Clinical Trial Protocol

Title: Two-dimension tailor-made therapy (2dTMT): a new salvage therapy after multiple eradication failures for *Helicobacter pylori* infection

Researchers and Affiliations: *Responsibility

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Aim: To clarify the effect of 14-day 2-dimension tailor-made therapy (2dTMT) as the salvage therapy after twice or more eradication failures.

Subjects: Patients aged 20yo or older who visited to the Outpatient Departments of Gastroenterology or General Medicine, JCHO Shiga Hospital from June 2004 until April 2016 to receive salvage therapy to eradicate *H. pylori* after twice failures with PPI-based first and second eradication therapies. Those who have received more than twice therapies are also included if *H. pylori* is still positive after the last therapy.

Exclusion criteria: Those who have severe liver or renal diseases or other conditions which are thought to be inadequate. Those who discontinued previous eradication therapies because of adverse events are also excluded.

Informed Consent: Candidates are informed of the following tests and therapies for 2dTMT. Those who agreed are the subjects of the study and

undergo the following tests. Finally, the subjects who take medicine must sign the paper of participation.

Tests before the therapy: Blood sample is obtained from each patient after informed consent for measuring serum *H. pylori* antibody and single nucleotide polymorphism (SNP) in CYP2C19 gene. Patients undergo esophagogastroduodenoscopy to take two biopsy specimens from the greater curvature of the antrum and the middle corpus of the stomach for *H. pylori* culture and antibiotics susceptibility test (AST).

Eradication therapy: A proton pump inhibitor (PPI) and two antibiotics are prescribed for 14 days as in the followings. A PPI is selected from the available four PPIs: lansoprazole 30mg, omeprazole 20mg, esomeprazole 20mg, and rabeprazole 10mg. The dose of PPI per day is determined according to the CYP2C19 genotype: twice for poor metabolizer (PM) or four times for extensive metabolizer (EM) (dimension 1). Two antibiotics are selected from the results of AST: MIC smaller than the breakpoint of European Committee

on Antimicrobial Susceptibility Testing (EUCAST) is considered susceptible (dimension 2). The priority order to choose antibiotics is amoxicillin (AMPC), clarithromycin (CAM), metronidazole (MNZ), levofloxacin (LVFX) and minocycline (MINO) according to the history of the proposal of the Japanese Society for Helicobacter Research. For those who have enough information from the AST, a PPI and 2 susceptible antibiotics are prescribed for 14 days (2dTMT). For those who do not have enough information to select two susceptible antibiotics, AMPC and an antibiotic is selected empirically: the priority order is LVFX and then MINO. For those who use MINO, 0.5g bismuth subnitrate is added four times a day (2g per day) because classical quadruple therapy contains tetracycline and bismuth compound (MINO is one of the tetracycline-family antibiotics).

Evaluation of the therapy: Eradication success/failure is evaluated with urea breath test 2 months after the therapy or later. For those who are not confirmed eradication with urea breath test, either stool antigen test, pathology or serum antibody test were added to confirm eradication success/failure. Adverse events are questioned by the doctor at the first visit

after the therapy.

Withdrawal: Patient who wants to withdraw the study can decline the tests or therapy anytime he/she wants.

Ethics: The protocol was approved by the Ethics Committee of JCHO Shiga Hospital. This retrospective study was also approved by the Institutional Review Board of JCHO Shiga Hospital.

Study enrollment: This study is enrolled as UMIN000022154.