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

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Study protocol

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Abstract

Background: Antimicrobial therapy with appropriate biliary drainage is considered the standard of care of 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 recent retrospective cohort study suggested shorter duration might be effective enough. 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 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 LCT group. The primary outcome is clinical cure at 30 days after their onset. Patients will be randomly assigned with 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 able to shorten the treatment duration for acute cholangitis for the benefit of the 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 recent retrospective cohort study suggested shorter duration might be equally effective [6]. Shorter duration of antimicrobial therapy can be beneficial in decreasing the length of hospital stay, improving patients' quality of life, decreasing adverse effects of antibiotics such as *Clostridioides difficile* infection, and even contributing to decrease in the occurrence of antimicrobial resistance [7–10].

In this trial, we will compare antimicrobial therapy of shorter duration with 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 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 test abnormality, or imaging studies will be eligible for the 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 accept to participate in the trial, the patients will be registered as the 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. Patients will be included if they (1) are 20 years or older; (2) are diagnosed as acute cholangitis by treating gastroenterologists; (3) 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. Presence of bacteraemia is not an exclusion criterion.

Patients will be excluded if (1) they did not provide written informed consent; (2) biliary duct obstruction was not removed, or (3) treating physicians or the investigators judged that inclusion of to the study inappropriate.

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 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 at the study centre. We will use electronic data capture system to conduct randomization and data collection.

Trial interventions

Antibiotics given to the study participants should be commercially available and approved to use in Japan. They will be used as marketed accepted dosage as in each package insert. Initial antibiotics will be selected as discretion of either treating physician or 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 suspected/occurred to 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 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) there was maintenance of body temperature under 37.8^{o}C for more than 48 hours; (2) systolic blood pressure became above 90 mmHg; (3) heart rate is below 100/minute; (4) respiratory rate is below 24/minute; and oxygen saturation at room air is above 90%. In LCT group, intravenous antibiotics will be given for the duration of usual care, at least for 7 days, as discretion of both treating gastroenterologists and consultant infectious diseases doctors, provided that there are no biliary duct obstructions remaining, as in inclusion/exclusion criteria. In 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, and either treating physicians or consultant infectious diseases doctors can drop the case from the intervention. They will still be included to the analysis as 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 occurrence of 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 α 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 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.

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 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 specific data and safety monitoring board but will perform an interim analysis by the steering committee to make sure 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 the numbers of registration. 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].

To the best of our knowledge, this will be the first ever trial to answer the clinical question whether shortening of antimicrobial therapy for the treatment of acute cholangitis can be possible without impairing treatment safety and efficacy. We wish the trial aid 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 recruit 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 available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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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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Additional file

Additional file 1: SPIRIT checklist.

References

1. Lee, C.-C., Chang, I.-J., Lai, Y.-C., Chen, S. Y., and Chen, S. C. Epidemiology and prognostic determinants of patients with bacteraemic cholecystitis or cholangitis. Am J Gastroenterol. 2007; 102: 563–569
2. Ortega, M., Marco, F., Soriano, A., Almela, M., Martinez, J. A., López, J. et al. Epidemiology and prognostic determinants of bacteraemic biliary tract infection. J Antimicrob Chemother. 2012; 676:

1508–1513
3. Sung, Y. K., Lee, J. K., Lee, K. H., Lee, K. T., and Kang, C. I. The clinical epidemiology and outcomes of bacteraemic biliary tract infections caused by antimicrobial-resistant pathogens. Am J Gastroenterol. 2012; 107: 473–483
4. Melzer, M., Toner, R., Lacey, S., Bettany, E., and Rait, G. Biliary tract infection and bacteraemia: presentation, structural abnormalities, causative organisms and clinical outcomes. Postgrad Med J. 2007; 83: 773–776
5. Dooley, J. S., Hamilton-Miller, J. M., Brumfitt, W., and Sherlock, S. Antibiotics in the treatment of biliary infection. Gut. 1984; 25: 988–998
6. Doi A, Morimoto T, Iwata K. Shorter duration of antibiotic treatment for acute bacteraemic cholangitis with successful biliary drainage: a retrospective cohort study. Clinical Microbiology and Infection. 2018;24:1184–9.
7. Hayashi, Y. and Paterson, D. L. Strategies for reduction in duration of antibiotic use in hospitalized patients. Clin Infect Dis. 2011; 52: 1232–1240
8. Rice, L. B. The Maxwell Finland Lecture: for the duration-rational antibiotic administration in an era of antimicrobial resistance and clostridium difficile. Clin Infect Dis. 2008; 46: 491–496
9. Johnson, M. T., Reichley, R., Hoppe-Bauer, J., Dunne, W. M., Micek, S., and Kollef, M. Impact of previous antibiotic therapy on outcome of Gram-negative severe sepsis. Crit Care Med. 2011; 39: 1859–1865
10. Stevens, V., Dumyati, G., Fine, L. S., and van Wijngaarden, E. Cumulative antibiotic exposures over time and the risk of Clostridium difficile infection. Clin Infect Dis. 2011; 53: 42–48
11. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trial: extension of the CONSORT 2010 statement. JAMA. 2012;308:2594–604.
12. Chow S-C, Shao J, Wang H, Lokhnygina Y. Sample Size Calculations in Clinical Research. 3rd ed. Boca Raton: Chapman and Hall/CRC; 2017.
13. Spellberg B, Talbot GH, Boucher HW, Bradley JS, Gilbert D, Scheld WM, et al. Antimicrobial agents for complicated skin and skin-structure infections: justification of noninferiority margins in the absence of placebo-controlled trials. Clin Infect Dis. 2009 Aug;49(3):383–91.

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

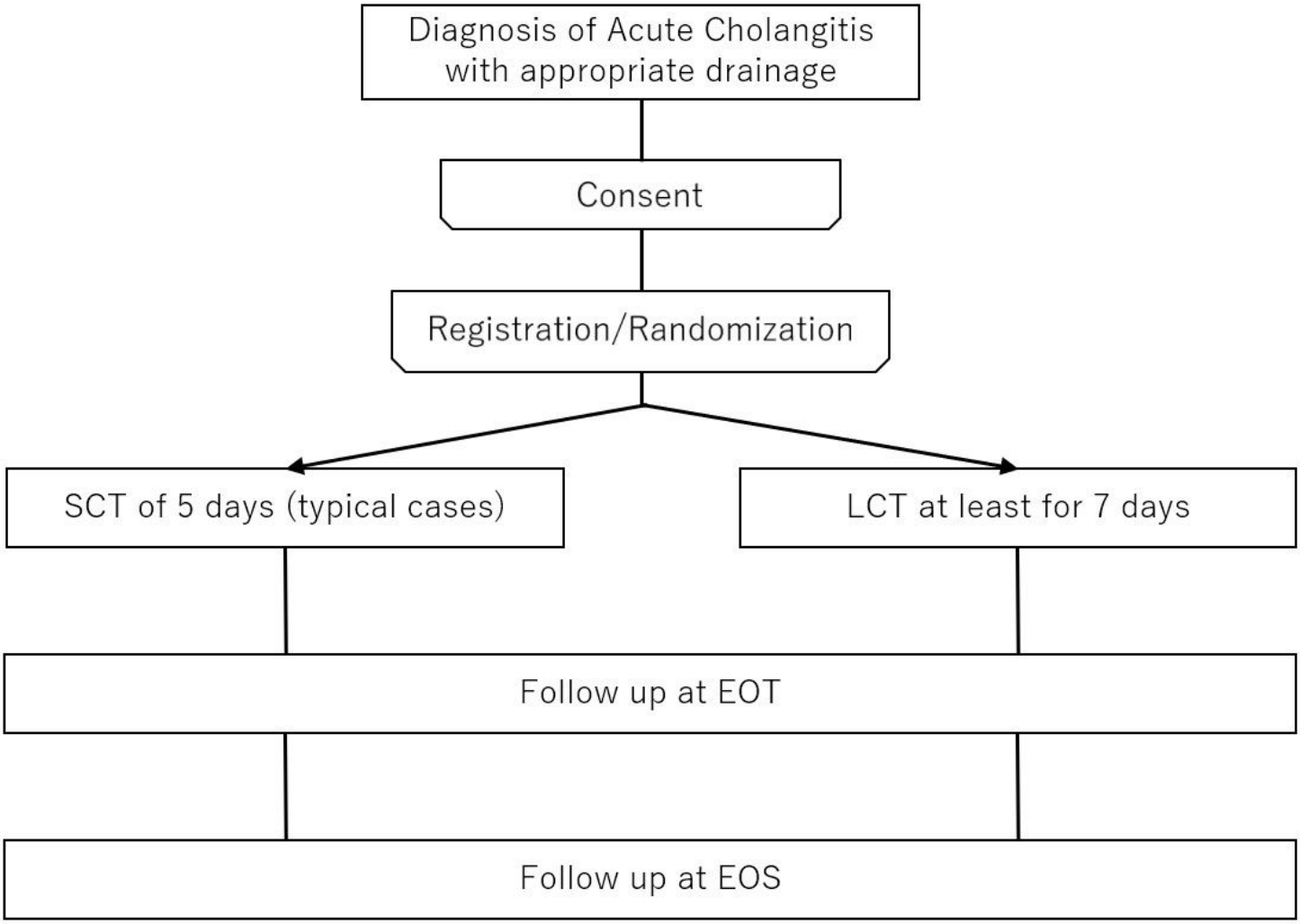

Figure 1

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

	Diagnosis	Screening	Treatment	EOT	EOS
Day	1	1	1-	-	30
Informed consent	X				
Check inclusion/exclusion criteria		X			
Randomization		X			
Blood cultures		X			
Biliary cultures (if possible)		X			
Laboratory data		X	X		
qSOFA score		X	X		
Check presence/absence of septic shock		X			
Clinical cure/improvement				X	X
Change of antibiotics (if any)			X		
Adverse effects			X	X	X
Recurrence					X
Complications			X	X	X
Mortality			X	X	X

Figure 2

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

Supplementary Files

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