Treatment of complicated urinary tract infection in adults: combined analysis of two randomized, double-blind, multicentre trials comparing ertapenem and ceftriaxone followed by appropriate oral therapy

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The efficacy and safety of parenteral ertapenem, a Group 1 carbapenem, 1 g once a day, for the treatment of complicated urinary tract infections (UTIs; i.e. acute pyelonephritis, UTI in men, or UTI associated with obstruction, foreign body or a urological abnormality interfering with normal voiding) in adults, were compared with those of parenteral ceftriaxone, 1 g once a day, in two similarly designed prospective, double-blind, randomized studies. In both studies, patients could be switched to an oral agent after ≥3 days of parenteral study therapy. At entry, 850 patients were stratified according to whether they had acute pyelonephritis or other complicated UTI without acute pyelonephritis. Two hundred and fifty-six patients in the ertapenem group and 224 in the ceftriaxone group were microbiologically evaluable. Ninety-six per cent of these patients were switched to oral therapy, usually ciprofloxacin; the median (range) duration of parenteral and total therapy, respectively, was 4 (2–14) days and 13 (14–18) days for ertapenem and 4 (2–14) days and 13 (3–17) days for ceftriaxone. The most common pathogens were Escherichia coli and Klebsiella pneumoniae, which accounted for 64.7% and 9.8% of isolates, respectively. At the primary efficacy endpoint 5–9 days after treatment, 229 (89.5%) patients who received ertapenem and 204 (91.1%) patients who received ceftriaxone had a favourable microbiological response (95% confidence interval, −7.4 to 4.0), indicating that outcomes in the two treatment groups were equivalent. Success rates in both treatment groups were similar when compared by stratum and severity of infection. The frequency and severity of drug-related adverse events were generally similar in both treatment groups. In this combined analysis, ertapenem was highly effective therapy for the treatment of complicated UTIs in adults with moderate-to-severe disease.

Keywords: acute pyelonephritis, carbapenems, antimicrobial agents, efficacy, safety

Introduction

Urinary tract infections (UTIs) are amongst the most common problems managed by primary care physicians. In 1995 in the USA, an estimated 11.3 million women had one or more UTIs diagnosed by a physician, and the total cost of UTIs treated with prescription antibiotics was US$1.6 billion.¹ Most UTIs are uncomplicated cystitis caused by Escherichia coli in otherwise healthy young women. These infections are easily managed with short-term oral antimicrobial therapy, usually without the need for follow-up urine cultures. Treatment of complicated UTI, including infection of the renal parenchyma, in contrast, is often less successful. Ten to 14 days of therapy with an antimicrobial agent active against a more extensive list of Gram-negative bacilli is recommended.¹² For serious infections, initial empirical therapy with a broad-spectrum parenteral antimicrobial agent, often followed by an oral agent to which the responsible uropathogen is susceptible, is standard therapy.¹⁻⁴ Follow-up urine cultures are also an important component of management because bacterial eradication is difficult, and recurrence after completion of therapy is not uncommon.

Ertapenem (formerly MK-0826; Merck & Co., Inc.), a once-a-day parenteral β-lactam antimicrobial agent, was licensed in the USA in November 2001 and in Europe in 2002. This Group 1 carbapenem⁵ has excellent in vitro activity (i.e. ≥90% of isolates have an ertapenem MIC ≤ the susceptibility breakpoint) against many Enterobacteriaceae, the pathogens most commonly responsible for UTI, but is not effective against Pseudomonas aeruginosa or enterococci, which are more often associated with nosocomial infection but may

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be responsible for community-acquired UTI.6,7 Ertapenem is cleared primarily by renal secretion and excretion, resulting in sustained high levels of the active agent in the urine. Approximately 45% of the recommended 1 g daily dose is excreted in the urine over 24 h as unchanged, active drug.8 At 36–48 h post-dose, the mean concentration of ertapenem in the urine is 2.4 mg/L, which is well above the MIC90 for the target pathogens.9 Based on these pharmacokinetic data, two clinical trials comparing the efficacy of ertapenem, 1 g once a day, with that of ceftriaxone, 1 g once a day, both with an option to switch to oral therapy, for the treatment of complicated UTI were conducted. Each of these studies alone showed that ertapenem was highly effective and as effective as ceftriaxone.10,11 This report contains a combined analysis of these two comparative trials, and describes the combined safety and efficacy experience of ertapenem compared with ceftriaxone for the treatment of complicated UTI.

Materials and methods

Study design

This is a combined analysis of the results of two individually reported prospective, double-blind (with sponsor blinding), randomized, clinical trials conducted from April 1998 through March 2000 in accordance with guidelines from the Infectious Diseases Society of America.3 Written consent was obtained from all patients, and the institutional review board at each participating site approved the protocol. Eligible patients from US and international centres were stratified according to whether they had acute pyelonephritis (with or without an abnormality of the urinary tract) or other complicated UTI without acute pyelonephritis. The designs of the two studies were identical with two exceptions: (i) in the first study patients were randomized 1:1 to receive ertapenem or ceftriaxone,11 whereas in the second study patients were randomized 2:1 (ertapenem:ceftriaxone);10 (ii) in the second study parenteral administration of ertapenem or ceftriaxone was via the intravenous (iv) or intramuscular (im) route,10 whereas in the first study iv infusion only was permitted.11 Patients were randomized to receive ertapenem or ceftriaxone using a computer-generated random number allocation schedule.

Patients

Patients aged ≥18 years diagnosed with a complicated UTI (i.e. acute pyelonephritis, UTI in men or UTI associated with obstruction, foreign body or urological abnormality interfering with normal voiding) were eligible for the study if initial parenteral antimicrobial therapy was required and if the infection was caused by a pathogen susceptible to the study drugs. Patients could be enrolled based on results of a urinalysis, pending urine culture results, but were considered evaluable only if they met the criteria for a positive culture (i.e. ≥105 cfu/mL of a recognized uropathogen to be fully evaluable). Criteria for acute pyelonephritis were fever, flank pain or costovertebral angle tenderness, pyuria (≥10 white blood cells (WBC) per mm³) and positive urine culture, as defined earlier, within 48 h of enrolment. Criteria for other complicated UTI in a male were signs or symptoms of UTI, pyuria and positive urine culture; female patients without pyelonephritis were additionally required to have an indwelling catheter or current instrumentation or functional or anatomical abnormality of the urinary tract.

Exclusion criteria were pregnancy or lactation in women, history of serious allergy or intolerance to study therapy (patients with a history of mild rash to β-lactams could be enrolled), complete obstruction of the urinary tract, perinephric or intrarenal abscess, prostatitis, any rapidly progressive disease, immune-compromising illness or therapy, the need for concomitant antimicrobials in addition to study therapy, acute hepatic failure, requirement for peritoneal dialysis or haemodialysis, a baseline pathogen resistant to either study drug, treatment with a systemic antimicrobial agent for >24 h within 72 h prior to enrolment, aspartate transaminase or alanine transaminase >6 times upper limit of normal (ULN), bilirubin or alkaline phosphatase >3 times ULN, absolute neutrophil count <1000/mm³, platelet concentration <75 000/mm³, haematocrit <25% or coagulation tests >1.5 times ULN. Men with a history or physical findings suggestive of acute or chronic prostatitis were also excluded.

Antimicrobial therapy

Initially, both ertapenem and ceftriaxone were given once a day as a 1 g iv dose infused over 30 min. Each day patients received one iv infusion of study antimicrobial and one infusion of a colour-matched saline placebo. In one study, administration of either antimicrobial by im injection was permitted after one iv dose. Study therapy was begun in the hospital or clinic but, after ≥2 days, could be completed at home. At the investigator’s discretion, patients who had improved clinically after ≥3 days of parenteral therapy could be switched to oral ciprofloxacin, 500 mg twice daily, if a urine culture was obtained. Other oral agents were permitted if the patient could not tolerate ciprofloxacin or if the causal pathogen was resistant. The suggested total duration of parenteral plus optional oral therapy was 10–14 days.

Clinical and microbiological assessments

Patients were evaluated at enrolment and daily thereafter while on parenteral study therapy. At the time of enrolment, patients with an indwelling catheter were to have had the catheter removed or replaced. Clinical response was assessed on days 3–5 of parenteral therapy, at the completion of parenteral therapy, on days 5–9 post-therapy [test of cure (TOC) visit], and at 4–6 weeks post-therapy [late follow-up (LFU) visit]. The severity of a patient’s infection was assessed prior to unblinding based on pre-specified criteria and was considered severe if the patient was bacteremic, had signs of sepsis (diastolic blood pressure <60 mmHg, altered mental status or requiring vasopressors), or had three of the following: moderate-to-severe flank pain, temperature >38.3°C, chills, nausea or vomiting, or WBC ≥15 000/mm³. All other infections were considered mild to moderate. Clinical responses at the TOC visit were assessed as cure, failure or indeterminate (data not available for evaluation of efficacy). At the LFU visit, clinical responses were assessed as sustained cure, failure, relapse or indeterminate.

Urine cultures with quantification and blood cultures were performed at baseline. All isolates were identified at the site laboratory, and pathogens were tested for in vitro susceptibility to ertapenem, ceftriaxone and ciprofloxacin by disc diffusion or microdilution following NCCLS guidelines.12,13 Microbiological efficacy was assessed by quantitative urine culture on days 3–5 of parenteral therapy, at completion of parenteral therapy, and at the TOC and LFU visits. After ≥48 h of study parenteral therapy, failure was defined as a urine culture with ≥105 cfu/mL of any uropathogen present in the admission culture at ≥105 cfu/mL. Microbiological responses during therapy and at the TOC assessment were eradication (uropathogen present at ≥105 cfu/mL at entry reduced to <104 cfu/mL), persistence (urine culture performed after 2 days of study therapy grew ≥105 cfu/mL of an original uropathogen), persistence acquiring resistance, superinfection [during therapy, a new pathogen cultured from urine (≥105 cfu/mL) or a distant site], new infection (urine cultured after completion of therapy grew ≥105 cfu/mL of an organism other than baseline pathogen) or indeterminate (microbiological response cannot be determined for any reason). Additional responses at LFU were recurrence (urine culture with ≥105 cfu/mL of an original uropathogen that had been eradicated at the TOC visit) and recurrence with acquisition of resistance.
Efficacy and safety of ertapenem in UTI

Populations for analysis
The treated population included all randomized patients who received one or more doses of study therapy. The microbiological modified intent-to-treat (MITT) population included treated patients who met the minimum disease definition and who had a baseline uropathogen in any quantity and a follow-up quantitative urine culture after completion of parenteral therapy. The clinically evaluable population comprised patients who met both the minimum disease definition and the following criteria: clinical evidence of a UTI, information was sufficient to determine outcome at the TOC assessment, baseline urine pathogens were present in a quantity of $\geq 10^5$ cfu/mL ($\geq 10^4$ cfu/mL if the patient was bacteraemic) and one or more baseline pathogens were susceptible to both parenteral study antimicrobials. Microbiologically evaluable patients were clinically evaluable patients who had a follow-up quantitative urine culture at the TOC visit. The LFU clinically evaluable population included clinically evaluable patients who had clinical cure at the TOC assessment and in whom there was sufficient information to determine outcome at the LFU visit. The LFU microbiologically evaluable population comprised LFU clinically evaluable patients who had eradication of baseline pathogen(s) at the TOC visit and a urine culture at LFU.

Efficacy variables
The primary efficacy variable in this study was the microbiological response assessment in the microbiologically evaluable population at the TOC visit. Additional efficacy assessments were the microbiological response rates in the microbiological MITT population, microbiological response rates in the microbiologically evaluable patients at completion of parenteral therapy, combined microbiological and clinical response rates in microbiologically evaluable patients at completion of parenteral therapy, and cure rates in clinically evaluable patients at the TOC assessment. Microbiological recurrence rates were also assessed in LFU microbiologically evaluable patients.

Safety and tolerability assessment
All patients who received one or more doses of the study therapy were evaluated for safety. Patients were monitored for adverse events (AEs) daily during parenteral therapy and for 14 days after all study therapy (parenteral plus oral) was completed. The investigator categorized the intensity of the AE (mild, moderate or severe) and the likelihood of its relation to the study drug (definitely not, probably not, possibly, probably or definitely). The tolerability of each parenteral study drug at the local infusion site was evaluated daily by the investigator. Evaluation was based on investigator inspection and patient comments regarding the intensity of erythema, induration, swelling, pain, burning, tenderness, warmth and phlebitis. At the discretion of the investigator, these or other local reactions may also have been reported as AEs.

Statistical analyses
Each study was designed to test independently for equivalence in efficacy of ertapenem and ceftriaxone in the microbiologically evaluable populations. Equivalence for this combined analysis was determined by the 95% (two-sided) confidence interval (95% CI) for the difference in response rates between the two treatment groups (ertapenem minus ceftriaxone). If the observed response rate in the comparator group was $>90\%$, for equivalence to be demonstrated, the CI of the difference had to contain zero and its lower limit could not be less than $-10\%$. CIs about the difference were calculated using the normal approximation to the binomial distribution and were adjusted for strata using the Cochran–Mantel–Haenzel approach. The treatment by stratum interaction was investigated using the Breslow–Day test of homogeneity of odds ratios and the Gail–Simon test, if needed. No formal tests were performed based on baseline demographics or disease characteristics.

Results
Patients
The distribution of study patients is summarized in Figure 1. Of the 850 patients randomized, 256 (54.1%) in the ertapenem group and 224 (59.4%) in the ceftriaxone group were microbiologically evaluable. One hundred and sixty-three (41.2%) patients with acute pyelonephritis and 207 (45.6%) in the ceftriaxone group were microbiologically evaluable. One hundred and sixty-three (41.2%) patients with acute pyelonephritis and 207 (45.6%) with other complicated UTIs were considered not microbiologically evaluable; the most common reason was failure to isolate $\geq 10^5$ cfu/mL of a uropathogen at enrol-
ment. Baseline demographics and disease characteristics of patients in both treatment groups in the randomized and microbiologically evaluable populations were generally similar (Table 1). In the microbiologically evaluable population, 131 (51.2%) patients in the ertapenem group and 120 (53.6%) in the ceftriaxone group had one or more urinary tract abnormalities (Table 2); indwelling bladder catheters or stents were present in 30 (11.7%) and 22 (9.8%) patients in the ertapenem and ceftriaxone treatment groups, respectively.

**Therapy**

Of the randomized patients, 15 (3.2%) in the ertapenem group and 7 (1.9%) in the ceftriaxone group received parenteral study therapy. In the microbiologically evaluable population, 248 (96.9%) patients treated with ertapenem and 213 (95.1%) patients treated with ceftriaxone were switched to oral antimicrobial therapy; most (93.3%) received ciprofloxacin and were switched by study day 4. The median (range) duration of parenteral and total therapy, respectively, in the microbiologically evaluable patients was 4 (2–14) days and 13 (4–18) days for those treated with ertapenem and 4 (2–14) days and 13 (3–17) days for those treated with ceftriaxone. Among all treated patients, the median (range) duration of parenteral therapy was 3 (1–14) days for patients who received ertapenem and 4 (1–14) days for patients who received ceftriaxone.

**Baseline microbiology**

The distribution of pathogens from randomized patients in each treatment group and their susceptibility profiles were comparable. Of the 726 total isolates, the most common pathogens were *E. coli* [470 isolates (64.7%)] and *Klebsiella pneumoniae* [71 isolates (9.8%)]. As expected, the pathogens resistant to ertapenem and ceftriaxone were enterococci and *P. aeruginosa*. Twenty-nine microbiologically evaluable patients who received ertapenem and 25 treated with ceftriaxone were bacteremic at baseline; the aetiologic agent in 41 (75.9%) of these patients was *E. coli*.

**Efficacy**

All efficacy data refer to microbiologically evaluable patients unless otherwise stated. At the primary efficacy endpoint, 89.4% of patients in the ertapenem group and 91.1% in the ceftriaxone group had a favourable microbiological response assessment (95% CI, adjusting for strata: −7.4 to 4.0), indicating the equivalence of the two treatments. In the supportive microbiological MITT analysis, which included 663 patients (78.0% of randomized patients), 90.1% in the ertapenem group and 89.0% in the ceftriaxone group had a favourable microbiological response (95% CI, −3.8 to 6.1). This also shows that success rates in the two treatment groups were similar, and is consistent with the results of the primary efficacy analysis.

Microbiological response rates are shown by stratum, subgroup and time of assessment in Table 3, and by pathogen in Table 4. As expected, response rates were lower in men and in patients with an indwelling catheter. At the TOC visit, 166 (91.7%) of 181 women in the ertapenem group and 141 (92.2%) of 153 in the ceftriaxone group had a favourable microbiological response, compared with 63 (84.0%) of 75 men in the ertapenem group and 63 (88.7%) of 71 in the ceftriaxone group. Among catheterized patients, 25 (83.3%) of 30 treated with ertapenem and 18 (81.8%) of 22 treated with ceftriaxone had a favourable microbiological response at the TOC assessment, compared with 204 (90.3%) of 226 and 186 (92.1%) of 202, respectively, who did not have an indwelling catheter. Among those with

**Table 2.** Urinary tract abnormalities in microbiologically evaluable patients with complicated UTI

<table>
<thead>
<tr>
<th>Urinary tract abnormality</th>
<th>No. (%) of patients with abnormality in group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitourinary structural abnormality</td>
<td>etrapenem (n = 256) ceftriaxone (n = 224)</td>
</tr>
<tr>
<td>Partial obstruction, acquired</td>
<td>44 (17.2) 35 (15.6)</td>
</tr>
<tr>
<td>High post-voiding residual</td>
<td>31 (12.1) 42 (18.8)</td>
</tr>
<tr>
<td>Neurogenic bladder</td>
<td>26 (10.2) 18 (8.0)</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>35 (13.7) 25 (11.2)</td>
</tr>
</tbody>
</table>

* *Patients with complete obstruction were excluded from both studies.*
Infections developed in one patient treated with ertapenem and four and 147 (70.7%) of 208 patients in the ceftriaxone group. The pre-
treated with ceftriaxone. Enterococci were the most common cause
s of patients in the ertapenem group and 27 (12.1%) in the ceftriaxone group; super-

to persistent bacteriuria; no patient had persistent bacteraemia. Clinical
cure rates at the TOC assessment were similar in the two treat-
mental groups: 90.9% for ertapenem and 92.4% for ceftriaxone (95%

At completion of parenteral therapy
acute pyelonephritis 119/121 98.3 (96.1–100) 101/102 99.0 (97.1–100)
other complicated UTI 121/122 99.2 (97.6–100) 106/113 93.8 (89.3–98.3)
overall 240/243 98.8 (97.4–100) 207/215 96.3 (93.7–98.8)

At test of cure
acute pyelonephritis 116/127 91.3 (86.4–96.2) 99/106 93.4 (88.6–98.1)
other complicated UTI 113/129 87.6 (81.9–93.3) 105/118 89.0 (83.3–94.7)
mild-to-moderate infection 117/135 86.7 (80.9–92.4) 107/120 89.2 (83.6–94.8)
severe infection 112/121 92.6 (87.9–97.3) 97/104 93.3 (88.4–98.1)
overall 229/256 89.4 (85.6–93.2) 204/224 91.1 (87.4–94.9)

n/m, number of patients cured/number of patients with assessment.

bacteraemia, 25 (86.2%) of 29 patients in the ertapenem group and 21 (84.0%) of 25 patients in the ceftriaxone group had a favourable
microbiological response. Failures in bacteraemic patients were due
to persistent bacteriuria; no patient had persistent bacteraemia. Clinical
cure rates at the TOC assessment were similar in the two treat-
mental groups: 90.9% for ertapenem and 92.4% for ceftriaxone (95%

At completion of parenteral therapy, 234 (97.1%) of 241 patients in the ertapenem group and 199 (94.8%) of 210 patients in the
ceftriaxone group had both a favourable microbiological response (bacterial eradication) and a favourable clinical response (improvement in signs and symptoms, with worsening in none) (95% CI, –1.8 to 6.3). Additionally, at completion of parenteral therapy, all baseline signs and symptoms had improved in 248 (98.0%) of 253 patients in the ertapenem group and 215 (98.6%) of 218 in the ceftri-
oxone group, and all signs and symptoms had resolved in 139 (54.9%) of 253 patients in the ertapenem group and 107 (49.1%) of 218 patients in the ceftriaxone group. By the TOC assessment, signs
and symptoms associated with acute infection, including fever, chills, nausea, vomiting, flank, costovertebral angle or suprapubic
pain, and dysuria, had completely resolved in >85% of patients in both
treatment groups, and all signs and symptoms had completely
resolved in 171 (70.7%) of 242 patients in the ertapenem group and 147 (70.7%) of 208 patients in the ceftriaxone group. The pre-
dominant unresolved symptom was incontinence, which was still
present at the TOC assessment in 22 (32.8%) of 67 patients in the
er tapenem group and 19 (34.5%) of 55 patients in the ceftriaxone

group. This is probably a reflection of the underlying urological
abnormality rather than a persistent symptom of ertapenem.

Bacterial recurrence rates at the LFU assessment were similar in the
two treatment groups: 8.9% among the 175 patients in the ertap-
em group and 7.6% in the 167 patients in the ceftriaxone group
(95% CI, –5.3 to 8.0). Non-baseline, emergent, new infections
occurred in 40 (15.6%) microbiologically evaluable patients in the
ertapenem group and 27 (12.1%) in the ceftriaxone group; super-

Table 3. Favourable microbiological response assessments in microbiologically evaluable patients with
complicated UTI, by stratum or subgroup

<table>
<thead>
<tr>
<th>Stratum/subgroup</th>
<th>Ertapenem n/m</th>
<th>% response (95% CI)</th>
<th>Ceftriaxone n/m</th>
<th>% response (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At completion of parenteral therapy</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>acute pyelonephritis</td>
<td>119/121</td>
<td>98.3 (96.1–100)</td>
<td>101/102</td>
<td>99.0 (97.1–100)</td>
</tr>
<tr>
<td>other complicated UTI</td>
<td>121/122</td>
<td>99.2 (97.6–100)</td>
<td>106/113</td>
<td>93.8 (89.3–98.3)</td>
</tr>
<tr>
<td>overall</td>
<td>240/243</td>
<td>98.8 (97.4–100)</td>
<td>207/215</td>
<td>96.3 (93.7–98.8)</td>
</tr>
<tr>
<td>At test of cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute pyelonephritis</td>
<td>116/127</td>
<td>91.3 (86.4–96.2)</td>
<td>99/106</td>
<td>93.4 (88.6–98.1)</td>
</tr>
<tr>
<td>other complicated UTI</td>
<td>113/129</td>
<td>87.6 (81.9–93.3)</td>
<td>105/118</td>
<td>89.0 (83.3–94.7)</td>
</tr>
<tr>
<td>mild-to-moderate infection</td>
<td>117/135</td>
<td>86.7 (80.9–92.4)</td>
<td>107/120</td>
<td>89.2 (83.6–94.8)</td>
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<tr>
<td>severe infection</td>
<td>112/121</td>
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<td>overall</td>
<td>229/256</td>
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</table>

n/m, number of patients cured/number of patients with assessment.

In this combined analysis of two independent, large, randomized
trials, ertapenem, 1 g once a day, with the option to switch to oral ther-
apy, was highly effective for the treatment of complicated UTI, and
equivalent to standard therapy. At the TOC assessment, 89.4% of
both treatment groups was pain. Of patients who received im therapy,
30/15 in the ertapenem group and 1/7 in the ceftriaxone group experi-
enced reactions of moderate-to-severe intensity at the local infusion site. The most common symptom in both treatment groups was pain. Of patients who received im therapy, 0/15 in the ertapenem group and 1/7 in the ceftriaxone group experi-
enced local symptoms (bruising) of moderate-to-severe intensity.

Discussion
In this combined analysis of two independent, large, randomized
trials, ertapenem, 1 g once a day, with the option to switch to oral ther-
apy, was highly effective for the treatment of complicated UTI, and
equivalent to standard therapy. At the TOC assessment, 89.4% of
patients treated with ertapenem had a favourable microbiological
response. Both trials in this report included a diverse population and,
as shown in Tables 1 and 2, the studies included a broad range of
patients with serious complicated UTIs for whom initial empirical
parenteral antimicrobial therapy was indicated. Approximately half
of the patients had acute pyelonephritis, approximately one-third
were males and approximately one-third were aged ≥65 years. The
∼40% of patients. Over half of the patients had one or more urological abnormality, and ∼10% had an
indwelling bladder catheter or stent. A potential limitation of these
analyses, however, was that within the category complicated UTI
other than acute pyelonephritis, neither study controlled for the specific type of urological abnormality, nor did the studies control for the reason for or duration of catheterization prior to study enrolment. The possible effect of these variables on the overall outcome, therefore, cannot be assessed.

In this report, to measure the specific contribution of the parenteral agent to the total treatment regimen, microbiological and clinical assessments were made at the time parenteral therapy was discontinued, before the institution of oral therapy, in addition to the primary endpoint 5–9 days after all therapy was completed. In the microbiological response assessments, as well as in the combined microbiological and clinical response assessments, the response rate to ertapenem therapy (≥98%) was as high as, or higher than, that to ceftriaxone therapy, further demonstrating that ertapenem was highly effective in the initial management of complicated UTI. Additional verification of the contribution of ertapenem to the treatment regimen is apparent in the analysis of patients with baseline bacteremia: of those evaluable, 25 (86.2%) of 29 treated with ertapenem compared with 21 (84.0%) of 25 treated with ceftriaxone showed eradication of all pathogens from both urine and blood and were microbiologically favourable overall. In all bacteraemic patients from whom follow-up blood cultures were obtained, the bloodstream infection was eradicated; no-one had persistent bacteraemia documented at any time after initiating therapy.

Treatment of complicated UTI is usually initiated empirically, before identification of the causative organism(s). In the two trials reported here, as well as in previously reported studies, Enterobacteriaceae accounted for the overwhelming majority of pathogens; in the Old World, Enterobacteriaceae resistant to ertapenem are exceedingly rare. Enterobacteriaceae resistant to ertapenem are increasingly resistant to ampicillin and trimethoprim–sulfamethoxazole, especially those strains isolated from patients who have received prior antimicrobial therapy. Patients with underlying urinary tract abnormalities are also at increased risk of infection with other Enterobacteriaceae that may be more resistant to antimicrobial agents.

### Table 4. Eradication rates at the TOC visit in microbiologically evaluable patients with complicated UTI, by baseline uropathogen in urine and/or blood

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Ertapenem (n = 256)</th>
<th>Ceftriaxone (n = 224)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n/m</td>
<td>% response (95% CI)</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
<td>7/10</td>
<td>70.0 (40.1–99.9)</td>
</tr>
<tr>
<td>enterococci</td>
<td>3/6</td>
<td>50.0</td>
</tr>
<tr>
<td>S. aureus</td>
<td>2/2</td>
<td>100.0</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>1/1</td>
<td>100.0</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>1/1</td>
<td>100.0</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>229/255</td>
<td>89.8 (86.1–93.5)</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>176/191</td>
<td>92.1 (88.3–96.0)</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>24/28</td>
<td>85.7 (72.5–98.9)</td>
</tr>
<tr>
<td>other Klebsiella spp.</td>
<td>3/4</td>
<td>75.0</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>9/12</td>
<td>75.0</td>
</tr>
<tr>
<td>Citrobacter spp.</td>
<td>2/2</td>
<td>100.0</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>4/4</td>
<td>100.0</td>
</tr>
<tr>
<td>Pantoea agglomerans</td>
<td>4/4</td>
<td>100.0</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>4/7</td>
<td>57.1</td>
</tr>
<tr>
<td>other*</td>
<td>3/3</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 5. Most common drug-related clinical and laboratory AEs reported during ertapenem and ceftriaxone therapy in patients with complicated UTI

<table>
<thead>
<tr>
<th>No. (%) patients in treatment group</th>
<th>ertapenem (n = 468)</th>
<th>ceftriaxone (n = 372)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diarrhea</td>
<td>29 (6.2)</td>
<td>26 (7.0)</td>
</tr>
<tr>
<td>nausea</td>
<td>23 (4.9)</td>
<td>17 (4.6)</td>
</tr>
<tr>
<td>headache</td>
<td>22 (4.7)</td>
<td>14 (3.8)</td>
</tr>
<tr>
<td>infused vein complication</td>
<td>16 (3.4)</td>
<td>14 (3.8)</td>
</tr>
<tr>
<td>vaginitis</td>
<td>12 (2.6)</td>
<td>12 (3.2)</td>
</tr>
<tr>
<td>abdominal pain</td>
<td>6 (1.3)</td>
<td>11 (3.0)</td>
</tr>
<tr>
<td>increased ALT</td>
<td>17/420 (4.0)</td>
<td>16/327 (4.9)</td>
</tr>
<tr>
<td>increased AST</td>
<td>16/445 (3.6)</td>
<td>12/348 (3.4)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*aNumber of patients who experienced a laboratory AE/total number of patients for whom the laboratory test was performed.

**Includes Morganella morgani, Pseudomonas spp. and *Serratia liquefaciens* in the ertapenem group; *M. morgani*, *Flavobacterium* spp., *Pseudomonas* spp., *Proteus penneri*, *Serratia marcescens* (two isolates) and *Escherichia fergusonii* in the ceftriaxone group.
Efficacy and safety of ertapenem in UTI

The safety profile and local tolerability of ertapenem in the two studies reported here were similar to those of ceftriaxone. The drug-related clinical AEs reported most frequently for both agents were diarrhoea and nausea. The most commonly reported drug-related laboratory AEs for both drugs were mild-to-moderate elevations in aminotransferase levels, which tended to be transient and without clinical consequence. In all ertapenem clinical trials, the clinical AEs most commonly reported in patients treated with ertapenem were diarrhoea (5.5%), infected vein complication (3.7%), nausea (3.1%), headache (2.2%), vaginitis in females (2.1%), phlebitis/thrombophlebitis (1.3%) and vomiting (1.1%); and, as in both of the UTI trials, the most frequently reported laboratory AEs were elevations in aminotransferase levels.

In summary, ertapenem 1 g once a day, with the option to switch to an appropriate oral antimicrobial agent after clinical improvement, was highly effective both clinically and microbiologically for the treatment of moderate-to-severe complicated UTI requiring initial parenteral therapy in adults. The results of these studies demonstrate that ertapenem was excellent therapy for complicated UTIs in adults with moderate-to-severe disease.

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Transparency declarations

W.G.W., as the medical director of Alabama Research, has participated in clinical trials with ertapenem, but has no financial connection with Merck & Co., Inc., and has not received any reimbursement, speaking fees or consultancy fees from the Company; nor have any of the staff of Alabama Research. R.G. is an employee of Merck & Co., Inc., and potentially owns stock and/or holds stock options in the Company. Q.J. and G.W. are former employees of Merck & Co., Inc., and potentially own stock in the Company.

References


