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RESEARCH ARTICLE

Biliary Absorption of Dalbavancine: A Prospective Monocentric Protocol in Liver Transplant Recipients at Grenoble University Hospital (Dalbatrans)

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Abstract

Introduction: Liver transplantation (LT) is the last-resort procedure indicated for end-stage liver diseases, cirrhosis, or carcinoma. Biliary tract complications are the one of the most frequent complications after LT. Biliary stenosis combined with immunosuppressive therapy, which is required to prevent graft rejection, increases the risk of biliary tract infection in LT patients.

During follow-up, in the case of biliary tract infection such as biloma or liver abscess, LT patients benefit from regular endoscopic or radiological biliary recanalization, which occurs every 2 months on average along with biliary sampling.

Patients undergoing LT have often received several lines of therapy, notably antibiotics, which alters the microbial ecology with an overrepresentation of *Enterococcus faecium.* With this microbiology, a treatment of interest is dalbavancin, which enables prolonged outpatient treatment. However, no pharmacokinetic data are currently available on the biliary distribution of this antibiotic. Here, we report the protocol of DALBATRANS, a prospective observational descriptive monocentric study.

Methods: After the diagnosis of severe biliary complication and study inclusion, the patients undergo biliary drainage with antibiotic dosage in bile and blood every 2 months throughout the 6 months of follow-up. The primary endpoint is dalbavancin concentration after 2 months of treatment.

Highlights

- We report the protocol of a pharmacokinetic prospective study.
- This is the first study in humans to explore the biliary diffusion of dalbavancin.
- We investigate dalbavancin to treat biliary infections in liver transplant patients.

Keywords

Dalbavancin, Transplant patient, Biliary diffusion, Biliary tract complication, Liver abscess

Introduction

Liver transplantation (LT) represents the last-resort procedure indicated for patients with end-stage liver disease, fulminant hepatitis, or liver cancer. The French biomedicine agency (*Agence de la Biomédecine*) reported 1,439 liver transplants in 2024 alone [1], while the number of patients with a functional graft on December 31, 2017, was 13,988 [1]. One of the most frequent post-transplant complications concerns the biliary tract with an incidence of 5-32% [2]. The management of biliary complications in the case of biloma or liver abscess is mixed, combining endoscopic

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or radiologic treatment with biliary protheses and antibiotics over several months [3]. Biliary tract dysfunction can lead to infection, with some studies reporting a frequence of more than 10% [4].

Patients typically undergo LT after several years of liver disease progression. In this context, a combination of factors can modify their bacterial ecology, including repeated hospitalization and previous antibiotic therapy. For example, one study exploring the microbiology of biliary infections in LT patients showed that a modified microbial profile due to biliary infection leads to an overrepresentation of Enterococci, with *Enterococcus faecium* representing up to 15% of post-LT infections [4]. This international epidemiological study was confirmed in a cohort study conducted at the Grenoble Alpes University Hospital in France [5], showing a high prevalence of *E. faecium* during biliary complications. This epidemiology complicates treatment due to the natural resistance to cephalosporins and penicillin, with the study [5] notably reporting 60% resistance to amoxicillin, the first-line treatment for biliary infection [6,7]. In this situation, therapeutic alternatives are limited [8,9].

Treatment of abscess or biloma is based on prolonged antibiotic therapy and may require weeks or months depending on the clinical course [3]. Usual antibiotic therapy for *E. faecium* requires daily injections of daptomycin and vancomycin. This regimen is difficult to maintain over the long term in ambulatory care. Alternative therapy for outpatient treatment is dalbavancin, which is a lipoglycopeptide with a half-life of 14 days, making it ideal for use in outpatients [10]. Currently approved for acute skin and soft-tissue infections, its use in osteoarticular and endovascular infections has also been well documented [11]. No study to date has analyzed the pharmacokinetics of dalbavancin in biliary tract infections; however, one study provides data on animal bile [12] and another on the peritoneal diffusion of dalbavancin [13].

The main objective of this study is to analyze the biliary diffusion of dalbavancin in LT patients in a prospective single-center study using biliary samples taken in the routine care of this population.

Methods

Study design

DALBATRANS is a prospective pharmacokinetic single-center study conducted on LT patients in Grenoble Alpes University Hospital in France. Patient recruitment started on November 6, 2024, with an estimated inclusion period of 1 year.

Participants and eligibility criteria

Patients are included if they meet the following inclusion criteria: Age > 18 years, liver transplant, hospitalized in Grenoble Alpes University Hospital, presenting biliary tract complications, and benefiting from endoscopic or radiologic bile drainage after initiating dalbavancin.

Exclusion criteria are patients under guardianship or unable to give consent and contraindication for dalbavancin.

Outcome measures

The primary outcome measure is the biliary concentration of dalbavancin at month 2 (M2).

As a secondary outcome, we compare the concentrations of antibiotics obtained in bile with the minimum inhibitory concentration (MIC) of bacteria at M2. It is often assumed that bile concentration must be 10 times greater than the MIC. We evaluate the biliary concentration of dalbavancin in relation to the plasma concentration using the biliary/plasma concentration ratio of dalbavancin.

We evaluate the proportion of patients with good clinical evolution at M2 and M6. A positive clinical outcome is defined by the presence of the following three criteria:

- Disappearance of fever (T < 38°C) or absence of febrile spike at M2 and M6 (in the absence of post-procedure biliary complications) or during follow-up.
- Disappearance or regression of abdominal pain and absence of new abdominal pain at M2 and M6 after the endoscopic procedure (apart from complications associated with the endoscopic or radiologic procedure) or during follow-up (in the absence of any other causes that could explain the pain).
- Disappearance or regression of icterus and absence of new cutaneous-mucosal icterus at M2 and M6 after the endoscopic procedure or during follow-up (in the absence of any other causes that could explain the cutaneous-mucosal icterus).

We also describe the proportion of patients with a positive biological evolution at M2 and M6. To validate successful biological progression, three of the four following criteria must be met:

- CRP reduction of 50 mg/L or 20% CRP reduction if initial CRP < 50 mg/L in follow-up at M2 and M6.
- 50% reduction or normalization of bilirubin in follow-up at M2 and M6.
- 50% reduction in cytolysis and cholestasis in follow-up at M2 and M6.
- Clearance of the implicated germ in bile samples 2 months after antibiotic treatment.

We evaluate the proportion of patients with good radiological evolution at M2 and M6, defined by one of the following:

- Regression of biloma or abscess size by > 50% or 2 cm after 2 months of treatment (compared to imaging performed at the onset of the complication);
- Complete removal of biloma or liver abscess at M2 or M6.

We also evaluate the efficacy of antibiotic treatment with dalbavancin by assessing the proportion of patients with a correct clinical, biological, and radiological course according to the dalbavancin-bilirubin concentration at the different study time points.

Sample size

There are currently few clinical studies evaluating the biliary diffusion of antibiotics, which limits the number of subjects to be included. The number of patients included will correspond to the active population of patients meeting the inclusion criteria at Grenoble Alpes University Hospital. Between 2019 and 2022, 25 patients were admitted to Grenoble Alpes University Hospital for liver abscess following LT. In 2009, Pea et al. published a study on the biliary diffusion of linezolid in six patients. Based on these data, the minimal sample size for this study is set to 10 patients.

Study intervention (Figure 1)

The time lapse of this study is represented in (Figure 1). All patients included in the study benefit from iterative radiologic or endoscopic interventions (biliary stent changing) for the treatment of biliary complications. For each intervention, blood and bile samples are taken to measure the dosage of dalbavancin.

Plasma and biliary assays will be checked at M2 and M4 follow-up. These tests will be carried out when the biliary stents are changed as part of routine patient care. Clinical, biological, and morphological features are also monitored for 6 months.

Data collection

For each patient, demographic, anthropometric, and LT characteristics are recorded. During follow-up, in addition of blood samples of CRP and liver enzymes, the morphological evolution of the biliary complications is also assessed using computed tomography or magnetic resonance imaging.

Statistical analysis

The characteristics of the study population will

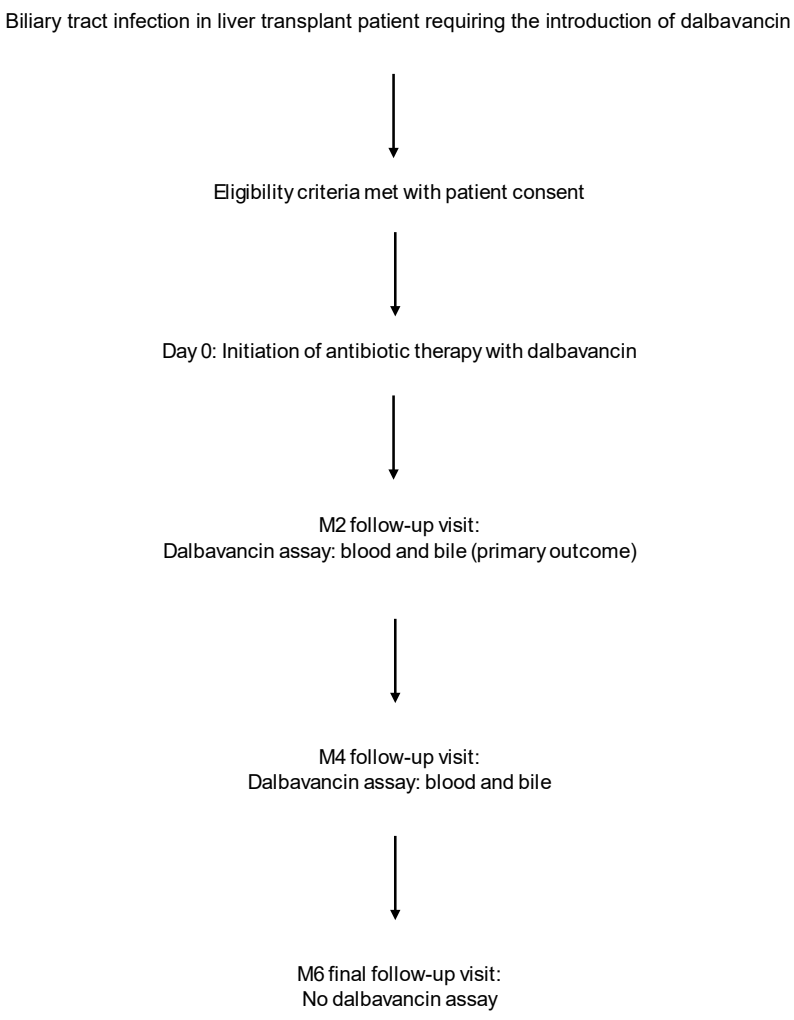

Figure 1: Time lapse of the study with dalbavancin.

be described using frequencies and percentages for qualitative variables, and medians and standard deviations for quantitative variables due to the small sample size. Univariate comparative analysis for two qualitative variables will be performed using Fisher's exact test. Univariate comparative analysis for one qualitative and one quantitative variable will be performed using the Mann-Whitney test. Given the small sample size, the statistical power will not be set at the usual 80%. The type I error risk (alpha) will be maintained at 5%.

Timeline

The study was approved on September 6, 2024. The duration of patient follow-up in this study is 6 months. The inclusion of patients is still open.

Ethics statement

Ethics approval was obtained through Paris Protection of Persons Committee (Number: 2024-A01124-43; CHU Promoteur 38RC24.0165; IDRCB: 2024-A01124-43).

Discussion

As a growing threat to public health worldwide, antibiotic resistance was defined as a major public health issue by the World Health Organization in 2017. Antibiotic pressure resulting from different courses of anti-microbial treatment contributes to the selection of resistant pathogens.

LT patients often have a long and complicated medical history, which explains the presence of resistant bacterial and fungal pathogens in their digestive and biliary flora. Some studies report an overrepresentation of enterococcus species in post-transplant bile infections [14].

Based on data from the National Healthcare Safety Network Pathogen of the Centers for Disease Control and Prevention, between 2015 and 2018, 30% of surgical site infections after LT procedures were attributed to *E. faecium* [15]. At Grenoble Alpes University Hospital, 2124 samples (all types) were positive for *Enterococcus sp.* in 2024, including 434 *E. faecium* resistant to amoxicillin in 64.6% of cases. Among these identifications, nine *Enterococcus* resistant to glycopeptide were found, and 0.3% of strains were resistant to daptomycin.

Biliary tract infections like biloma or liver abscess require several months of treatment. For infections caused by *E. faecium* and other resistant pathogens, treatment options are very limited, with vancomycin, daptomycin, and tigecycline requiring daily injections. Long-acting treatments therefore appear to be of interest to improve patient quality of life, limit the length of hospital stays, and reduce the costs generated by prolonged hospitalization. Dalbavancin has proved its worth for osteoarticular infections associated with multi-resistant germs [16] and for serious infections such as bacteremia, endocarditis, osteomyelitis, and septic arthritis in specific populations [11,17]. Using this literature in endovascular and osteoarticular infections, dalbavancin is used as a last resort in LT patients with biliary infections but without data concerning biliary diffusion.

Assessing the biliary diffusion of an antibiotic is a complex process, as demonstrated by the lack of data available in the literature. LT patients represent a population of choice for this study given the regular biliary recalibration procedures required post-surgery. Although this is a specific population whose results must be extrapolated with caution, these are the first available data on the diffusion of dalbavancin in bile in humans.

This study could consolidate clinical practice carried out as a last resort in patients requiring prolonged management for severe infection. This preliminary study opens the door to further studies to evaluate the efficacy of dalbavancin in abdominal infections.

The study certainly has limitations, as it only applies to LT patients and includes a small sample size. Due to its monocentric nature and the chosen inclusion criteria, patient inclusion will take longer than expected.

Conclusion

DALBATRANS is the first study to investigate the biliary diffusion of dalbavancin in humans and could provide evidence for the use of this antibiotic in common biliary and digestive infections.

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Declaration for Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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