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Safety and Efficacy of Long-Term Outpatient Ertapenem Therapy

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Ertapenem is increasingly utilized in outpatient parenteral antimicrobial therapy (OPAT), but data regarding the efficacy and safety of long-term ertapenem therapy have been limited. We conducted a retrospective cohort study of adult patients who received outpatient ertapenem therapy at our center between 2010 and 2013. Among 306 unique patients who were discharged on ertapenem therapy, the most common indications were intra-abdominal infections (38%), followed by pneumonia (12%), bone and joint infections (11%), bloodstream infections (10%), urinary tract infections (10%), surgical site infections (5%), and skin and soft-tissue infections (4%). Of these 306 patients, 68 received regular outpatient follow-up visits at our infectious disease clinic, where the majority of patients (91%) were successfully treated with ertapenem by the end of therapy. Of the 6 patients who experienced clinical failure, 2 had adverse events leading to discontinuation of therapy and 4 required additional source control for clinical success. In addition, 2 patients had recurrent infection at 6 months.

Ertapenem is a parenteral carbapenem which is currently approved in the United States for use in the treatment of intra-abdominal infections, complicated skin and soft-tissue infections, community-acquired pneumonia, and complicated urinary tract infections (1). Ertapenem is unique for its long elimination half-life, which allows for once-daily dosing (2). Because of its broad spectrum of activity, it is often used for the treatment of infections requiring prolonged parenteral therapy.

The use of outpatient parenteral antimicrobial therapy (OPAT) has markedly increased in the United States and worldwide (3–5). Conditions commonly managed by OPAT include intra-abdominal infections, skin and soft-tissue infections, bone and joint infections, pneumonia, and urinary tract infections (5, 6). Ertapenem is one of the antimicrobial agents that is highly utilized in outpatient settings for the aforementioned reasons (7). However, data regarding efficacy and safety of long-term ertapenem therapy remain relatively limited (8). The purpose of the present study was 2-fold, (i) to examine the trends and indications for the use of ertapenem in outpatient settings and (ii) to evaluate the efficacy, tolerability, and safety of ertapenem in patients who receive long-term outpatient therapy.

MATERIALS AND METHODS

Study design and patients. This was a retrospective cohort study of patients who received outpatient ertapenem therapy. Adult patients discharged from a tertiary medical center in Pittsburgh, PA, between January 2010 and June 2013 were included. The study was approved by the institutional review board of the University of Pittsburgh (PRO12070602). Initial screening was conducted by querying electronic discharge summaries that contained the term ertapenem. Each discharge summary was then manually reviewed by the investigators to identify subjects who actually had discharge orders for ertapenem therapy. This cohort made up the "all-study group." The indications for posthospitalization ertapenem therapy were recorded for this group. The outpatient electronic medical record system was screened for follow-up visits of patients included in the all-study group. Those who received at least 2 weeks of outpatient ertapenem therapy and had follow-up visits at one of the University of Pittsburgh Medical Center Infectious Disease Clinics made up the "outpatient antibiotic therapy (OPAT) group." Each follow-up visit was reviewed by the investigators to assess the clinical status and progress of the patient. The variables reviewed for this group included demographics, microbiology data, type of infection, underlying diseases, Charlson's comorbidity index score (9), indications for ertapenem use, surgical interventions, physician assessment at outpatient follow-up visits, radiology data, blood chemistries, duration of ertapenem use, and possible or probable adverse events related to its use. Types of infections were defined according to standardized definitions by the National Healthcare Safety Network (10).

Outcome measures. For patients in the OPAT group, the clinical response to ertapenem therapy was defined as, by the end of therapy, (i) cure (resolution of clinical signs and symptoms of infection and evidence of improvement either on radiology studies or blood chemistries or both), (ii) presumed cure (resolution of clinical signs and symptoms of infections without evidence from radiology studies or blood chemistries), or (iii) failure (no improvement in signs and symptoms of infection, persistence of infection with evidence from radiology data or blood chemistries, or development of adverse events resulting in discontinuation of therapy). We also collected data on recurrent infection at 6 months after discharge when available. The electronic medical records were systematically reviewed to identify possible adverse events while the patients were on ertapenem. For laboratory studies, values outside 1.5-fold of the normal reference range were collected as potentially related to ertapenem use. The RIFLE criteria (risk, injury, failure, loss, and end-stage kidney disease) were used to assess renal function (11).

RESULTS

Indications for postdischarge ertapenem therapy. A total of 306 unique patients who received ertapenem outpatient therapy were identified during the study period. There had been a steady increase in the use of outpatient ertapenem therapy with 59, 73, 116, and 58 patients discharged on ertapenem in 2010, 2011, 2012, and the first 6 months of 2013, respectively. The most common indication for outpatient ertapenem therapy in this all-study group was intra-abdominal infection ($n = 116$; 38%), followed by pneumonia ($n = 36$; 12%), bone and joint infection ($n = 35$; 11%), bloodstream infection ($n = 31$; 10%), urinary tract infection ($n = 31$; 10%), surgical site infection ($n = 14$; 5%), and skin and soft tissue infection ($n = 12$; 4%).

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TABLE 1 Characteristics and clinical outcomes of patients on outpatient ertapenem therapy

Type of infection	No. of patients	Age (median [range]) (yr)	Charlson's comorbidity index (median [range])	No. of wk on ertapenem (median [range])	No. of patients with clinical success/total no. of patients[a] (%)	No. of patients with clinical failure/total no. of patients (%)	No. of patients with adverse events requiring discontinuation/ total no. of patients (%)	No. of patients with adverse events not requiring discontinuation/ total no. of patients (%)	No. of patients with recurrence at 6 mo/total no. of patients (%)
Intra-abdominal	46	59 (24–74)	2 (0–11)	4 (3–10)	42/46 (91)	4/46 (9)	2/46 (4)	1/46 (2)	1/46 (2)
Osteomyelitis	12	56 (22–65)	4 (0–7)	8 (4–16)	10/12 (83)	2/12 (17)	0	0	0
Skin and soft tissue	5	54 (38–60)	3 (1–3)	4 (3–8)	5/5 (100)	0	0	1/5 (20)	0
Empyema	2	77 (76–78)	2 (2–3)	4 (3–6)	2/2 (100)	0	0	0	0
Vascular graft infection	1	73	3	6	1/1 (100)	0	0	0	0
Mediastinitis	1	69	7	8	1/1 (100)	0	0	0	0
Pyelonephritis	1	47	0	3	1/1 (100)	0	0	0	1/1 (100)
Total	68			4 (3–16)	62/68 (91)	6/68 (9)	2/68 (3)	2/68 (3)	2/68 (3)

[a] Clinical success includes patients with cure and presumed cure.

Among the 306 patients in the all-study group, 238 patients were excluded due to various reasons. A total of 157 patients received ertapenem therapy for <2 weeks; 43 patients had follow-up visits with their primary care physicians, while 38 were discharged to long-term health care facilities and were followed up by physicians at the respective facilities. After their exclusion, 68 patients were identified as having received at least 2 weeks of ertapenem and had regular outpatient follow-up visits at the Infectious Disease Clinic and constituted the OPAT group. The clinical outcomes of these patients are summarized in Table 1. Of these 68 patients, 65 received ertapenem for >80% of the entire treatment duration, and 53 of them received ertapenem alone for >80% of the entire treatment duration.

Clinical management and outcomes for patients with intra-abdominal infections. Of the 46 patients with intra-abdominal infections, 38 had an intra-abdominal abscess, 6 had an infected pancreatic pseudocyst, and 2 had an infected biloma. The common comorbid conditions included diabetes mellitus ($n = 15$), malignancy ($n = 9$), solid organ transplantation ($n = 7$), chronic obstructive pulmonary disease (COPD) ($n = 6$), and coronary artery disease ($n = 6$). During the hospital care, intra-abdominal cultures were obtained from 44 patients (96%), of which 34 revealed microbiologic growth, while 10 had no growth. All patients with no microbiologic growth had received empirical antimicrobial therapy before the cultures were obtained. Organisms recovered from the intra-abdominal cultures included *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Bacteroides* spp., *Citrobacter freundii*, *Fusobacterium* spp., *Peptostreptococcus* spp., microaerophilic streptococci, viridans streptococci, *Serratia marcescens*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *Providencia* spp. Only 2 patients had growth of extended-spectrum β-lactamase (ESBL)-producing organisms, which were *E. coli* in both patients. Fifteen patients had polymicrobial infection. Among them, *Enterobacteriaceae* were the most commonly isolated organisms ($n = 14$). Forty-two patients (91%) underwent surgical intervention during their hospital stay, with 37 having a drain placement and 5 having incision and drainage of abscesses. Twenty-two patients (48%) were started on ertapenem in the hospital, while 24 (52%) were switched from another agent to ertapenem upon discharge. Among these 24 patients, 15 and 9 had received piperacillin-tazobactam and ampicillin-sulbactam before discharge, respectively, with a median duration of 7 days (range, 2 to 15 days). Eight patients (17%) were discharged on a second Gram-positive agent in addition to ertapenem (6 and 2 on vancomycin and daptomycin, respectively). Forty-two (91%) and 4 (9%) patients were discharged to home and nursing home, respectively. The first posthospitalization follow-up at the Infectious Disease Clinic was at a median of 3 weeks after discharge (range, 2 to 4 weeks). One patient who received ertapenem and vancomycin developed a rash after 2 weeks of therapy, which resulted in discontinuation of both agents. For the duration of outpatient antimicrobial therapy, 41 patients (89%) had a complete blood count (CBC), a basic metabolic profile (BMP), and a liver function test (LFT) performed every week, while 5 patients (11%) had this laboratory monitoring performed every other week. One patient developed 4-fold asymptomatic transaminase elevation after 2 weeks of receiving ertapenem and daptomycin, which resulted in discontinuation of both agents. The values normalized within a week after their discontinuation. Another patient had 2-fold asymptomatic transaminase elevation after 5 weeks, but ertapenem was continued to complete the planned 6 weeks of therapy. The values normalized after completion of ertapenem therapy. Two patients had clinical failure at the time of the first visit, with computed tomography (CT) scans showing increasing sizes of the abscesses. At the time, one patient was on ertapenem and vancomycin, while the other was on ertapenem alone. One patient subsequently underwent upsizing of the drain and the other had laparotomy with resection of an enterocutaneous fistula. In all, 44 patients (96%) completed the planned course of ertapenem and 42 (91%) had cure with resolution of signs and symptoms of infection and evidence of improvement on computed tomography (CT) scan with ertapenem therapy, without the need of further surgical interventions. All 15 patients who received only ertapenem for the entire duration of therapy (33%) had a cure and none reported adverse events. Twenty-three patients (50%) were switched from other agents to ertapenem alone upon discharge, one of whom had treatment failure. Twenty-two patients, including the two who had clinical failure, had a second follow-up visit in the Infectious Disease Clinic a median of 6 weeks after discharge (range, 5 to 8 weeks). All had cure at this second visit. The median duration of ertapenem therapy was 4 weeks (range, 3 to 10 weeks). Of 44 patients whose clinical status 6 months after discharge was known, one had recurrence after receiving ertapenem and vancomycin. The remaining 2 patients had their last follow-up visits at 2 and 4 months, respectively, and did not have recurrence of infection at that time.

Clinical management and outcomes for patients with osteomyelitis. Among the 12 patients with osteomyelitis, the sites of

infection were the foot ($n = 5$), sacrum ($n = 3$), mandible ($n = 2$), vertebra ($n = 1$), and tibia ($n = 1$). All patients had osteomyelitis from a contiguous source and not from hematogenous spread. The common comorbid conditions were diabetes mellitus ($n = 7$), solid organ transplantation ($n = 3$), and chronic renal disease ($n = 3$). Magnetic resonance imaging (MRI) was the diagnostic modality in all cases. Eight patients underwent surgical intervention, 4 with debridement of wounds, 3 with drain placement, and 1 with removal of hardware. Organisms recovered from the bone cultures included *Peptostreptococcus* spp., *Enterococcus* spp., *S. aureus*, viridans streptococci, *Bacteroides* spp., microaerophilic streptococci, *E. cloacae*, and ESBL-producing *E. coli*. Three cultures had polymicrobial growth. All but two patients were discharged home. Ten were started on ertapenem while in the hospital, whereas 2 were switched to ertapenem upon discharge after 8 or 10 days of ampicillin-sulbactam therapy. Six patients were discharged on a combination of vancomycin and ertapenem. The first posthospitalization follow-up at the Infectious Disease Clinic was at a median of 4 weeks after discharge (range, 4 to 6 weeks). Ten patients (83%) had cure with resolution of signs and symptoms and normalization of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) by the end of therapy. Four patients received only ertapenem for the entire duration of therapy, 2 patients were switched to ertapenem upon discharge, and the remaining 6 patients received a combination of ertapenem and vancomycin. Two patients had failure, with one patient requiring repeated debridement and extension of ertapenem therapy up to 16 weeks and the other patient requiring below-knee amputation. Both patients with failure had received a combination of ertapenem and vancomycin after discharge. The median duration of outpatient antimicrobial therapy was 8 weeks (range, 4 to 16 weeks). None had adverse events, including abnormal laboratory values, with ertapenem use. Nine patients had CBC, BMP, and LFT examined every week, while 3 had laboratory monitoring every other week for the duration of therapy. At 6 months after discharge, none of the 12 patients had recurrence.

Clinical management and outcomes for patients with skin and soft tissue infections. Among 5 patients with skin and soft tissue infections, 1 had periorbital cellulitis and 4 had abscesses, including rectal abscess, breast abscess, iliac abscess, and periorbital abscess. Comorbid conditions included diabetes mellitus ($n = 2$), and COPD ($n = 1$). Four patients underwent surgical intervention: 2 had drain placement and 2 underwent incision and drainage. Two patients had growth of microaerophilic streptococci and *K. pneumoniae* from deep wound cultures, respectively. Two patients had polymicrobial growth; one had *K. pneumoniae*, *Peptostreptococcus* spp., and *Prevotella* spp., while the other had *E. coli* and *C. freundii*. Two patients were started on ertapenem while in the hospital, whereas 3 patients were switched to ertapenem at discharge after receiving ampicillin-sulbactam for a median duration of 4 days (range 4 to 10). All patients were discharged home. The first posthospitalization follow-up at Infectious Disease Clinic was at a median of 3 weeks (range, 2 to 4 weeks). Four patients had cure, with resolution of signs and symptoms and improvement on CT scans, while one patient with cellulitis had presumed cure. Median duration of outpatient ertapenem therapy was 4 weeks (range, 3 to 8 weeks). Four patients had CBC, BMP, and LFT performed every week, while 1 patient had laboratory monitoring every other week. One patient was found to have 2-fold asymptomatic transaminase elevation after 2 weeks, but ertapenem was continued to complete the planned 4 weeks of therapy. The values remained stably elevated while the patient was on ertapenem and returned to normal after the completion of therapy. No patient had a recurrence at 6 months after discharge.

Clinical management and outcomes for patients with miscellaneous infections. Two patients had empyema. Cultures from surgical drainage had polymicrobial growth, one with microaerophilic streptococci and *Peptostreptococcus* spp. and the other with *E. coli*, *K. pneumoniae*, and viridans streptococci. One patient was on ertapenem while an inpatient, while the other was switched to ertapenem therapy at the time of discharge. They received ertapenem for 2 and 6 weeks, respectively. Both patients had cure of infection at the end of therapy.

One patient had bloodstream infection with *Bacteroides fragilis*, *S. aureus*, and *E. faecalis* secondary to an infected vascular graft, which was subsequently removed. He had received cefepime and vancomycin while in the hospital. He received ertapenem and vancomycin for a total of 6 weeks and had cure.

One patient had mediastinitis with *Bacteroides* spp. and *Prevotella* spp. after sternotomy. He underwent multiple incision and drainage procedures. He was started on ertapenem in the hospital, and it was continued for 8 weeks after discharge, resulting in cure.

One patient with renal transplant had pyelonephritis with ESBL-producing *E. coli*. He was started on ertapenem in the hospital, was continued on it for 3 weeks after discharge, and had presumed cure at the end of therapy. However, he had recurrent infection after 4 weeks, for which he received ertapenem for another 4 weeks, resulting in cure. Of note, this patient was dependent on an indwelling urinary catheter for high postvoid urinary volume.

No adverse events or laboratory abnormalities were noted among these patients with miscellaneous infections.

DISCUSSION

Our study found that at our center ertapenem is increasingly utilized in posthospitalization, outpatient settings for various infectious disease diagnoses, which is consistent with a previous report (7). The overall clinical success rate among patients who completed the course of ertapenem was 91% (62/68), while 3% (2/68) had discontinuation of ertapenem therapy due to adverse events and another 6% (4/68) had clinical failure at the end of ertapenem therapy requiring additional surgical intervention for source control. Additionally, 3% (2/68) had recurrent disease at 6 months. The most common indications for ertapenem therapy were intra-abdominal infections and osteomyelitis. The clinical success rate was 91% for intra-abdominal infections, which is slightly higher than the rates reported in previous studies (12, 13). The difference may be due to higher proportions of patients who underwent surgical interventions for source control in our study (91%). The success rate for osteomyelitis was 83%, which is consistent with a previous study (14). As would be expected, the median duration of ertapenem therapy was significantly longer for patients with osteomyelitis than for those with other diagnoses (8 versus 4 weeks, $P = 0.008$). Another noteworthy finding was that therapies for 46% of the patients (31/68) were changed from another agent to ertapenem upon discharge.

Adverse events in patients treated with ertapenem were relatively rare, which was consistent with previous studies (12, 14). One patient developed a skin rash within 2 weeks of ertapenem therapy, resulting in its discontinuation. Ertapenem use has been

associated with skin rash, which usually occurs several weeks into therapy (1). Another patient developed significant elevation of transaminase levels after 2 weeks of ertapenem therapy. This was a transient rise and the levels returned to normal after discontinuation of ertapenem. Two other patients developed mild elevations in transaminase levels that did not require discontinuation and normalized after completion of ertapenem therapy. Transaminase elevation is a known side effect of ertapenem but has not been associated with clinical consequences (1, 3).

Our study is limited by its observational nature and relatively small number of patients from a single center, as we limited our analysis to patients who had regular follow-up in our own clinic postdischarge from the hospital. In addition, it was a single-arm study, and there was no comparator group.

In conclusion, ertapenem is increasingly utilized for a broad range of bacterial infections which require long-term therapy at our center. The data presented here provide insights into the efficacy and safety of long-term ertapenem therapy in OPAT settings.

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