Moxifloxacin in Pediatric Patients With Complicated Intra-abdominal Infections

Results of the MOXIPEDIA Randomized Controlled Study

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Background: This study was designed to evaluate primarily the safety and also the efficacy of moxifloxacin (MXF) in children with complicated intra-abdominal infections (cIAIs).

Methods: In this multicenter, randomized, double-blind, controlled study, 451 pediatric patients aged 3 months to 17 years with cIAIs were treated with intravenous/oral MXF (N = 301) or comparator (COMP, intravenous ertapenem followed by oral amoxicillin/clavulanate; N = 150) for 5 to 14 days. Doses of MXF were selected based on the results of a Phase 1 study in pediatric patients (NCT01049022). The primary endpoint was safety, with particular focus on cardiac and musculoskeletal safety; clinical and bacteriologic efficacy at test of cure was also investigated.

Results: The proportion of patients with adverse events (AEs) was comparable between the 2 treatment arms (MXF: 58.1% and COMP: 54.7%). The incidence of drug-related AEs was higher in the MXF arm than in the COMP arm (14.3% and 6.7%, respectively). No cases of QTc interval prolongation-related morbidity or mortality were observed. The proportion of patients with musculoskeletal AEs was comparable between treatment arms; no drug-related events were reported. Clinical cure rates were 84.6% and 95.5% in the MXF and COMP arms, respectively, in patients with confirmed pathogen(s) at baseline.

Conclusions: MXF treatment was well tolerated in children with cIAIs. However, a lower clinical cure rate was observed with MXF treatment compared with COMP. This study does not support a recommendation of MXF for children with cIAIs when alternative more efficacious antibiotics with better safety profile are available.

Key Words: moxifloxacin, pediatric patients, complicated intra-abdominal infection, comparator, safety

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Complicated intra-abdominal infections (cIAIs) represent a spectrum of conditions including peritonitis, intraperitoneal abscess and visceral abscess and are defined as infections that extend beyond the hollow viscus into a normally sterile area of the abdomen.[1]

Typically, patients with cIAIs present with clinical signs and symptoms of either peritonitis or abscess formation. Among the spectrum of intra-abdominal conditions that may lead to a cIAI in children, perforation of the appendix is the most common. Infections can also occur if the bowel wall integrity is compromised, for example, by ischemia or trauma.[2,3]

As for adults, general treatment principles for cIAIs in children involve surgical or percutaneous radiologic intervention followed by antimicrobial therapy[4] and the recommended regimens, including aminoglycosides, carbapenems, β-lactam/β-lactamase inhibitor combination or advanced-generation cephalosporins.[4]

Moxifloxacin (MXF) is a fourth-generation fluoroquinolone antimicrobial with good in vitro activity against most causative organisms involved in cIAIs. MXF penetrates well into inflamed gastrointestinal tissues,[5,6] and the benefits in adult cIAIs have been demonstrated in 4 double-blind, randomized, active-controlled clinical studies.[7–10] Hence, it is a recommended treatment option for cIAIs in adults.[4]

The use of fluoroquinolones in children is limited to special indications, such as inhalation anthrax, and only when alternative antibiotics with a more favorable safety profile are not available.[11] These recommendations are regularly updated in the light of new information and address the safety concerns with these agents in pediatric patients. Thus, cardiac adverse events (AEs), tendon disorders and polyneuropathy[12,13] may be a particular concern in pediatric patients.

The MOXIPEDIA (Moxifloxacin in Pediatric Subjects With Complicated Intra-abdominal Infection) study was designed to evaluate the safety of intravenous/oral MXF compared with sequential treatment with intravenous ertapenem followed by oral amoxicillin/clavulanate in children with cIAIs, focusing on musculoskeletal AEs and cardiac AEs, and also on heart rate–corrected QT interval prolongation according to Bazett (QTcB) and Fridericia (QTcF) formulae.

METHODS

Study Design and Population

The MOXIPEDIA study (NCT01069900) was a prospective, randomized, double-blind, double-dummy, active-controlled, parallel group, multicenter Phase 3 study in pediatric and adolescent patients with cIAIs. The patient population was divided into 4 age groups: adolescents (aged 12 to <18 years), school children (aged 6 to <12 years), preschool children (aged 2 to <6 years) and infants and toddlers (aged 3 months to <2 years).

Patients with the diagnosis of cIAI including a single or multiple intra-abdominal abscess or macroscopic intestinal perforation with localized or diffuse peritonitis either surgically confirmed or supported with radiologic evidence were eligible. All patients had undergone an initial surgical or interventional radiology procedure with or without postoperative drainage of abdominal cavity at baseline. The main exclusion criteria are shown in Supplemental Digital Content 1, http://links.lww.com/INF/C949.

The study was conducted in agreement with the Declaration of Helsinki, current amendment, the guideline for Good Clinical Practice and local regulatory requirements. The protocol was approved by the ethics committee at each participating site. Informed consent was obtained from patients' parents or guardians before enrollment into the study.

Study Medications

Eligible patients were assigned in a 2:1 ratio to receive either intravenous/oral MXF or intravenous ertapenem followed by oral amoxicillin/clavulanate suspension (COMP) (Table 1), commencing immediately before or after surgery and interventional radiology. The total treatment duration was 5 to 14 days at the discretion of the investigator, with a minimum duration of 3-day intravenous administration.

The MXF dosing regimens (Table 1) were based on a complementary Phase 1 study (NCT01049022)[14,15] and physiologically based pharmacokinetic modeling (data not shown) to ensure an adequate dosing of MXF, equivalent to the recommended 400 mg dose for adults. Age- and body weight–scaled intravenous infusions of MXF were administered over a period of 60 minutes, and oral MXF doses were provided as 50 or 400 mg tablets. Ertapenem and amoxicillin/clavulanate doses were based on their respective labels (Table 1).

TABLE 1. Dosing Regimens for MXF and COMP

Age and BW Category	Intravenous	Oral
MXF		
3 months to <2 years	6 mg/kg BW bid*	No switch to oral
≥2 to <6 years		
BW <20 kg	5 mg/kg BW bid*	No switch to oral
BW ≥20 kg	5 mg/kg BW bid*	5 mg/kg BW bid*†
≥6 to <12 years		
BW <20 kg	4 mg/kg BW bid*	No switch to oral
BW ≥20 kg	4 mg/kg BW bid*	4 mg/kg BW bid*†
≥12 to <18 years		
BW <45 kg	4 mg/kg BW bid*	4 mg/kg BW bid*†
BW ≥45 kg	400 mg od	400 mg od‡
COMP		
	Ertapenem	Amoxicillin/Clavulanate
3 months to <2 years	15 mg/kg BW bid§	No switch to oral
≥2 to <6 years		
BW <20 kg	15 mg/kg BW bid§	No switch to oral
BW ≥20 kg	15 mg/kg BW bid§	22.5/3.2 mg/kg BW bid¶
≥6 to <12 years		
BW <20 kg	15 mg/kg BW bid§	No switch to oral
BW ≥20 kg	15 mg/kg BW bid§	22.5/3.2 mg/kg BW bid¶
≥12 to <18 years		
12 years	15 mg/kg BW bid§	22.5/3.2 mg/kg BW bid¶
≥13 to <18 years	1 g od	22.5/3.2 mg/kg BW bid¶

*Not exceeding 400 mg daily.
†Provided in 50 mg tablets.
‡Provided as a 400 mg tablet.
§Not exceeding 1 g daily.
¶Not exceeding 875 mg amoxicillin/125 mg clavulanate bid.
bid indicates twice daily; BW, body weight; od, once daily.

Primary and Secondary Endpoints

The primary objective was safety in the overall pediatric population during the entire study period and during the follow-up period, with endpoints of overall AEs and cardiac and musculoskeletal AEs. Secondary endpoints included clinical and bacteriologic responses determined at test of cure (TOC) (Supplemental Digital Content 1, http://links.lww.com/INF/C949).

Safety Assessments

Safety data were collected at regular visits comprising pretreatment (baseline), treatment Day 1, during therapy (treatment Days 3–5), on the day of switch from intravenous to oral therapy if applicable, at end of treatment (EOT, last administration of MXF or COMP) and TOC (28 to 42 days after EOT). Assessments comprised AEs (according to the Medical Dictionary for Regulatory Activities [MedDRA], version 17.1); vital signs (maximum body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure); a complete physical examination including abdomen and evaluation of surgical wound (except at pretreatment); laboratory assessments (blood chemistry, hematology, coagulation, urine analysis) and concomitant prescribed medication. In female patients of childbearing potential, a pregnancy test was performed before administration of any study medication and at EOT.

Standard 12-lead electrocardiogram (ECG) was recorded in each patient using Mortara ELI 250 ECG machines (Mortara Instrument Inc., Milwaukee, WI) before and after cessation of MXF or COMP infusion on treatment Days 1 and 3. The digital ECG recordings were transmitted electronically to a specified ECG core laboratory (Quintiles, United Kingdom) for semiautomated and manually verified analyses of ECG parameters (RR, PR, QRS and QT intervals). All ECG parameters were verified by a physician with pediatric cardiology expertise. QT intervals were given as heart rate–uncorrected QT, as well as QTcB and QTcF.

A standardized thorough musculoskeletal assessment examining shoulder, elbow, wrist, hip, knee, ankle, Achilles tendon and patellar tendon at both sides regarding swelling, pain, tenderness, warmth or any loss of normal function was performed at regular visits and additionally at 3 months and 1 year after EOT. Parents also completed a musculoskeletal questionnaire relating to existence in medical history of psoriasis, chronic inflammatory bowel disease (eg, Crohn's disease or ulcerative colitis), bone and/or cartilage defects, congenital diseases (eg, cerebral palsy), cystic fibrosis and current limitations in age-appropriate physical activity behaviors of the child. All patients who had musculoskeletal AEs 1 year after EOT were to be followed-up until resolution or yearly for up to 5 years, if resolution did not occur before.

Statistical Methods

Sample Size

The study was designed as safety trial, with planned enrollment of approximately 300 MXF-treated patients and 150 COMP-treated patients. With this number of MXF-treated patients, if a specific AE is not seen, its event rate can be assumed with 95% confidence to be <1%.

Statistical Analysis

All statistical analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC). The analysis of safety and efficacy data was descriptive, and no formal statistical testing was performed. The main analysis was performed on the safety population, comprising all randomized patients receiving at least one dose of study medication. Efficacy data were also analyzed for the modified intent-to-treat population, defined as all patients valid for safety

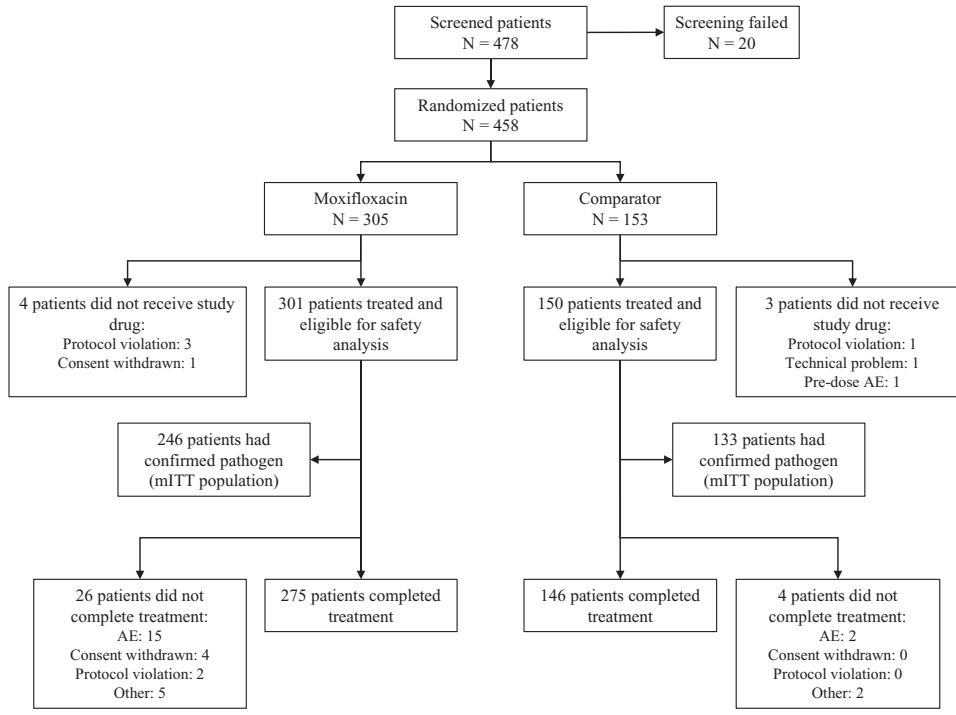

FIGURE 1. Patient disposition. mITT indicates modified intent-to-treat.

who had at least one pretreatment causative organism from the primary site of infection or from blood cultures. Results are expressed as frequency counts and percentages unless otherwise stated. In addition, within-treatment group 95% confidence intervals (CIs) are provided for the safety parameters.

RESULTS

Patient Disposition

Of 478 children screened between January 2010 and 2015, 458 were eligible for inclusion and were randomized (Fig. 1). Seven children (MXF: n = 4 and COMP: n = 3) discontinued after randomization but before taking any study medication. Altogether, 301/305 patients in the MXF arm and 150/153 patients in the COMP arm were treated. Thirty patients (MXF: n = 26 and COMP: n = 4) did not complete study medication; the most common reasons were occurrence of an AE (n = 17) and withdrawal of parental consent (n = 4).

Patient Demographics and Baseline Characteristics

The median (range) overall age of the population was 13 years (3 months to 17 years), the majority (>90%) being 6 to 17 years of age; only 22 patients <6 years of age were treated (Table 2). Clinically, most children presented with abdominal pain, rigidity of abdominal wall and abdominal tenderness. The most frequent diagnoses were localized or diffuse peritonitis. Most patients (95%) had undergone an appendectomy. None of the patients in the MXF arm and 2 patients in the COMP arm received any antibiotic (ie, cefoxitin plus levofloxacin plus metronidazole and ciprofloxacin, respectively) before surgery or interventional radiology.

The mean (range) duration of treatment was 8.7 (1–24) days for MXF and 8.7 (1–14) days for COMP. The mean (range) duration of intravenous treatment was 6.2 (1–15) days for MXF and 6.3 (1–14) days for COMP, and oral treatment was 4.4 (1–12) days for MXF and 4.3 (1–11) days for COMP, respectively. Seven children received MXF for >14 days (up to 24 days).

Safety

The overall incidence rate of any AE was similar between the treatment arms: 175/301 patients (58.1%; 95% CI: 52.6–63.7%) for MXF and 82/150 patients (54.7%; 95% CI: 46.7–62.6%) for COMP (Table 3). The majority of AEs were mild or moderate. The incidence rate of severe AEs was 12/301 (4.0%) for MXF and 3/150 (2.0%) for COMP. Drug-related AEs occurred in 14.3% (43/301) of MXF-treated patients (95% CI: 10.3–18.2%) and 6.7% (10/150) of COMP patients (95% CI: 2.7–10.7%). The incidence rate of serious AEs was similar between the 2 treatment arms, and no drug-related serious AEs occurred. All but one AE (one patient had newly diagnosed Crohn's disease receiving MXF) recovered/resolved by the end of the study. No death was reported in the study. More patients in the MXF arm discontinued the treatment because of an AE compared with those in the COMP arm (Table 3).

The most common AEs by MedDRA Preferred Term were ECG QT prolonged, incision site pain, vomiting and wound infection (Table 4). No relevant differences in incidence rates of the most common AEs were observed between the 2 treatment arms, except for ECG QT prolongation (28/301 [9.3%] of MXF-treated patients versus 4/150 [2.7%] of COMP-treated patients). The incidence of the most commonly reported AEs was not higher in the younger age groups.

Electrocardiographic QT/QTc Changes

The incidence of drug-related QT prolongation in ECG recordings was 7.0% in the MXF arm (95% CI: 4.4–10.3; one event being assessed by the investigator as a severe AE) and 1.3% in the COMP arm (95% CI: 0.2–4.7).

No cases of QTc interval prolongation–related morbidity or mortality (ie, clinical cardiac signs and symptoms) were observed.

TABLE 2. Patient Demographics and Baseline Characteristics (Safety Population)

Variable	MXF (N = 301)	COMP (N = 150)	Total (N = 451)
Age (years)			
Mean	12.03	12.05	12.04
SD	3.68	3.48	3.61
Median	13	13	13
Range	0.25–17	3–17	0.25–17
Age group (years), N (%)			
0.25–<2	1 (0.3)	0	1 (0.2)
2–<6	14 (4.7)	7 (4.7)	21 (4.7)
6–<12	100 (33.2)	51 (34.0)	151 (33.5)
12–<18	186 (61.8)	92 (61.3)	278 (61.6)
Gender, N (%)			
Male	179 (59.5)	98 (63.5)	277 (61.4)
Female	122 (40.5)	52 (34.7)	174 (38.6)
Race, N (%)			
White	289 (96.0)	142 (94.7)	431 (95.6)
Black	1 (0.3)	1 (0.7)	2 (0.4)
Hispanic	8 (2.7)	6 (4.0)	14 (3.1)
Native Hawaiian or other pacific islander	1 (0.3)	0	1 (0.2)
Uncodable	2 (0.7)	1 (0.7)	3 (0.7)
Body temperature (°C)			
Mean	37.67	37.59	37.64
SD	0.76	0.71	0.75
Median	37.7	37.6	37.7
Range	35.20–40.70	35.30–39.00	35.20–40.70
Abdominal pain, n (%)			
Mild	45 (15.0)	17 (11.3)	62 (13.7)
Moderate	116 (38.5)	60 (40.0)	176 (39.0)
Severe	91 (30.2)	47 (31.3)	138 (30.6)
None	49 (16.3)	26 (17.3)	75 (16.6)
Abdominal tenderness with rebound, N (%)			
Present	185 (61.5)	93 (62.0)	278 (61.6)
Absent	116 (38.5)	57 (38.0)	173 (38.4)
Primary diagnosis, N (%)			
Single intra-abdominal abscess	50 (16.6)	23 (15.3)	73 (16.2)
Multiple intra-abdominal abscesses	2 (0.7)	0	2 (0.4)
Localized peritonitis (limited to one quadrant)	148 (49.2)	74 (49.3)	222 (49.2)
Diffuse peritonitis (2 or more quadrants)	101 (33.6)	53 (35.3)	154 (34.1)

SD indicates standard deviation.

Ten patients (3.3%) discontinued MXF early because of uncorrected QT interval prolongation. A case of QTcB (+24 ms) and QTcF (+13 ms) prolongation after 400 mg MXF infusion at Day 1 resolved on the same day after MXF withdrawal.

Musculoskeletal Adverse Events

A comparable proportion of patients in the MXF and COMP arms experienced a musculoskeletal AE [13/301 patients (4.3%; 95% CI: 2.3–7.3) and 5/150 patients (3.3%; 95% CI: 1.1–7.6), respectively]. No musculoskeletal events were assessed by the investigators as being related to either study medication (Table 5).

Most events were mild and started from 3 weeks to 1 year after start of study medication. There was one serious musculoskeletal AE, a forearm fracture in an 11-year-old male patient occurring about 7 months after EOT with MXF. All events recovered/resolved at the end of the study.

TABLE 3. Summary of Adverse Events (Safety Population)

AEs	MXF (N = 301), N (%)	COMP (N = 150), N (%)
Any AE	175 (58.1)	82 (54.7)
Any drug-related AE	43 (14.3)	10 (6.7)
Any serious AE	20 (6.6)	6 (4.0)
Any drug-related serious AE	0	0
Discontinuation of study medication because of AE	16 (5.3)	2 (1.3)
Discontinuation of study medication because of serious AE	1 (0.3)	0 (0)
Death	0 (0)	0 (0)

Efficacy

In the modified intent-to-treat population, bacteriologic success and clinical cure at TOC were achieved in 208/246 (84.6%) MXF-treated patients and 127/133 (95.5%) COMP-treated patients (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/C949). Similar results were found in the safety population. Clinical success rates were similar across all age groups. One of the COMP-treated patients who received antibiotics before surgery or interventional radiology (cefoxitin plus levofloxacin plus metronidazole) was assessed as clinical and bacteriologic success at TOC, whereas the other patient who received preoperatively ciprofloxacin was graded as failure because of occurrence of a mechanical ileus 17 days after the end of COMP treatment.

Clinical failure was reported in 38/246 [15.4%; of which 21/246 (8.5%) had indeterminate clinical response] MXF-treated patients and 6/133 [4.5%; of which 3/133 (2.3%) had indeterminate response] COMP-treated patients. Among patients treated with MXF, 8.1% (20/246 patients) had either relapse of cIAI, or abscess formation or retention of purulent exudate in abdominal cavity, or presumed persistence of causative pathogen was observed or administration of other antimicrobial agents additional to study medication or after EOT, while 1.5% (2/133 patients) among COMP-treated patients had an infectious failure (Table 6).

Further details on efficacy are given in Supplemental Digital Content 1, http://links.lww.com/INF/C949.

DISCUSSION

In this study, the safety and efficacy of intravenous/oral MXF was compared with that of intravenous ertapenem followed by oral amoxicillin/clavulanate in pediatric patients (3 months to 17 years) with cIAIs. Both treatment regimens were well tolerated by patients regardless of their age, although there were more drug-related AEs with MXF compared with COMP. In both treatment arms, a similar proportion of patients experienced musculoskeletal AEs. Clinical success rates at TOC were lower with MXF compared with COMP.

Approximately 90% of cIAIs in children are because of perforated appendicitis.[16–19] In this study, 95% of the patients in each treatment arm across all age groups underwent an appendectomy, indicating a high incidence of appendicitis. The most frequent diagnoses were localized peritonitis (limited to one quadrant) in older children (aged 12 to <18 years) and diffuse peritonitis (2 or more quadrants) in children below 12 years of age, the latter being consistent with the inability of the underdeveloped omentum to limit purulent effusion from a perforation.[20]

In the present study, clinical cure and bacteriologic success rates with MXF were comparable to those previously reported in adults with cIAIs.[7,10,21] Considering that MXF shows a

TABLE 4. Incidence of Adverse Events by MedDRA Preferred Term Occurring in ≥2% Patients in Either Treatment Arm Irrespective of Relation to Study Medication (Safety Population)

	MXF (N = 301), N (%)		COMP (N = 150), N (%)	
MedDRA Preferred Term	Any AE	Drug-related	Any AE	Drug-related
Abdominal pain	8 (2.7)	0	3 (2.0)	0
Diarrhea	11 (3.7)	6 (2.0)	1 (0.7)	0
Vomiting	20 (6.6)	1 (0.3)	12 (8.0)	2 (1.3)
Procedural vomiting	0	0	4 (2.7)	0
Pyrexia	6 (2.0)	0	4 (2.7)	0
Wound infection	14 (4.7)	0	6 (4.0)	0
Incision site pain	26 (8.6)	0	14 (9.3)	0
Procedural pain	16 (5.3)	0	10 (6.7)	1 (0.7)
Incision site inflammation	2 (0.7)	0	3 (2.0)	1 (0.7)
AST increased	2 (0.7)	0	3 (2.0)	2 (1.3)
ECG QT prolonged	28 (9.3)	21 (7.0)	4 (2.7)	2 (1.3)
Headache	6 (2.0)	0	2 (1.3)	0
Phlebitis	8 (2.7)	0	0	0

AST indicates aspartate aminotransferase.

TABLE 5. Incidence of Musculoskeletal Adverse Events (Safety Population)

	MXF (N = 301), N (%)		COMP (N = 150), N (%)	
MedDRA Preferred Term	Any AE	Drug-related	Any AE	Drug-related
Forearm fracture	1 (0.3)	0	0	0
Joint injury	0	0	1 (0.7)	0
Ligament sprain	1 (0.3)	0	1 (0.7)	0
Muscle strain	0	0	1 (0.7)	0
Arthralgia	9 (3.0)	0	1 (1.3)	0
Joint swelling	0	0	1 (0.7)	0
Musculoskeletal pain	3 (1.0)	0	0	0
Myalgia	1 (0.3)	0	0	0

concentration-dependent bactericidal activity driven by the maximum drug concentration in plasma and the area under the plasma concentration–time curve, effective dosing regimens are needed for pediatric patients to achieve comparable systemic drug exposures as in adults treated with 400 mg MXF once daily.[5,6] This was attained by the age- and body weight–dependent dosing scheme of MXF, which was developed using physiologically based pharmacokinetic modeling on the basis of MXF exposure parameters that are considered safe and efficacious in adults.[14,15] Achievement of adequate systemic MXF exposure in pediatric patients was confirmed by a subsequent retrospective population pharmacokinetic analysis (data not shown).

TABLE 6. Overview of Causes of Clinical Failure at Test of Cure (mITT Population)

Clinical Response	MXF (n = 246), N (%)	COMP (n = 133), N (%)
Any clinical failure	38 (15.4)	6 (4.5)
Infectious failure*	20 (8.1)	2 (1.5)
Reoperation	1 (0.4)	1 (0.7)
Wound infection	7 (2.8)	1 (0.7)
Early withdrawal from study because of AE†	9 (3.7)	2 (1.5)
Other‡	1 (0.4)	0
Death	0	0

*Includes relapse of cIAI, abscess formation, retention of purulent exudate in abdominal cavity, administration of other antimicrobial agents additional to study medication or after EOT or presumed persistence of causative pathogen.

†Includes prolongation of QT interval (7 MXF-treated patients and 1 COMP-treated patient) and administration of other antimicrobial agents because of AE (2 MXF-treated patients presenting endocarditis or mechanical ileus and 1 COMP-treated patient presenting mechanical ileus).

‡Includes unavailability of study medication at investigational site.

The efficacy of MXF was numerically lower than that of COMP. No historical data exists on the efficacy of intravenous ertapenem followed by oral amoxicillin/clavulanate in children with cIAIs. In studies with ertapenem in adults, clinical success rates were between 79% and 93% for a 14-day regimen for cIAIs[10,22–26] and 97% for a 3-day regimen for localized peritonitis.[27] In children with cIAIs, clinical success rates of 82%–94% have been described for ertapenem.[19,28] Interestingly, in the present study, the clinical cure rate with MXF treatment tended to be higher in Europe than in North America (87.8% vs. 70.8% at the TOC visit). However, the overall number of patients treated with study medication in the North America region was low.

Differences in physiology and pharmacokinetics between children and adults can profoundly affect the safety and efficacy of antibiotics in children.[29] In particular, potential fluoroquinolone-related musculoskeletal toxicity is a serious safety concern. While this has been observed in animal studies, with damage to articular cartilage in weight-bearing joints in juvenile animals,[30–32] there is no comparable documentation of fluoroquinolone-induced arthropathy in humans. Overall, fluoroquinolone-associated musculoskeletal toxicity is relatively infrequent and transient in clinical studies.[33] In our study, no relevant difference between treatment arms in the proportion of patients experiencing musculoskeletal events was observed.

In general, the safety and tolerability of MXF in children was comparable to that in adults, and no unexpected adverse drug reactions were observed. As expected, MXF induced a small ECG QTc prolongation. The mean QTc interval with intravenous MXF was within the range of that reported in adults receiving MXF 400 mg,[13] despite higher heart rate values in pediatric patients. Prolongation of the QTc interval increases the risk of *Torsade de Pointes* (*TdP*) arrhythmia, which might be a fatal arrhythmia, especially when the QTc interval exceeds 500 ms or the prolongation is greater than 60 ms compared with the pretreatment value. Currently, information on the potentially low risk of MXF-associated *TdP* or other ventricular arrhythmias are based only on data in adult patients, and no information is available for pediatric patients.[34] Furthermore, it is unknown if any predisposing factors identified in adults (excluding older age) such as female sex, bradycardia, hypokalemia, hypocalcemia, hypomagnesemia, history of cardiac disease and treatment with more than one QTc-prolonging medication[13] also apply to pediatric subjects. Subjects with some of these risk factors were excluded from the current study; therefore, any link between MXF-induced QTc prolongation and risk factors could not be established. Our data did not indicate a higher propensity for MXF-induced QTc prolongation in children compared with adults.

This study had some limitations, including that the sample size was not calculated for primary analysis of efficacy, and no noninferiority margin for the treatment effect of MXF compared with COMP was considered, thus, limiting the ability to make conclusive inferences on efficacy. Also, the variety of cIAI diagnoses was limited. The time point for primary assessment of clinical success differs from that of the current FDA guidance[35] because the study was designed before its availability.

In summary, the sequential administration of MXF treatment was well tolerated in children with cIAIs. The general safety profile and efficacy of MXF was consistent with that in adult patients. However, MXF monotherapy appeared less efficacious than ertapenem followed by amoxicillin/clavulanate, an antimicrobial treatment regimen recommended by evidence-based guidelines for children. These results do not support MXF to be recommended for pediatric patients with cIAIs when alternative efficacious antibiotics with better safety profile are available.

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