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Original article

# Efficacy and safety of metronidazole injection for the treatment of infectious peritonitis, abdominal abscess and pelvic inflammatory diseases in Japan

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ABSTRACT

Although metronidazole (MNZ) has been used worldwide for more than 4 decades as a standard therapy for trichomoniasis, anaerobic and amebic infections, resistance to MNZ is still low. MNZ is available as oral, intravenous, and vaginal formulations, but the intravenous formulation of MNZ has not been approved in Japan. We conducted a phase 3 study to evaluate the efficacy and safety of intravenous MNZ combined with ceftriaxone (CTRX) in Japanese subjects with infectious peritonitis, abdominal abscess or pelvic inflammatory diseases (PIDs) to obtain regulatory approval. A combination of MNZ/CTRX at doses of 500 mg 3 or 4 times a day/1 or 2 g twice a day was administered intravenously to a total of 38 hospitalized subjects. MNZ/CTRX was well tolerated and exhibited excellent clinical and bacteriological efficacy with clinical efficacy rates of 100% (20/20) in infectious peritonitis or abdominal abscess subjects and 90.0% (9/10) in PID subjects, and the eradication rates in infectious peritonitis or abdominal abscess subjects and PID subjects were 100% (16/16) and 100% (4/4), respectively, at the test of cure. MNZ/CTRX was effective in 1 subject in whom a metallo-β-lactamase-producing *Bacteroides fragilis* strain (MIC of MNZ, 2 μg/ml) was identified. The most common treatment-related adverse event was diarrhea (23.7%), followed by nausea (5.3%). No new safety signals were identified. MNZ/CTRX demonstrated excellent efficacy and was well tolerated in Japanese infectious peritonitis, abdominal abscess and PID subjects. This treatment regimen can be useful for anaerobic infections.

Clinical registration number: NCT01473836.



## 1. Introduction

Metronidazole (MNZ) is a nitroimidazole antimicrobial agent with a potent anti-anaerobic, amebicidal, and antiprotozoal activity. Intravenous (IV) MNZ (MNZ-IV) has been used worldwide for more than 30 years as the standard therapy for the treatment of trichomoniasis, anaerobic and amebic infections [1–5]. Harrison's Principles of Internal Medicine and the Sanford Guide to Antimicrobial Therapy recommend the use of MNZ-IV for the treatment of infections involving commonly encountered anaerobic gram-negative rods [6] and anaerobic infections [7] respectively. The guideline of the Infectious Diseases Society of America (IDSA) for the Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children, the 2010 Sexually transmitted disease treatment guidelines of the Centers for Disease Control and Prevention (CDC), and the IDSA practice guidelines for the diagnosis and management of skin and soft-tissue infections [8–10] also recommended the use of MNZ for various infections.

MNZ-IV has not been developed in Japan. Antimicrobial agents presently used for the treatment of anaerobic infections in Japan are penicillins, β-lactam/β-lactamase inhibitor combination drugs, and some cephalosporins, carbapenams, and clindamycin. However, the emergence of resistance to penicillins, cephalosporins and clindamycin among clinically isolated pathogenic anaerobes has raised great concern [11–13]. In recent years, a high prevalence of resistance to clindamycin has been observed among the *Bacteroides*

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*fragilis* group and non-*fragilis Bacteroides* spp., which are the most common anaerobes isolated from intra-abdominal infections, as well as *Prevotella* spp., a causative pathogen of aspiration pneumonia [14,15]. Decreased susceptibility and the emergence of resistance to carbapenems among the *B. fragilis* group and non-*fragilis Bacteroides* spp. have also been reported [16].

Although MNZ has been used as a therapeutic drug for infections for longer than 45 years, the rate of resistance to MNZ among anaerobes is still generally low. Therefore, MNZ is still successfully used for the treatment of anaerobic infections caused by *Bacteroides* spp., *Fusobacterium* spp., and *Clostridium* spp [17].

Infectious anaerobic diseases often result in a serious condition and treatment with appropriate antimicrobials is crucial, because patients are highly compromised when the primary disease is severe. It is desirable that MNZ-IV would also be available in Japan for the treatment of severe infectious diseases in hospitalized patients who cannot take oral medication.

We planned this phase 3 study to evaluate the efficacy and safety of MNZ-IV administered at a dose of 500 mg 3 times a day (TID), or 4 times a day (QID) in severe cases, to Japanese adult patients with infectious peritonitis, abdominal abscess or PID in combination with IV ceftriaxone (CTRX).

## 2. Subjects and methods

This study was conducted in accordance with the International Conference on Harmonisation of Good Clinical Practice Guidelines, the principle of the Declaration of Helsinki, and all applicable laws and regulations at 15 medical centers nationwide in Japan between November 2011 and October 2012. The protocol was reviewed and approved by the Institutional Review Boards of all participating study sites. All subjects provided written informed consent before enrollment.

### 2.1. Study design

This multicenter, non-randomized, unblinded, non-comparative phase 3 study was designed to investigate the safety and efficacy profile of MNZ-IV in Japanese subjects with infectious peritonitis, abdominal abscess or PID in combination with CTRX. A Data Review Committee (DRC) was organized as an independent organization to perform objective and unified efficacy evaluation based on the clinical condition and diagnostic imaging findings. All subjects received 500 mg MNZ administered by intravenous infusion over 20 min TID (or QID in subjects with refractory or severe infection) for 3–14 days in general. At the investigator's discretion, the duration of treatment could be prolonged for up to 21 days depending on the subject's condition. All subjects received CTRX as a combination drug for the same period as MNZ-IV. CTRX, a 3rd-generation cephalosporin with broad-spectrum activity against aerobic bacteria is widely used in Japan and its efficacy and safety profiles are well established. Overseas textbooks and guidelines recommend MNZ combined with agents that have antibiotic activity against aerobic pathogens, and for infectious peritonitis or abdominal abscess subjects, the target of this study, MNZ combined with 3rd generation cephalosporin antibacterial drugs, because infections caused by anaerobic pathogens, the target diseases of this study, are often mixed infections including aerobic pathogens, and MNZ is not effective against them. Since CTRX can be given to subjects once a day, it is considered useful in terms of decreasing the burden on subjects. We therefore decided to use CTRX as the combined drug. MNZ-IV was studied based on the following: (1) The safety and efficacy of MNZ-IV has been demonstrated; and (2) the development of MNZ-IV was requested by the committee on "Unapproved Drugs and Indications with Unmet Medical Needs" under the Ministry of Health, Labour, and Welfare of Japan, because it is an unapproved drug with high medical needs. As a result of a consultation with the Pharmaceutical and Medical Devices Agency of Japan, the target number of subjects who meet the eligibility criteria and receive the test drugs was set at 30, provided that we could enroll at least 7 subjects in whom bacterial transition could be evaluated with more than 80% probability, since the detection rate of causative pathogens was assumed to be approximately 30%.

### 2.2. Eligibility criteria

Male and female subjects (for pelvic infections, subjects had to be female) aged 16 years or older who had been diagnosed as having infectious peritonitis, abdominal abscess or PID, required hospitalization, and initial IV antibacterial therapy were eligible.

The diagnostic criteria for infectious peritonitis or abdominal abscess included: confirmed infectious peritonitis or abdominal abscess based on the presence of symptoms and signs of an inflammatory response (fever, increased white blood cell [WBC] count, CRP elevation), imaging findings, and the abdominal signs and symptoms (lower abdominal pain, lower abdominal tenderness, upper abdominal pain, upper abdominal tenderness, abdominal rebound, abdominal guarding, nausea, vomiting, decreased appetite, abdominal distension, diarrhea, constipation, drainage, or abscess), and meeting either of the following criteria: 1) planned (or performed within the previous 24 h) drainage of infective sites; and 2) for postoperative infectious peritonitis or abdominal abscess, confirmed gastrointestinal tract secretion or purulent discharge from an indwelling drain.

The diagnostic criteria for PID and related diseases (endometritis, myometritis, adnexitis, salpingitis, oophoritis, parametritis, pelvic peritonitis, pelvic abscess, Douglas' abscess, perihepatitis, and perihepatic abscess) included: (1) one of the following symptoms should be observed: 1) lower abdominal pain or lower abdominal tenderness; 2) uterus/uterine adnexa pain or uterus/uterine adnexa tenderness; and 3) hypochondrial pain or hypochondrial tenderness; (2) negative for *Chlamydia trachomatis*; (3) once the above criteria are satisfied, one of the following 6 conditions should be observed: 1) fever $\geq$37 °C (axillary); 2) WBC count > upper limit of normal range; 3) CRP > upper limit of normal range; 4) purulent discharge or pus observed by culdocentesis or laparoscopy; 5) pelvic abscess confirmed by ultrasonography; and 6) positive for *Neisseria gonorrhoeae*.

Exclusion criteria included the following: subjects who had undergone surgery for perforation of the digestive tract within 12 h, or who had undergone surgery for perforation of gastroduodenal ulcers within 24 h; subjects with suspected or confirmed simple appendicitis, necrotizing pancreatitis, infectious mononucleosis, non-infectious peritonitis, or non-infectious endometriosis; subjects who did not undergo appropriate drainage; subjects expected to be cured only by the surgical procedures (e.g., drainage) without antimicrobial treatment; subjects who had open abdominal cavity drainage; subjects with hypersensitivity to, intolerance of or another contraindication to MNZ or CTRX or other cephem antibiotics; subjects with alcohol abuse; subjects with severe renal dysfunction; subjects with hepatic dysfunction; subjects with severe underlying disease or other complications; subjects who required additional systemic antibiotics; subjects who had received treatment with systemic antibiotics within 7 days before the study; subjects who had already received MNZ for the disease; subjects whose causative pathogens were insusceptible to MNZ; and pregnant or lactating women.

The following concomitant medications were prohibited up to the test of cure (TOC) assessment: systemic antibiotics (oral, injection); human immunoglobulin; colony-stimulating factor;