Shortening Antibiotic Duration in the Treatment of Acute Cholangitis. Rationale and Study Protocol for an Open Label Randomized Controlled Trial.

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| Acute cholangitis, Antimicrobial therapy, Short course therapy, RCT
Abstract

Background: Antimicrobial therapy with appropriate biliary drainage is considered the standard of care for acute cholangitis, but the optimal duration of antimicrobial therapy remains unknown. Seven to 10 days of antimicrobial therapy is common for the treatment of acute cholangitis, but a recent retrospective cohort study suggested a shorter duration might be effective. A shorter duration of antimicrobial therapy can be beneficial in decreasing the length of hospital stay, improving patients’ quality of life, decreasing adverse effects, and even contributing to a decrease in the occurrence of antimicrobial resistance.

Methods/design: We will conduct a multi-center, open-label, randomized, non-inferiority trial to compare short course therapy (SCT) with conventional long course therapy (LCT) in treating patients with acute cholangitis. SCT consists of 5-day intravenous antimicrobial therapy if the patients had clinical improvement, while at least 7 days of intravenous antibiotics will be provided to the LCT group. The primary outcome is clinical cure at 30 days after onset. Patients will be randomly assigned in an open label fashion. A total sample size of 150 was estimated to provide a power of 80% with a one-sided alpha level of 2.5% and a non-inferiority margin of 10%.

Discussion: This trial is expected to reveal whether SCT is non-inferior to conventional LCT or not, and may provide evidence that one can shorten the treatment duration for acute cholangitis for the benefit of patients.

Background

Acute cholangitis is a common disorder, which places a substantial burden on
patients and the acute care system [1-4]. Antimicrobial therapy with appropriate biliary drainage is considered the standard of care [4,5], but the optimal duration of antimicrobial therapy remains unknown. Seven to 10 days of antimicrobial therapy is common for the treatment of acute cholangitis [5] but a recent retrospective cohort study suggested a shorter duration might be equally effective [6]. A shorter duration of antimicrobial therapy can be beneficial in decreasing the length of hospital stay, improving patients’ quality of life, decreasing the adverse effects of antibiotics such as *Clostridioides difficile* infection, and even contributing to a decrease in the occurrence of antimicrobial resistance [7-10].

In this trial, we will compare antimicrobial therapy of a shorter duration with a conventional, longer duration, to investigate whether the short course therapy (SCT) is non-inferior to conventional long course therapy (LCT) in terms of clinical cure and other clinically important outcomes.

**Methods/design**

**Design**

We will conduct a multi-centre, open-label, randomized, non-inferiority trial to compare SCT with conventional LCT in treating patients with acute cholangitis. The final trial report will follow the Consolidated Standards of Reporting Trials (CONSORT) statement and its extension to non-inferiority trials [11]. This study was registered at the University Hospital Medical Information Network under registry number UMIN000028382. The study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Additional file 1).
Setting
The study will be conducted at four tertiary referral hospitals in Japan (Table 1).

Patients
Patients with acute cholangitis diagnosed by gastroenterologists based on findings such as fever, abdominal pain, liver function test abnormality, or imaging studies will be eligible for trial entry. If the infectious diseases doctors were allowed to participate in the care of the patients, and if the treating physicians and the patients agreed to participate in the trial, the patients will be registered as potential study participants. The study participants will be enrolled in this trial if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria
Patients are 20 years or older
They are diagnosed as acute cholangitis by treating gastroenterologists.
Biliary duct obstruction was removed via procedures such as endoscopic retrograde cholangiopancreatography (ERCP), or there is no evidence of biliary duct obstruction by tests such as imaging studies to begin with.

Exclusion criteria
Patients did not provide written informed consent.
Biliary duct obstruction was not removed.
Treating physicians or the investigators judged that inclusion in the study was inappropriate.
The presence of bacteraemia is not an exclusion criterion.

Ethics and informed consent
The clinical trial will be carried out according to the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Involving Human Subjects published by the Ministry of Health, Labour and Welfare of Japan and the Japanese Ministry of Education, Culture, Sports, Science and Technology. The study protocol was approved by the ethics committees of the participating hospitals. Written
informed consent will be obtained from all patients or their representatives.

**Randomization and allocation concealment**

Patients are randomly allocated to each treatment arm at a 1:1 ratio before or within 24 hours after initiating antimicrobial therapy. Randomization will be performed using a stochastic minimization procedure centrally at the study centre (Division of Infectious Diseases Therapeutics, Kobe University Graduate School of Medicine). We will use an electronic data capture system to conduct randomization and data collection.

**Trial interventions**

The antibiotics given to the study participants should be commercially available and approved for use in Japan. They will be used at the marketed accepted dosage as in each package insert. The initial antibiotics will be selected at the discretion of either the treating physician or the consultant infectious diseases doctor. Selected antibiotics can be changed to other antibiotics during the treatment based on culture/susceptibility tests results, or potential adverse reactions that are suspected or occurred in the patient. Dose adjustments based on patients’ renal function or others are performed as judged appropriate and necessary by the consultant infectious diseases doctors.

In the SCT group, intravenous antibiotics will be continued at least for five days, and can be discontinued if all of the following criteria were fulfilled: (1) maintenance of body temperature under 37.8°C for more than 48 hours; (2) systolic blood pressure above 90 mmHg; (3) heart rate below 100/minute; (4) respiratory rate below 24/minute; and oxygen saturation at room air above 90%. In the LCT
group, intravenous antibiotics will be given for the duration of usual care, at least for 7 days, at the discretion of both the treating gastroenterologists and the consultant infectious diseases doctors, provided that there are no biliary duct obstructions remaining, as in the inclusion/exclusion criteria. In the SCT group, positive blood culture results will not alter the duration of the treatment unless other complications which necessitate prolongation of the treatment, such as abscess or infective endocarditis, occur and either the treating physicians or the consultant infectious diseases doctors can drop the case from the intervention. They will still be included to the analysis on an intention to treat (ITT) basis, but will be excluded from the per-protocol analysis.

Assessment and follow-up
Clinical assessment is performed at baseline and daily throughout the study treatment, at the end of therapy (EOT) and at discharge from the hospital or 30 days after the onset (end of study, EOS).

Outcome measures
The primary outcome is clinical cure at 30 days after their onset (EOS). Clinical cure is defined as disappearance of all clinical symptoms which were present upon the diagnosis.

The secondary outcomes are clinical improvement after 30 days, mortality at day 30 after the diagnosis, or in-hospital mortality, occurrence of adverse effects, and recurrence or complications of acute cholangitis. Clinical improvement is defined as decrease but not disappearance of clinical symptoms which were present upon the diagnosis.

Sample size
The primary efficacy analysis will assess the non-inferiority of the clinical cure rate of SCT compared with LCT. The margin of non-inferiority is set at 10% on the statistically acceptable tolerance and clinical acceptable margin. This margin has been used as accepted in the field of infectious diseases [12,13]. Therefore, the non-inferiority of SCT is concluded if the upper limit of the one-sided 97.5% confidence interval (CI) for the difference in clinical response (standard-SCT) is less than 10%. To achieve the power of 80% with $\alpha$ level of 2.5%, assuming as stated in the previous retrospective study with the clinical cure rate of 95% with standard therapy with the same cure rate in SCT [6], with a non-inferiority margin of -10%, 75 patients are required in each group.

**Statistical analysis**

We will analyse data using both intention-to-treat and per-protocol analysis. The per-protocol analysis population will consist of all randomized patients who are not lost to follow-up and have no major protocol deviations. We will attest the non-inferiority of the primary outcome on the basis of the normal theory test for binomial proportions. We will conduct the primary analysis without adjustment of potential confounders.

Secondary outcomes will also be analysed under a non-inferiority assumption, as appropriate. Pre-defined subgroup analyses for the primary and secondary outcomes include; (1) presence or absence of septic shock at diagnosis, (2) presence or absence of bacteraemia, (3) initial antibiotics covering or not covering causative organisms, (4) Gram positive organisms causing cholangitis, and (5) qSOFA score. Clinical outcomes are confirmed by the investigators either by calling the patients using telephone or at an outpatient clinic visit, or by checking the clinical chart if
the patients were still hospitalized.

All P-values are one-sided, and P<0.025 is considered statistically significant. All statistical analyses will be performed using STATA version 15.0 (StataCorp, College Station, TX, USA), and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

**Trial oversight**

The trial will be managed by the Division of Infectious Diseases, Kobe University Hospital, Kobe, Japan. The data centre is located at the same place, and the data managers will centrally monitor the data during the study period. A steering committee was involved in protocol development and will oversee study progress (Table 2). We will not have a specific data and safety monitoring board but the steering committee will perform an interim analysis to ensure the safety and efficacy of the trial therapy and will monitor the integrity and validity of the data collected and the conduct of the clinical trial. The data management team will report to the steering committee monthly with the numbers of patients registered. The data management team will also report mortality and occurrence of serious adverse events immediately to the committee.

**Discussion**

The current trial will examine whether SCT for acute cholangitis with appropriate biliary duct drainage is not inferior to conventional LCT. A retrospective cohort study with propensity score analysis suggested that the efficacy of SCT as well as occurrence of complications are similar to LCT [6]. If non-inferiority was achieved, SCT has several advantages over LCT in terms of length of hospital stay, potential adverse effects from antimicrobial therapy, cost, and emergence of antimicrobial
resistance [7-10].

The current proposed trial has some inherent limitations. First, for practical reasons, we were not able to design the study to be double-blinded. Both patients and investigators will know which group the patients belong to. However, we consider the outcomes we set are quite obvious and would not be likely to be impaired significantly by the trial being an open label design, as demonstrated in a previous similar study [14]. Second, because this study is conducted solely in Japan, although the study is a multi-centre trial, the results of the study might not be applicable in different settings outside the country. The results of the proposed study are not applicable to those patients with acute cholangitis when bile duct obstruction remains.

To the best of our knowledge, this will be the first ever trial to answer the clinical question of whether shortening of antimicrobial therapy for the treatment of acute cholangitis can be possible without impairing treatment safety and efficacy. We wish the trial aids in establishing a novel therapy to optimize the duration of antibiotic therapy for this rather common disease.

Trial status

The protocol number is ver 1.3 dated September 21, 2018. Patient recruitment began on December 19, 2018. We recruited the first patient on June 27, 2019. The trial is Scheduled to end on December 31, 2021.

Abbreviations

SCT: short course therapy; LCT: long course therapy; ERCP: endoscopic retrograde cholangiopancreatography; EOT: end of treatment; EOS: end of study; qSOFA: quick
Sequential Organ Failure Assessment; RCT: randomized controlled trial.

Declarations

Ethics approval and consent to participate
The protocol and consent form were approved by the ethics committee at Kobe University Graduate School of Medicine and each of the participating institutions. All substantial protocol modifications will be notified as protocol amendments to them. All patients or their legally authorized representatives will provide written informed consent before randomization by the investigators.

Consent for publication
Not applicable.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Funding is provided by the Division of Infectious Diseases, Kobe University Hospital, i.e., our study is self-sponsored without outside funding sources.

Authors’ contributions
AD conceived of and designed this study and drafted the manuscript. KI conceived
of and designed this study and was responsible for drafting, editing and submission of the manuscript. TK critically contributed to the concept and design of the study. YO, HM, KE, MN, SN, AM, HS, and YK contributed to the design of the study and reviewed the manuscript. KY had a major influence on the design of this study, such as statistical and methodological expertise, and helped in reviewing and revising the manuscript for intellectual content. All authors read and approved the final manuscript.

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Supplementary File Legend

Additional file

Additional file1: SPIRIT checklist.

Tables

Table 1 Participating institutions and investigators

| Institution                                      | Investigators          |
|-------------------------------------------------|------------------------|
| Kobe University Hospital                        | Kentaro Iwata, MD, PhD |
| Kobe City Medical Center General Hospital       | Asako Doi, MD          |
| Osaka General Medical Center                    | Yuichiro Oba, MD       |
| Hyogo Prefectural Amagasaki General Medical Center | Hiroo Matsuo, MD      |

Table 2 Study oversight
| Role in study          | Name               | Institution                                                                 |
|------------------------|--------------------|----------------------------------------------------------------------------|
| Principal investigator | Kentaro Iwata      | Division of Infectious Diseases, Kobe University Hospital                  |
| Steering Committee     | Asako Doi          | Department of Infectious Diseases, Kobe City Medical Center General Hospital |
| Steering Committee     | Yuichiro Oba       | Department of General Medicine, Osaka General Medical Center               |
| Steering Committee     | Hiroo Matsuo       | Department of Infectious Diseases, Hyogo Prefectural Amagasaki General Medical Center |
| Data management        | Kei Ebisawa        | Division of Infectious Diseases, Kobe University Hospital                  |
| Data management        | Sho Nishimura      | Division of Infectious Diseases, Kobe University Hospital                  |
| Data management        | Manabu Nagata      | Division of Infectious Diseases, Kobe University Hospital                  |
| Event Adjudication Committee | Atsuhiro Masuda | Department of Gastroenterology, Kobe University Graduate School of Medicine |
| Event Adjudication Committee | Hideyuki Shiomi | Department of Gastroenterology, Kobe University Graduate School of Medicine |
| Event Adjudication Committee | Yuzo Kodama | Department of Gastroenterology, Kobe University Graduate School of Medicine |
| Study Statistician     | Kenichi Yoshimura  | Innovative Clinical Research Center (iCREK), Kanazawa University Hospital  |
| Study secretariat      | -                  | Division of Infectious Diseases, Kobe University Hospital                  |
| Project management     | -                  | Division of Infectious Diseases, Kobe University Hospital                  |

**Figures**
Study design. SCT short course therapy, LCT long course therapy, EOT end of treatment, EOS end of study.

**Figure 1**

![Flowchart](image)

**Figure 2**

Schedule of assessments. EOT end of treatment, EOS end of study, qSOFA quick Sequential Organ Failure Assessment.
Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

SPIRITchecklistAC20181214.doc