- Study Protocol -

Study title	Vascular liver disease study (VALID study)
Principle Investigator	Sarwa Darwish Murad, MD, PhD
Institution	Erasmus Medical Center Department of Gastroenterology and Hepatology Dr. Molewaterplein 40 3015 GD Rotterdam The Netherlands
Study Initiator/Sponsor	Department of Gastroenterology and Hepatology Erasmus MC, University Medical Center Rotterdam Dr. Molewaterplein 40, Room NA-605 3015 GD Rotterdam The Netherlands Tel: +31 10 703 5942 (secr.) Fax: +31 10 703 0352 email: s.darwishmurad@erasmusmc.nl

Introduction

Vascular disorders of the liver, though rare (estimated <5/10,000 patients), collectively count for a number of important liver related problems (1). These include, but are not limited to, Budd-Chiari Syndrome (2), splanchnic vein thrombosis or stenosis (i.e. portal vein and/or mesenteric vein and/or splenic vein) (3), hepatic artery thrombosis or stenosis usually seen in the transplant setting (4), congestive hepatopathy due to right-sided heart failure (5), sinusoidal obstruction syndrome (6), hepatic vascular malformations (7) and non-cirrhotic portal hypertension (8, 9). These disorders can occur in the native liver with or without cirrhosis, or after liver transplantation. The common characteristic of these disorders is that it gives rise to portal hypertension, which causes significant clinical morbidity and even mortality. Moreover, vascular disease in non-cirrhotic livers generally affects younger patients, in whom life expectancy may be hampered if not adequately managed (10). Most of these have underlying reasons for hypercoagulopathy which require specific anticoagulant treatment, but due to simultaneous portal hypertension and risk of variceal bleeding, treatment is not straightforward. At the same time, patients with cirrhosis, irrespective of the cause, all share complex alternations in the hemostatic system, which makes them prone to develop thrombosis in the hepatic vasculature (11), leading to further deterioration of portal hypertension.

Much of what we know about vascular liver disease comes from observational case series, often - at least those which are considered high quality- effectuated by multicenter collaborations. This is needed to optimize the statistical power needed for quality research in such orphan diseases, as often randomized trials are practically challenging. Therefore, collaboration will be sought with other medical centers in the Netherlands, and beyond. The currently established scientific international multicenter network is the VALDIG (Vascular Liver Disease Group), which is endorsed by EASL (European Association for the Study of the Liver). Erasmus MC (SDM) is represented in the board (www.valdig.eu).

Clinically, given the complexity of dealing with vascular liver diseases as well as its rarity, most patients end up in highly specialized centers where there is an established multidisciplinary team caring for these patients, including hepatologists, hematologists, (interventional) radiologists, pathologists and surgeons. In the Netherlands, Erasmus MC has a longstanding history in the treatment of these patients, and is considered the referral center. Here the multidisciplinary clinical and scientific expertise is bundled, a multidisciplinary meeting is in place and a high concentration of vascular liver disease patients are treated.

Ongoing research is the only way to move forward in our knowledge of vascular liver diseases in order for us to truly understand the underlying etiology, find better ways of establishing the diagnosis, and ultimately, to better treat the patients and change the outcome favorably.

Aim

The aim of this retrospective study is to investigate the etiology, methods of diagnosis, treatment options and disease progression in patients with vascular liver diseases, in order to eventually improve quality of clinical care and identify areas of further research.

Methods

Study type	Non-interventional retrospective follow-up study of an orphan disease.
Population	All consecutive patients with vascular liver diseases at the Erasmus MC will be asked to participate. Most of them will be seen at the outpatient clinic.
`	Vascular liver disease includes a group of disorders in which the inflow or outflow of the liver and portal system is compromised and portal hypertension develops. These include Budd-Chiari Syndrome, splanchnic vein thrombosis or stenosis (i.e. portal vein and/or mesenteric vein and/or splenic vein), hepatic artery thrombosis or stenosis, congestive hepatopathy, sinusoidal obstruction syndrome, hepatic vascular malformations and non-cirrhotic portal hypertension.
Data collection	Clinical data (symptoms, clinical signs and reports of laboratory, radiology, pathology, endoscopy and surgery) will be retrospectively collected from the electronic medical record system (HIX). Only data which are pre-existing and obtained during standard clinical practice will be used. Patients will not be asked to come for extra clinical or laboratory visits, and clinical care will not by any means be affected by our study. Patient will be asked by informed consent whether they give permission for data collection.
Samples	Patients will be asked by informed consent whether they give permission for the use of residual biomaterial. These biosamples (mostly serum and histology) have

been collected during the standard diagnostic work-up of the patient and stored at the biobank of the Virology department (viral hepatitis is usually excluded before vascular liver disease is diagnosed) and regular storage at pathology. This residual material is of no clinical use anymore. They can be used scientifically for example to test a novel biomarker in our patient population or to have a histological relook.

Ethics

The study will be conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol will be offered for review to the ethics committee of the Erasmus Medical Center in Rotterdam, the Netherlands. As this concerns a non-interventional retrospective study design, in which patient data will be collected in an anonymized dataset, this protocol will be offered for reviewed to the ethics committee as a '*niet-WMO-plichtig*' protocol. In line with the General Data Protection Regulation rules (*AVG*), we provide the patient with an informed consent form (which is included in this application).

Collaboration

Depending on the specific project and research question, collaboration with other (academic) groups will be explored in order to increase expertise and statistical power. Within EMC, established collaboration exists with departments of hematology (Prof. Dr. F.W.G. Leebeek and Dr. M. Lauw), interventional radiology (Dr. A. Moelker), pathology (Dr. M. Doukas) and surgery (Dr. W.G. Polak).

Nationally, collaboration with other, academic and non-academic hospitals may be sought. Internationally, this includes the well-established collaboration with the VALDIG network (Vascular Liver Disease Group), which is an international collaborative effort of independent scientific experts in the field of vascular liver disease, endorsed by the European Association for the Study of the Liver (EASL). The principle investigator (SDM) is a board member of VALDIG. More information can be found on www.valdig.eu. VALDIG is not industry sponsored and collaboration is purely based on expertise and common interest. VALDIG is member of the European Reference Network for rare liver diseases (ERN-RARE-

	LIVER). A centralized database is available for collaborative studies, located in Hamburg, Germany, which contains anonymous data, which cannot be traced back to personal data of the patient. Collected data will remain in the ownership of the contributing center (EMC). Management of individual authorship is agreed upon for each individual project and is the responsibility of the principle investigator of that project. Patients will be informed regarding this collaboration in the informed consent form.
Scientific Output	Scientific reports of this study, including but not limited to conference abstracts and original manuscripts, will be published in (inter)national peer-reviewed scientific medical journals.
Subject consequences	There are no (medical) risks for subjects who participate in the current study. Also, there is no direct (medical) benefit for those who are included in the study protocol.

References

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