SUPPLEMENTAL DIGITAL CONTENT 1

Moxifloxacin in Pediatric Patients with Complicated Intra-Abdominal Infections: Results of the MOXIPEDIA Randomized Controlled Study

METHODS

Exclusion criteria

The main exclusion criteria included: perforation of the upper gastrointestinal tract of less than 24 hours before surgery; complicated intra-abdominal infection (cIAI) secondary to pancreatitis, liver or splenic abscess; known severe immunosuppression; uncorrected electrolyte disturbances; prior quinolone use within the previous 12 months; systemic antibacterial treatment within the previous 7 days; requirement of concomitant systemic antibacterial agents; congenital or documented acquired QT prolongation;[1] concomitant treatment with drugs that are known to prolong the QT interval; clinically relevant bradycardia; history of symptomatic arrhythmias; history of tendon disorder related to quinolone treatment; abnormal musculoskeletal findings at baseline assessment; and history of myasthenia gravis.

Clinical Efficacy Evaluation

Clinical efficacy of moxifloxacin (MXF) and intravenous ertapenem followed by oral amoxicillin/clavulanate (COMP) was evaluated on treatment Day 1, during therapy (treatment Days 3 to 5), on the day of switch from intravenous to oral therapy if applicable, at end of treatment (EOT) and at test of cure (TOC). The clinical response rate at TOC was dichotomized in success and failure. Patients achieving a resolution or sufficient improvement of clinical signs and symptoms related to the infection, did not require any antibiotic therapy or surgical intervention, and did not present wound infections requiring systemic antibiotic treatment were defined as clinical success. Patients having reappearance of the signs and symptoms of the original infection or wound infection requiring further systemic antimicrobial therapy were considered as clinical failure. Furthermore, patients with an indeterminate clinical response, i.e., in whom a clinical assessment was not possible to determine, e.g. due to early withdrawal from the study because of adverse event (AE),

protocol violation, withdrawal of consent, etc. and patients who died regardless of when the death occurred were assessed as clinical failure.

Microbiological Efficacy Evaluation

Aerobic and anaerobic cultures and susceptibility testing were performed on samples obtained during surgery to identify causative pathogens. Peripheral blood cultures were also evaluated for the presence of pathogens, if clinically indicated. Bacteriological success at EOT and TOC was defined as absence of appropriate culture material for evaluation because the patient has responded clinically with clinical resolution and invasive procedures were not warranted. Bacteriological failure was considered for presence of the original causative organisms or new organism not previously isolated at baseline on culture, for patients judged as clinical failures without having culture material for evaluation, patients in whom the bacteriological response was not valid for any reason, e.g. pre-treatment culture was negative or culture was not obtained when material was available and the patient was not judged a clinical failure, and patients who died regardless of when the death occurred.

RESULTS

Safety Parameters

Changes in QT/QTc values are shown in Supplemental Table 1. The mean increase in QTcB and QTcF intervals compared with pre-dose values was >5 ms on treatment Days 1 and 3 with MXF but did not reach 5 ms with COMP. Post-dose prolongation of >60 ms from baseline values in QTcB were seen in 2 patients receiving MXF and 1 receiving COMP on Day 3 only. Similar changes were seen for QTcF on Day 1, in a patient receiving MXF, and on Day 3, in 5 patients receiving MXF and 1 receiving COMP. In the MXF arm, neither gender nor younger age influenced the incidence of events. No absolute QTcB values >500 ms and no absolute QTcF values >480 ms or >500 ms were observed in any patient. All changes in QT/QTc interval were reversible.

There was no difference between treatment arms in vital signs. Increased baseline heart rate, respiration rate and body temperature values were decreased by the end of treatment and test of cure. The observed changes were expected for this patient population during recovery from cIAIs. The laboratory parameters and further recorded electrocardiogram (ECG) parameters (RR, PR, QRS intervals) were unremarkable.

Efficacy

The most frequently isolated causative pathogens in this pediatric cIAI population were *Escherichia coli* (74.3%), *Bacteroides fragilis* (17.7%), *Pseudomonas aeruginosa* (16.6%) and *Streptococcus constellatus* (14.6%). The clinical cure rate among patients with monomicrobial infections was similar between the treatment groups [95/106 patients (89.6%) for MXF and 57/60 patients (95.0%) for COMP], while in those with polymicrobial infections clinical cure was achieved in 113/140 patients (80.7%) and 70/73 patients (95.9%) treated with MXF and COMP, respectively (modified intent-to-treat [mITT] population). The clinical and bacteriological success rates at EOT were slightly lower for MXF than for COMP (91.0% versus 97.7%, respectively).

Wirth S_MOXIPEDIA_Supplemental Digital Content 1.

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Reference

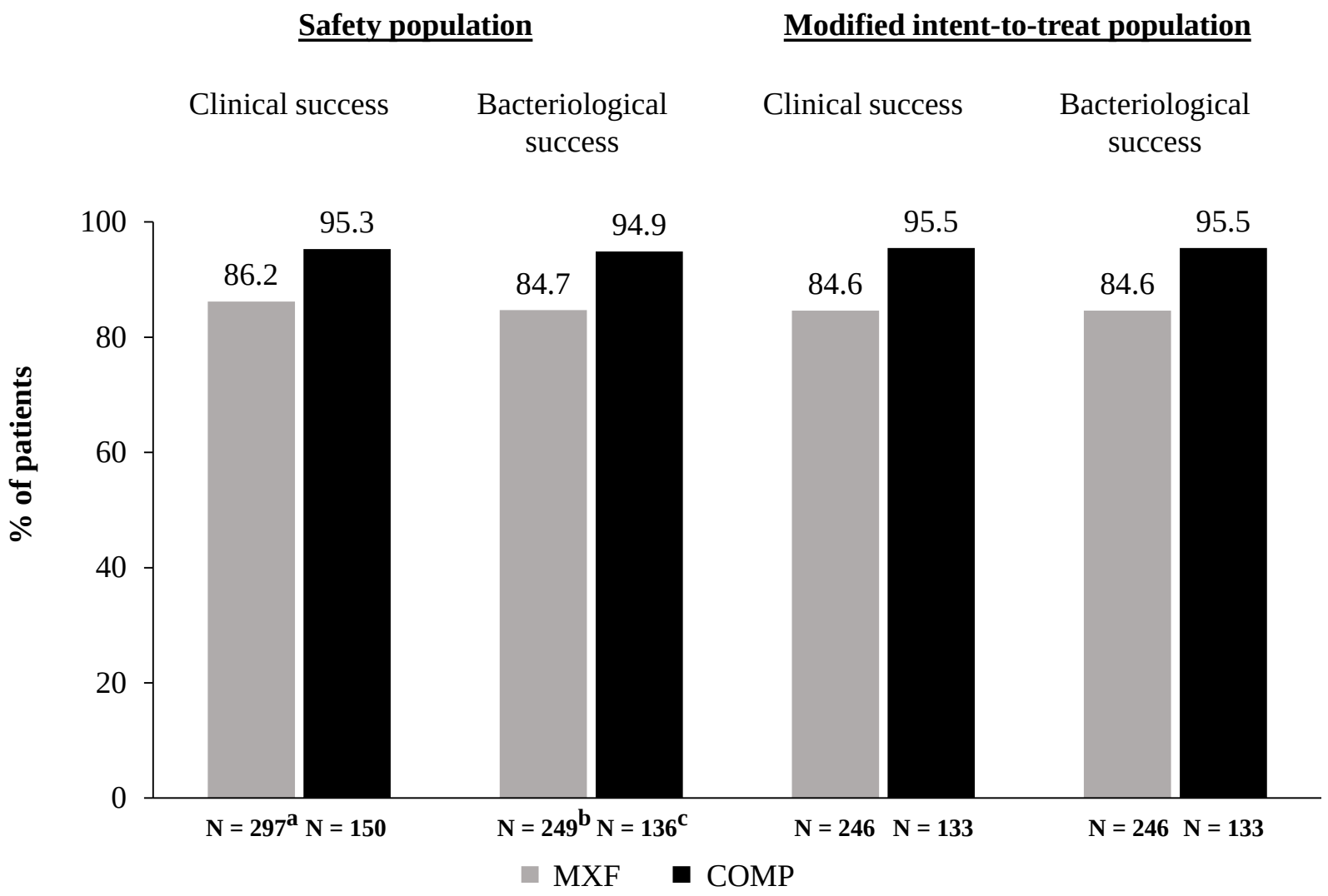
1. Avelox® (moxifloxacin hydrochloride). Summary of Product Characteristics 2015; Bayer AG, Berlin, Germany.

Supplemental Table 1. Changes in QT/QTc Values from Pre-Dose at Days 1 and 3 (Safety Population)

Parameter	Study Medication	Difference versus Pre-Dose Value (ms)[a]	
		Day 1	Day 3
QT (uncorrected)	MXF	2.58 (15.21)	6.09 (16.19)
		[-58.00; 67.00]	[-49.00; 57.00]
	COMP	1.12 (11.57)	3.16 (11.96)
		[-28.00; 36.00]	[-23.00; 40.00]
QTcB	MXF	9.73 (14.30)	9.25 (16.81)
		[-33.00; 56.00]	[-38.00; 63.00]
	COMP	2.29 (14.25)	1.00 (12.53)
		[-33.00; 30.00]	[-37.00; 45.00]
QTcF	MXF	7.07 (11.32)	8.12 (13.58)
		[-28.00; 61.00]	[-31.00; 58.00]
	COMP	1.19 (11.31)	1.77 (9.33)
		[-28.00; 28.00]	[-23.00; 25.00]

[a]Values are expressed as mean (standard deviation) [minimum; maximum].

Wirth S_MOXIPEDIA_Supplemental Digital Content 1 Figure 1.
Supplementary Figure 1. Clinical and bacteriological success rates at test of cure.



[a]4 patients were excluded due to missing assessment at test of cure; [b]52 patients were excluded due to missing assessment at test of cure; [c]14 patients were excluded due to missing assessment at test of cure; COMP: comparators; MXF: moxifloxacin