Studies on injury and repair of donor bile ducts after liver transplantation
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2013

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
General Introduction,
Rationale and Outline of the Thesis
Orthotopic liver transplantation (OLT) is a well-accepted treatment option for patients with acute liver failure and end-stage chronic liver disease. One- and five-year patient survival after OLT depends on the indication of transplantation but ranges between 80-90% and 70-80% respectively (1). One important clinical challenge in liver transplantation is the reduction in the incidence of biliary complications, which are a major cause of morbidity and mortality in liver transplant recipients (2, 3).

The human biliary tree consists of a converging network of bile ducts. Small intrahepatic bile ducts converge into larger bile ducts and eventually the extrahepatic bile duct, which terminates in the duodenum. A single layer of epithelial cells, called cholangiocytes, lines the inner surface of the lumen of the biliary tract. Cholangiocytes are thought to play a key role in the pathogenesis of biliary complications after liver transplantation, since they are known to be very vulnerable to the ischemia/reperfusion injury that inevitably occurs during transplantation (4,5). One of the most clinically important manifestations of biliary epithelial damage after liver transplantation is the formation of non-anastomotic biliary strictures (NAS). NAS are defined as any stricture located in the intra- or extrahepatic bile ducts of the donor, with the exception of strictures at the site of anastomosis, unrelated to hepatic artery thrombosis. NAS are often therapy resistant and frequently lead to graft loss and the need for retransplantation. Since NAS resemble the strictures seen in patients after hepatic artery thrombosis, the pathogenesis of NAS was initially believed to be primarily ischemic in nature. The model of ischemia/reperfusion injury resulting in biliary epithelial cell loss and subsequent scarring and stricture formation is well-accepted (6, 7). However, several other risk factors not directly related to ischemia/reperfusion injury, such as bile salt toxicity and immune-mediated injury, have recently been identified and suggest that NAS has a multifactorial etiology (8).

The majority of studies performed in this area have primarily been aimed at either identifying risk factors associated with development of NAS, or unraveling the mechanisms responsible for cholangiocyte death (5). Although progress has been made in understanding the pathogenesis of NAS (as will be discussed in Chapter 2), the condition is far from fully explained and the question of why a considerable percentage of NAS patients without any known risk factors develop NAS remains unanswered. In this thesis we hypothesize that differences in the initial reparative response of the bile duct after cholangiocyte damage contributes to differences in pathogenesis of NAS. This topic has not previously been investigated, particularly with respect to extrahepatic bile ducts, in spite of the fact that NAS most frequently occurs at this site (9).
This thesis focuses on: a) clinical risk factors and predictors of cholangiocyte injury related to NAS development; b) whether donor bile ducts have the capacity to regenerate after damage; c) whether machine preservation positively impacts bile duct integrity and maintenance of the regenerative potential of damaged sub-optimal grafts; d) if bile production as a reflection of hepatobiliary integrity is able to predict graft function during machine perfusion.

Chapter 2 provides a review of the existing literature on clinical risk factors for NAS and the mechanisms that lead to injury of cholangiocytes after transplantation. Chapters 3 and 4 investigate the clinical risk factors and predictors of NAS in two specific subpopulations of liver transplant patients already at higher risk of developing NAS: patients transplanted for primary sclerosing cholangitis (PSC; Chapter 3) and recipients that have received a liver graft from a donor after cardiac death (Chapter 4). In Chapter 3 we perform a retrospective analysis comparing the two most commonly used surgical methods for the reconstruction of biliary continuity in PSC patients: duct-to-duct anastomosis and the Roux-en-Y hepatico-jejunostomy. Duct-to-duct anastomosis is considered as the gold standard for the reconstruction of biliary continuity after OLT; however, Roux-en-Y hepatico-jejunostomy is also frequently used by transplant surgeons for patients with PSC since as much of the extrahepatic bile duct is resected as possible, which is thought to reduce the incidence of postoperative biliary complications. However, since there is no formal evidence for this assumption we evaluate our experience with the use of duct-to-duct anastomosis as the preferred method, and in doing so challenge the rationale for the use of the Roux-en-Y hepatico-jejunostomy. In Chapter 4 we investigate whether alanine-aminotransferase (ALT), a biomarker of ischemia/reperfusion injury, is predictive for the development of NAS. In particular we distinguish two clinical groups: donation after brain death (DBD) and donation after cardiac death (DCD) liver transplant recipients, and hypothesize that, since grafts from DCD patients have been subjected to an additional form of ischemia (i.e. warm ischemia during procurement) and are at higher risk of NAS development, that early postoperative ALT assessment is of predictive value.

In Chapter 5 we study the regenerative mechanisms of the (extrahepatic) bile duct. We hypothesize that human extrahepatic bile ducts possess specific sites of regeneration. This will be assessed by examining patterns of cholangiocyte proliferation in normal and pathological clinical models representing varying degrees of cholangiocyte damage. In addition, we seek to identify putative progenitor cells since these are thought to play a key role in the reparative process. Chapter 6 addresses whether there are cellular sources from outside the liver that contribute to regeneration after damage, as assessed by examining the presence of recipient (male) cells in the extrahepatic bile duct of a donor (female) after transplantation.
using fluorescence-in situ hybridization (FISH). Chapter 7 investigates whether oxygenated hypothermic machine perfusion (HMP) results in better preservation of the biliary system in a porcine model of DCD liver transplantation compared to the gold standard of simple cold storage (SCS). Chapter 8 investigates the hypothesis that bile production is a suitable parameter to predict liver function during oxygenated normothermic machine perfusion (NMP) of human liver grafts that were declined for transplantation.
REFERENCES


