1. General Information

1.1 Study identification

Title: Prospective multicenter follow-up of a cohort of patients with rare liver diseases

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1.2 Promoter identification

Nombre y dirección del promotor.
JUAN CARLOS GARCÍA-PAGÁN.
Hepatic Hemodynamic Laboratory
Liver Unit, Hospital Clínic de Barcelona
Villarroel 170, 08036 Barcelona

1.3 Identification of principal investigators from the participating centers

Name and title of all researchers responsible for carrying out the project and the address and telephone numbers of the study centers.

Last name: García-Pagán
Name: Juan Carlos
Qualification and degree: Doctor en Medicina y Cirugía
Professional category: Consultor senior. Jefe de sección.

Last name: Hernández-Gea
Name: Virginia
Qualification and degree: Doctora en Medicina y Cirugía
Professional category: Especialista

Last name: Parés
Name: Albert
Qualification and degree: Doctor en Medicina y Cirugía
Professional category: Especialista

Last name: Londoño Hurtado
Name: María Carlota

Qualification and degree: Doctora en Medicina y Cirugía

Professional category: Especialista

Last name: Mariño

Name: Zoe

Qualification and degree: Doctora en Medicina y Cirugía

Professional category: Especialista

Last name: Perez-Campuzano

Name: Valeria

Qualification and degree: Licenciado en Medicina y Cirugía

Professional category: Especialista

2. Background

Rare diseases, also known as orphan or minority diseases are disorders that affect a small percentage of the population. The term "rare diseases" encompasses a wide variety of diseases and conditions that are very different from one another, which have in common their low incidence. By definition, a disease is considered rare when it affects less than 1 in 2,000 inhabitants, often also expressed as less than 5 in 10,000 inhabitants. It is estimated that there are between 6,000-8,000 different rare diseases, currently affecting approximately 6-8% of the European population (1). In Europe alone, there are 30 million people suffering from a rare disease and 3 million in Spain (1,2).

There are currently more than 60 rare liver diseases in adults and children, and can be classified into (3, 4, 5):

1.- Autoimmune Liver Diseases:

- Autoimmune hepatitis (AIH)
- Primary Biliary Cholangitis (PBC).
- Sclerosing cholangitis: IgG4-related sclerosing cholangitis, Primary sclerosing cholangitis (PSC).

2.- Nonvascular genetic liver disease, Biliary atresia and related diseases.

- Alpha-1 Antitrypsin Liver Disease (AATD).
- Genetic Cholestatic Diseases: Alagille syndrome, Crigler-Najjar syndrome, Disorder of porphyrin and heme metabolism, Dubin-Johnson syndrome, Progressive familial intrahepatic cholestasis (PFIC), Rotor Syndrome.
- Wilson disease.
- Biliary Atresia.

3.- Structural Liver Disease:

- Biliary Malformations: Caroli disease, Choledochal cyst.
- Polycystic Liver Disease (PLD) / Congenital Fibrosis.
- Rare Liver Tumors: Fibrolamellar hepatocarcinoma, Hepatic epithelioid hemangioendotelioma & angiosarcoma, Hepatobiliary tumors with stem cell features & mixed types, Hepatoblastoma, Intrahepatic Cholangiocarcinoma, Primary hepatic neuroendocrine tumors (NET).
- Vascular Liver Disease: Budd-Chiari-Syndrome, non-cirrhotic portal vein thrombosis, portosinusoidal vascular disease, sinusoidal obstruction syndrome, hepatic vascular malformations in hereditary haemorrhagic telangiectasia, portal vein thrombosis in cirrhosis , Congestive liver disease after cardiac abnormalities or interventions.

Liver rare diseases are an important public health issue, and in order to establish a better understanding and offer possibilities of therapeutic options, in Europe we count with the European Reference Networks (ERN), with a referential section with the European Reference Network on Hepatological Diseases (ERN RARE-LIVER). ERN RARE-LIVER is a Europe-wide, government-endorsed and EU accredited, non-profit network of experts and patient representatives in the field of rare liver diseases (6, 7).

ERN RARE-LIVER is the prospective registry of ERN, which currently focuses on autoimmune liver diseases (AIH), Primary Biliary Cholangitis (PBC), Primary sclerosing cholangitis (PSC), polycystic liver disease and vascular liver diseases.

The objective of this study is to include the patients with a diagnosed rare liver disease of our center in the ERN RARE-LIVER registry to actively collaborate in the improvement of patient care.

2.1 References

1. https://globalgenes.org/rare-facts/
2. https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en
3. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol. 2016 Jan;64(1):179-202. doi: 10.1016/j.jhep.2015.07.040. Epub 2015 Oct 26. PMID: 26516032.
4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009 Aug;51(2):237-67. doi: 10.1016/j.jhep.2009.04.009. Epub 2009 Jun 6. PMID: 19501929.
5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015 Oct;63(4):971-1004. doi: 10.1016/j.jhep.2015.06.030. Epub 2015 Sep 1. Erratum in: J Hepatol. 2015 Dec;63(6):1543-4. PMID: 26341719.
6. https://rare-liver.eu/registry

7. Jones DEJ, Sturm E, Lohse AW. Access to care in rare liver diseases: New challenges and new opportunities. J Hepatol. 2018 Mar;68(3):577-585. doi: 10.1016/j.jhep.2017.11.004. Epub 2017 Nov 4. PMID: 29113911.

3. Objective and purpose of the study

1. Prospective registry of a large group of patients with rare liver diseases in order to add more information on their natural history, and to be able to develop and disseminate recommendations for their optimal management.
2. Improve the care of patients with rare liver diseases throughout European states.
3. Clarify and provide new data on the etiology, diagnosis and prognosis of rare liver diseases.
4. Describe prognostic factors of survival and of medical and/or interventional treatments.

4. Study Design

The European Reference Network on Hepatological Diseases is an international, government-endorsed and EU accredited, non-profit network that created the initiative of the registry of rare liver diseases with the prospective multicenter follow-up of European countries, in order to improve care of patients throughout European states.

The principles of work organization, membership and objectives are set by the European Commission (EC). All members and partners of ERN RARE-LIVER are health care providers (HCP), i.e. hospitals and academic institutions, which have to be nominated by their respective Board of Member States representative and have to fulfill the membership criteria set by the EC.

5. Patient selection

Inclusion Criteria

(1) Formal diagnosis of a rare liver disease.

(2) Informed written consent to register the patient in the specific database.

Exclusion Criteria

(1) Lack of informed written consent to register.

6. Treatments and study calendar

- We schedule the start of patient registration from April 2021.

- There will be no visits during the study.

- There will be no activities or complementary explorations to be carried out.

7. Organization and data collection

Hospital Clinic of Barcelona is an official member of ERN RARE-LIVER and will participate in the registry of patients with rare liver diseases and fulfill the membership criteria set by the EC.

Data collection include: Baseline and follow-up demographic, clinical, laboratory and imaging data, that will be recollected in a specifically pre designed electronic data-base on the ERN RARE-LIVER, and currently including: Autoimmune liver diseases, PBC, PSC, polycystic liver disease and vascular liver diseases.

The patients who meet the inclusion criteria, will sign an informed written consent to be included in the International Multicenter Registry of Patients with Rare Liver Diseases, all data collected is anonymous and will be given a code to be registered.

7.1 Statistical analysis

Normally distributed variables will be expressed as mean ± standard deviation and continuous variables with skewed distribution as median (range), the categorical variables will be shown as frequencies.

The statistical analysis will be carried out using the appropriate parametric or non-parametric test, using independent t-test for normally distributed data for the comparison of continuous variables between groups and the χ^2 test or Fisher's exact test for qualitative variables. A statically significant difference will be established with a value of $p < 0.05$.

A multivariate analysis based on a logistic regression procedure will be performed to identify independent predictive factors of TIPS placement. The selected variables to enter the step

regression will be those with P <0.1. The multivariate analysis will be performed through the Cox proportional risk analysis.

Statistical analysis will be carried out with the SPSS 22.0 package (SPSS, Chicago, IL, USA).

8. Ethics and legal aspects

This study will be carried out in compliance with the Declaration of Helsinki (current version; currently Fortaleza, Brazil, October 2013).

This study will be carried out in accordance with the protocol and with the relevant legal requirements in accordance with Law 14/2007 of July 3, on Biomedical Research. Informed consent in all patients before their inclusion in the study.

For the collection of clinical data in the ERN-RARE LIVER registry, a Data Sharing Agreement (DTA) will be signed between the contributing centre: Hospital Clínic of Barcelona and the site storing and handling the data: University Hospital of Hamburg-Eppendorf. Data collected will remain in the ownership of the health care provider.

Management of individual authorship is agreed upon for each individual project and is the responsibility of the Principal Investigator.

9. Treatment of Data and Archiving of Records. Confidentiality of the data.

The treatment, communication and transfer of personal data of all participants will comply with EU Regulation 2016/679 of the European Parliament and of the Council of April 27, 2016 regarding the protection of natural persons in terms of to the processing of personal data and the free circulation of data, being mandatory as of May 25, 2018. The legal basis that justifies the processing of your data is the consent given in this act, in accordance with the provisions of the Article 9 of EU Regulation 2016/679.

The data collected for this study will be identified only by a code on the electronic data-base of ERN RARE-LIVER, so no information will be included to identify the participants. Only the study doctor and his collaborators with the right of access to the source data (clinical history), may relate the data collected in the study with the patient's medical history.

The identity of the participants will not be available to any other person except for a medical emergency or legal requirement.

The health authorities, the Research Ethics Committee and personnel authorized by the study promoter may have access to the identified personal information, when necessary to verify data and study procedures, but always maintaining confidentiality in accordance with current legislation. Only coded data will be transferred to third parties and other countries, which in no case will contain information that can directly identify the participant (such as name and surname, initials, address, social security number, etc.). In the event that this transfer occurs, it would be for the same purpose of the study described and guaranteeing confidentiality.

If a transfer of encrypted data takes place outside the EU, either in entities related to the hospital center where the patient participates, to service providers or researchers who collaborate with us, the data of the participants will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities.

As promoters of the project, we undertake to process the data in accordance with EU Regulation 2016/679 and, therefore, to keep a record of the treatment activities that we carry out and to carry out a risk assessment of the treatments we carry out , to know what measures we will have to apply and how to do it. In addition to the rights that the previous legislation already contemplated (access, modification, opposition and cancellation of data, deletion in the new Regulation) now participants can also limit the processing of data collected for the project that are incorrect, request a copy or that moved to a third party (portability). To exercise these rights, they should contact the main investigator of the study or the Data Protection Delegate of the Hospital Clínic de Barcelona through protecciodades@clinic.cat. Likewise, they have the right to contact the Data Protection Agency if they are not satisfied.

The data cannot be deleted, even if a patient leaves the study, to ensure the validity of the investigation and to comply with legal duties and drug authorization requirements.

The Researcher and the Sponsor are obliged to keep the data collected for the study for at least 25 years after its completion. Subsequently, the personal information will only be kept by the center for the care of your health and by the promoter for other scientific research purposes if the patient has given their consent to do so, and if this is permitted by law and applicable ethical requirements.

10. Financing

This project does not entail any additional cost for the hospital.

11. Publishing policy

We pledge to make the results of the study public.