-trial patients who were treated in routine clinical practice after marketing authorisation.

Indication. As patients were treated predominantly in the surgery department, indication for tigecycline therapy was cIAI. The most common cIAI of trial patients were complicated appendicitis 7/21 (33%), perforated diverticulitis 5/21 (24%), intestinal perforation 5/21 (24%), intra-abdominal abscess 2/21 (10%) and gastric or duodenal ulcer perforation 2/21 (10%).

Only 69/165 (42%) non-trial patients received tigecycline for the approved indication of cIAI. In contrast to the trial patients, they were predominantly treated for serious infections such as postoperative intra-abdominal abscess 24/69 (35%), intestinal perforation 22/69 (32%), intra-abdominal abscess 7/69 (10%), gastric or duodenal ulcer perforation 3/69 (4%), and cholecystitis with perforation 3/69 (4%); 10/69 (14%) were diagnosed with other types of cIAI.

Although community-acquired pneumonia is an approved indication in the United States, this is not the case in Europe. The proportion of off-label use (pneumonia and other unapproved indications combined) in non-trial patients was therefore 93/165 (56%). Non-trial patients received tigecycline for pneumonia 43/165 (26%), fever of unknown origin 35/165 (21%), bloodstream infection 12/165 (7%) and urinary tract infection 3/165 (2%); 3/165 (2%) of non-trial patients received tigecycline for the treatment of cSSSI.

The majority of non-trial patients received tigecycline for nosocomial infections 158/165 (96%), which occurred at least 48 h after admission to our Hospital. However, only 5/22 (23%) of our trial patients were treated for nosocomial infections ($p<0.001$).

Prescribing patterns of tigecycline. Table I shows a summary of important eligibility criteria of published pivotal trials relevant for marketing authorisation with regard to indication, course of antibiotic treatment and MDR pathogens in comparison with the rates of these parameters in non-trial patients and trial patients of the present study.

Targeted versus empirical antibiotic therapy. It was possible to isolate bacteria at the start of tigecycline therapy in only

Table I. *Comparison of important eligibility criteria of pivotal randomised clinical trials (RCTs) with the present study. Summary of important inclusion and exclusion criteria of pivotal RCTs with regard to indication, antibiotic treatment and resistant pathogens, and the rates of these exclusion parameters that occurred in the particular trial.*

	Present study		Pivotal trials (ref)			
Characteristic	Non-trialpatients	Trialpatients	RCT (20)	RCT (7)	RCT (5)	RCT (6)
Indication	cIAI, cSSSI and off-label use	cIAI, cSSSI	cSSSI	cIAI	MRSA, VRE	ESBL
Number of patients	165	22	422[a]	685[a]	89[a]	66[a]
Combination treatment[b]	73 % (120/165)	18% (4/22)	EC	EC	EC	na
Second-line treatment[c]	75% (123/165)	23% (17/22)	[d]	EC	EC[e]	IC
VRE	13.9% (23/165)	4.5% (1/22)	EC	0.2% (1/512)[f]	3.4% (3/89)[f]	EC
MRSA	7.9% (13/165)	0% (0/22)	11.5% (32/279)[f]	0.8% (4/512)[f]	96.6% (86/89)[f]	EC
ESBL	13.9% (23/165)	0% (0/22)	0.7% (2/279)[f]	2.9% (15/512)[f]	EC	100% (36/36)[f]

cIAI, Complicated intra-abdominal infection; cSSSI, complicated skin and skin structure infection; VRE, vancomycin-resistant *Enterococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended spectrum β lactamase-producing Enterobacteriaceae; IC, inclusion criteria; EC, exclusion criteria; na, not available. [a]Clinically evaluable population treated with tigecycline; [b]concomitant treatment with other antibiotics within six hours before or after start of treatment with tigecycline, excluding perioperative single-shot prophylaxis; [c]considered second-line treatment if the patient was treated for more than 72 h with another antibiotic before the start of therapy with tigecycline; [d]patients received no more than two doses of nonstudy antibacterial therapy or were considered to have experienced previous antibiotic failure; [e]receipt of more than 24 h of potentially effective concomitant antibacterial therapy for VRE or MRSA after baseline culture was obtained, but before the first dose of the study drug; [f]microbiologically-evaluable population.

6/22 (27%) of cases for trial patients in our Hospital, in contrast to 120/165 (73%) in non-trial patients ($p<0.001$).

First-line versus second-line antibiotic therapy. The trial patients at our Hospital mostly received a first-line therapy 17/22 (77%). This finding is in accordance with the fact that treatment with other antibiotics previous to the study medication was an exclusion criterion in several RCTs. Non-trial patients at our Hospital received tigecycline predominantly as second-line treatment, starting six hours or more after the initial antibiotic treatment 123/165 (75%) ($p<0.001$).

As a special case of second-line therapy, previous antibiotic use for more than 72 h was considered as a failure of therapy (antibiotic change to tigecycline). This was the case in 3/22 (14%) of trial patients *versus* 78/165 (47%) of non-trial patients ($p=0.002$). Antibiotics used for these non-trial patients were: imipenem, meropenem, piperacillin/tazobactam, linezolid, ciprofloxacin, third-generation cephalosporines, levofloxacin and vancomycin.

Mono-versus combination antibiotic therapy. Differences also occurred between the two groups comparing monotherapy and combination therapy. Data are shown in Table II. Only 4/22 (18%) of trial patients received combination therapy, 1/22 (4,5%) as first-line, 3/22 (13,6%) as second-line treatment, while 120/165 (73%) of non-trial patients received concomitant antibiotic treatment ($p<0.001$), of those 15/165 (9.1%) as first-line and 105/165 (63.6%) as second-line treatment. For combination therapy in non-trial patients, mainly carbapenemes or piperacicllin/tazobactam were used.

Microbiological evaluation. In patients with culture-positive infections, a distinct difference in the number and types of pathogens was evident between the two groups in our hospital (Figure 1). MDR pathogens were presumably not isolated in the trial patients because the therapy was not targeted, and isolation of an ESKAPE pathogen would have been a criterion for discontinuation of the therapy, because comparative antimicrobial substance wouldn't have been active against all ESKAPE pathogens. In non-trial patients, the rates of ESKAPE pathogens other than VRE, MRSA and ESBL (Table I) were: 16/165 (9.7%) *Klebsiella pneumonia*, 3/165 (1.8%) *Acinetobacter baumanii* and 16/165 (9.7%) *Pseudomonas aeruginosa*. In trial patients the only isolated MDR pathogens were one VRE and one multidrug-resistant *Stenotrophomonas maltophilia* each 1/22 (4.5%).

Discussion

It is stated that characteristics of trial patients often do not reflect those of non-trial patients (8, 9, 13). This statement is often based on comparing real-life patient parameters with parameters of trial populations published in literature. Since we participated in three RCTs of tigecycline, we were able to compare trial patients actually enrolled in these clinical trials in our study centre with our non-trial patients treated after approval of the drug. To our knowledge, our study is the first comparing not only conceptional data but the two patient groups directly. Both groups were treated in the same hospital setting, by the same staff, under the same outpatient conditions. Thus, we were able to substantiate the suspected differences, while excluding bias in overall clinical practice and differences in clinical behaviour.

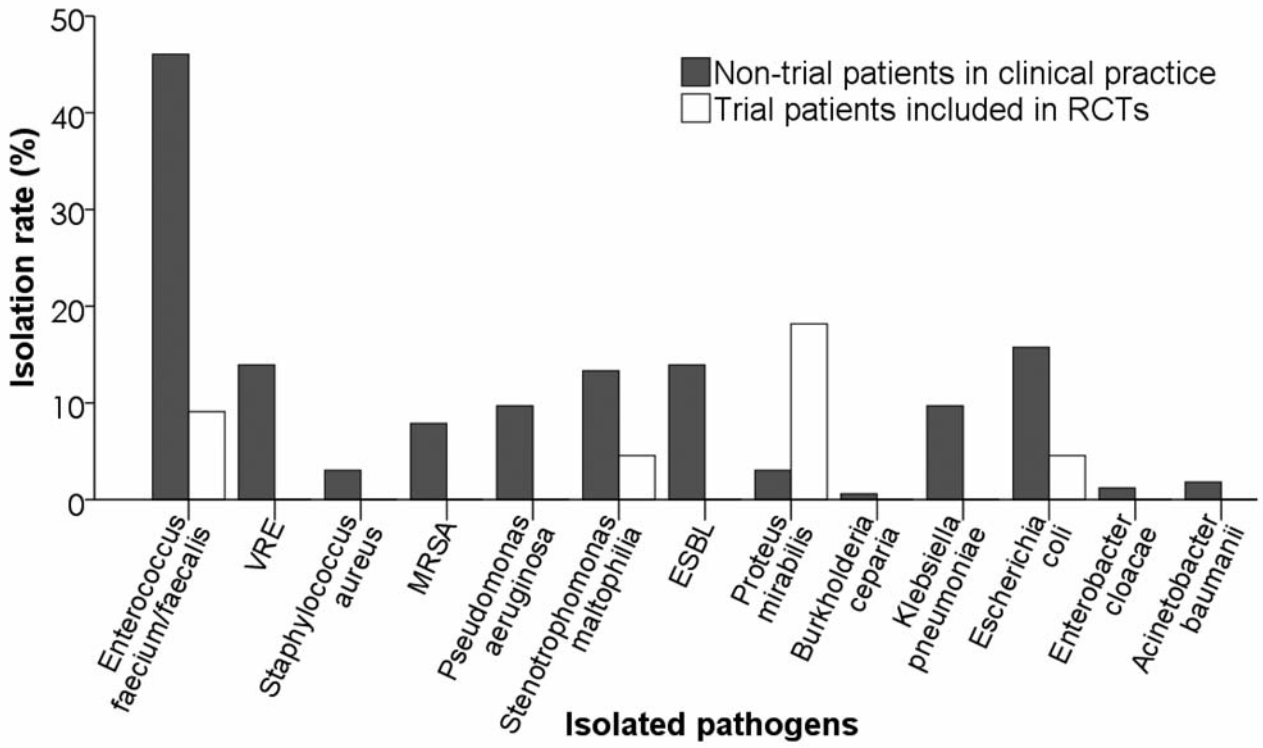

Figure 1. *Microbiological findings. Microbiologically-evaluable pathogens within 10 days of starting therapy with tigecycline, comparing trial patients included in randomised clinical trials (RCTs) and non-trial patients treated in clinical practice. Frequencies refer to the number of individuals in the comparison group (trial patients included in RCTs N=22, non-trial patients treated in clinical practice N=165). VRE, Vancomycin-resistant Enterococcus; MRSA, methicillin-resistant Staphylococcus aureus; ESBL, extended spectrum-β lactamase-producing Enterobacteriaceae.*

Our study shows considerable differences between trial patients and non-trial patients concerning prescribing patterns of tigecycline. Our observation of tigecycline use early after authorization shows that prescribing is mostly consistent with recent recommendations in the FDA boxed warning (in combination and after failure of previous antibiotic therapy) (14). Differences were found in the site of cIAI, prescribing patterns (first-/second-line; targeted/empirical; mono/combination therapy), off-label use, causative pathogens and amount of drug resistance.

In this evaluation, targeted-tigecycline treatment was much more common in non-trial patients than in trial patients. One of the most important criteria for starting and choosing an antibiotic regimen is a positive culture of pathogens (15). Although not statistically significant, the distinctly higher rate of MDR bacteria in non-trial patients points to the use of tigecycline in critically ill patients with persistent and postoperative infections after treatment failure with other anti-infective agents in contrast to less severe infections in trial patients. This too is attributed to the heterogenous types of infection in the two groups. The isolated spectrum of bacteria suggests community-acquired infections in trial patients as opposed to nosocomial infections in non-trial patients (16). Although tigecycline was tested against MDR bacteria in two clinical phase III trials, the microbiological data of trial patients in this evaluation does not match that of the non-trial patients. For tigecycline, the two clinical trials involving MDR pathogens were carried out in late phases of the authorisation process, so that results were available only after its completion. In addition, one study was designed for compassionate use, rather than for evaluation of efficacy.

The fact that the majority of non-trial patients receiving tigecycline are critically ill, often with severe infections, such as sepsis, has been highlighted before (17). The exclusion of prior antibiotic treatment and combination regimens tended to lead to the inclusion of participants with less serious infections. In accordance with our finding that patients in clinical practice are often treated with tigecycline for unapproved indications, an even higher rate of off-label use of 68% has been reported for south-American patients (8). A previous evaluation focused on the influence of recruitment and eligibility (11). Patients eligible for clinical trials were retrospectively compared with ineligible patients regarding baseline and clinical characteristics (11). It was shown that ineligible patients had a statistically

significantly higher mean length of ICU stay (11); inelegible patients also had a statistically significantly higher rate of mortality than eligible patients (11).

One possible reason for the differences found in this comparative study could be the strict eligibility criteria of RCTs (9), as a result of safety concerns of investigators and authorities. Further reasons for the different prescribing patterns in trial patients *versus* non-trial patients may be: prudent and economic second-line use of this last-resort antibiotic at our Hospital in clinical practice (therefore primarily based on microbiology) *versus* indication-based or location-based use (*e.g.* abdominal infection) in RCTs.

The need for new effective anti-infective substances is greatest for critically ill patients with severe nosocomial infections. It would, therefore, be especially important not to exclude these patients from future pivotal trials of last-resort antibiotics, in order to actually validate the efficacy of new antibiotics for this special group of patients. The entire topic should be addressed in RCTs and the approval procedure in the future. There should be data for microbiology-based indications as well as location-based indication before authorisation so that clinicians have evidence for empirical and calculated prescribing of last-resort antibiotics. On the other hand, one might argue that these last-resort antibiotics might never reach authorisation for marketing or be severely delayed if RCTs were restricted to severe nosocomial infections or to critically ill patients with infections who have failed on other antibiotics.

It is to be kept in mind that last-resort antibiotics should be used thoughtfully to prevent their overuse and thus the development of MDR bacteria (18). A lack of focus on MDR pathogens such as the ESKAPE bacteria in pivotal trials might also contribute to the differences between the two groups evaluated. Due to strict exclusion criteria of RCTs, which leads to highly selected participants being recruited, patients in clinical practice much more often suffer from infections caused by MDR bacteria (19).

One of the major limitations of this study is the uneven size of the two comparison groups. With only 22 patients, the group of RCT patients is quite small (compared to 165 non-trial patients from clinical practice), which makes it critical to generalize observations on differences and conclusions. The small number of trial patients results from the multicentre trial character of the pivotal trials. Furthermore, response rates were not documented due to the retrospective character of the evaluation.

Conclusion

Our findings should be understood as a call for further studies evaluating the therapeutic benefit of last-resort antimicrobials and defining the role of tigecycline in the treatment of infections due to MDR bacteria. As few new antimicrobial drugs are in the pipelines, our findings also confirm that critically ill patients are in particular need of potent new antimicrobial agents like tigecycline, which is valuable against a growing number of multi-resistant Gram-positive and Gram-negative bacteria.

Conflicts of Interest

Markus A. Weigand: Lectures for Astellas Pharma, MSD Sharp & Dohme, Pfizer Pharma, Novartis, Janssen, Gilead, Bayer, Astra Zeneca, Glaxo Smith Kline, BBraun, Biosyn, Eli Lilly, CLS Behring, Köhler Chemie, Orion Pharma; Advisory Boards of Astellas Pharma, MSD Sharp & Dohme, Pfizer Pharma, Novartis, Gilead, BBraun, Köhler Chemie, Covidien.

Torsten Hoppe-Tichy: Lectures for Novartis, MSD, Braun-Melsungen, Gilead, Pfizer, Astellas, Janssen, Nycomed, Sanofi; Advisory Boards of Pfizer, MSD, Schering-Plough, GSK.

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