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Original article

Efficacy and safety of intravenous azithromycin followed by oral azithromycin for the treatment of acute pelvic inflammatory disease and perihepatitis in Japanese women

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ABSTRACT

Pelvic inflammatory disease (PID) is mainly caused by ascending infection from the vaginal flora including the sexually transmitted organisms, *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and lower genital tract endogenous anaerobes, leading to serious consequences including infertility and ectopic pregnancy. To evaluate the efficacy and safety of azithromycin in the treatment of PID that requires initial intravenous therapy, we conducted a multicenter, unblinded, non-comparative phase 3 trial. Intravenous azithromycin (500 mg, once daily) for 1 or 2 days followed by oral azithromycin (250 mg once daily) to complete a total of 7 days treatment was administered to 60 Japanese women with acute PID. The clinical and bacteriological responses were assessed at the end of treatment, and on Days 15 and 29. The most commonly detected baseline causative pathogens were *C. trachomatis* (12 strains), *Prevotella bivia* (10 strains), *Streptococcus agalactiae* (7 strains), *N. gonorrhoeae* and *Peptostreptococcus anaerobius* (6 strains each). The clinical success rate on Day 15 was 94.1% (48/51 subjects including perihepatitis). The clinical efficacy and bacterial eradication rates against *C. trachomatis* and *N. gonorrhoeae* (including 2 quinolone-resistant strains) were both 100%. Common treatment-related adverse events were diarrhoea, injection site pain, and nausea. All adverse events were mild or moderate in severity. Azithromycin intravenous-to-oral switch therapy demonstrated excellent clinical and bacteriological effects for PID caused by various etiologic agents including quinolone-resistant strains and strains with low susceptibility to azithromycin at *in vitro* testing. The therapy was well tolerated in the treatment of PID in Japanese women.

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1. Introduction

Pelvic inflammatory disease (PID) is a common infection and consists of inflammation of the upper female genital tract caused by ascending infection from the endocervix in women in their reproductive years, and it frequently leads to serious consequences including infertility, ectopic pregnancy, and chronic pelvic pain [1–4]. In Japan, there is little epidemiologic data on PID available at the moment [5].

Based on the polymicrobial etiology of PID, antimicrobial therapy should provide broad spectrum coverage of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, mycoplama, and anaerobic and aerobic bacteria. The initial antimicrobial therapy for PID is usually empirical, and is complicated by the increasing global prevalence of antibiotic resistance, in particular resistance to β-lactams, quinolones and/or macrolides, among the common causative pathogens, especially gonorrhoea in PID [1,2,4]. Owing to the emergence of quinolone-resistant *N. gonorrhoeae* (QRNG), quinolones are no longer recommended for the treatment of PID associated with gonorrhoea [1,2,4].

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Azithromycin (AZM) is a macrolide antibiotic that has a broad spectrum of antimicrobial activity covering various causative pathogens in PID including *N. gonorrhoeae*, *C. trachomatis*, mycoplama, and endogenous anaerobic and facultative bacteria. Randomized controlled studies demonstrated that intravenous (IV) AZM 500 mg once daily for 1 or 2 days followed by oral AZM 250 mg once daily to complete a total of 7 days treatment produced high clinical success rates, both as monotherapy and combined with metronidazole [6]. AZM regimens are included in the Centers for Disease Control and Prevention (CDC) 2010 sexually transmitted disease (STD) treatment guidelines as alternative regimens for PID [4].

Since an AZM IV formulation was approved in the United States of America in 1997, it has been approved in more than 50 countries except for Japan. We conducted a phase 3 trial of IV AZM followed by oral AZM administration in Japanese adults to evaluate the clinical efficacy and safety for the treatment of PID requiring initial IV therapy in order to obtain regulatory approval.

2. Materials and methods

This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines, the principle of the Declaration of Helsinki and all applicable laws and regulations. The protocol was reviewed and approved by the Institutional Review Boards at participating study sites. All subjects or legally authorized representatives provided a written informed consent form before enrollment.

2.1. Study design

This multicenter, non-randomized, unblinded, non-comparative phase 3 study was designed to investigate the clinical efficacy and safety of AZM IV-to-oral switch therapy in Japanese female subjects with PID. An independent Data Review Committee (DRC) was organized to assure an objective and unified efficacy evaluation based on the clinical conditions and findings from the diagnostic imaging. To all subjects, 500 mg IV AZM was administrated once daily at an infusate concentration of 1 mg/ml over 2 h for 1 or 2 days, followed by 250 mg oral AZM once daily to complete a total of 7 days. Switching from IV-to-oral therapy was determined by the investigators according to the subject's condition.

2.2. Eligibility criteria

Females aged 16 years or older who were given a diagnosis of PID and required initial IV antibacterial therapy were eligible.

PID is defined as follows [4,6]:

(A) Either one or both of the following symptoms should be observed: (a) abdominal pain lower and/or lower abdominal tenderness (tenderness of the uterus or its adnexa); and (b) hypochondrial pain and/or hypochondrial tenderness.
(B) Once the above criterion is satisfied, then 2 of the 5 following conditions should be observed: (a) fever $\geq$ 37 °C (axillary); (b) increased white blood cell (WBC) count (>upper limit of the normal range); (c) raised CRP (>upper limit of the normal range); (d) purulent leucorrhea and purulent discharge that can be confirmed by Douglas puncture and laparoscopy; and (e) pelvic abscess that can be confirmed by ultrasonography.

Peritonitis (including perihepatitis) and Douglas abscess were included in PID as relevant diseases in this study. However, patients with these diseases were not enrolled if they did not meet the criteria for PID.

Exclusion criteria of the study included the following conditions or situations: hypersensitivity to AZM, or any macrolide or ketolide antibiotics, hepatic dysfunction, severe renal dysfunction, severe heart diseases, severe underlying disease or complication, causative pathogens resistant to AZM, pregnancy or lactation in women, immunodeficiency disease, or endometriosis without any infection.

The following concomitant medications during the primary evaluation period (up to Day 15) were prohibited: human immunoglobulin, colony-stimulating factors, corticosteroids, taking an analgesic antipyretic continuously, and other investigated drugs or medical devices.

2.3. Clinical and radiographic assessments

The primary endpoint was clinical response assessed by the DRC at the end of treatment (EOT), and on Days 15 and 29. The clinical response was evaluated as "effective" if both of the following criteria were met: (A) all signs and symptoms associated with PID resolved or improved; and (B) abnormal findings in the parameters in paragraph 2 of the diagnostic criteria, which had been found on Day 1, resolved or improved. The clinical response was evaluated as "ineffective" if any of the following criteria was met: (A) the criteria of "effective" were not satisfied; (B) the treatment failed and other systemic antibiotics were administered; (C) persistent infection or recurrence of infection in the abdominal cavity was confirmed by abdominal ultrasonography, percutaneous drainage, or second surgery; (D) surgical site infection was confirmed after surgery; and (E) death linked to infection of the same area was confirmed. The clinical response was evaluated as "indeterminate" if the above-mentioned criteria were not assessed for various reasons.

We also investigated the reasons for switching from IV-to-oral therapy.

2.4. Bacteriological assessment

The secondary efficacy endpoint was bacteriological response at EOT, and on Days 15 and 29 assessed by the DRC. All subjects provided clinical specimens, which were sent to a central laboratory for culture, and isolated pathogens were tested for susceptibility according to the Clinical and Laboratory Standards Institute procedures at the baseline visit, EOT, on Days 15 and 29. These specimens were also submitted for detection of *C. trachomatis*, *N. gonorrhoeae*, or *Mycoplasma* spp by antigen tests using polymerase chain reaction (PCR), strand displacement amplification, and/or enzyme immunoassays. Antigen tests were performed at baseline and on Days 15 and 29.

Bacteriological response was assessed as "eradication" if the original pathogen was not identified in the specimens, "presumed eradication" if the subject was not producing evaluable specimens from a focus of infection, "persistence" if the original pathogen remained in the specimens, "replacement bacterium" if the original pathogens were eradicated by treatment, and other new pathogens appeared in the same specimen, with symptoms and/or findings of an infection, and "indeterminate" if the above-mentioned criteria were not assessed for various reasons.

2.5. Safety assessment

Safety data were obtained from findings of clinical signs/symptoms, physical examinations, vital signs, and laboratory data up to 29 days. The causality and severity of the adverse events were evaluated by the investigators based on MedDRA terminology.