BACKGROUND

Hepatocellular adenomas (HCAs) are rare benign liver tumors characterized by the proliferation of mature hepatocytes. (1) HCAs are hormone-sensitive tumors putting at risk mainly women exposed to oral contraceptives. (1) The major complications are bleeding (15-20%) and, because of the monoclonal nature of HCA, potential for malignant transformation (4-8%) into hepatocellular carcinoma. (2)(3)

In the past years, major progresses have been made in the understanding of the complexity of HCAs thanks to a multidisciplinary approach by hepatologists, liver pathologists, radiologists, surgeons and molecular biologists. (3) HCAs are currently considered as an heterogeneous group of tumors affecting not only women of childbearing age with a healthy liver exposed to estrogen, but also men and patients of both sex with pre-existing chronic liver diseases (vascular liver diseases, nonalcoholic steatohepatitis, alcoholic cirrhosis...).(2)

The detailed study of their various underlying molecular pathways of development, phenotypically transcribed in histological and immunohistochemical characteristics, allowed their classification into specific subtypes associated with distinct clinical presentation, risk factors and complications. (1)(4) The understanding and identification of these subtypes allows a personalized and rational management in a multidisciplinary approach for this complex disease. (3)(5)(6)

The aim of this study is to create the first Swiss registry of patients with hepatocellular adenoma to provide a comprehensive description of clinico-pathological and epidemiological aspects of this disease in our country and reach a consensus for a multidisciplinary similar management. This study is needed since data on hepatocellular adenomas are scarce in Switzerland.

AIM

To provide the first retrospective and prospective collection of data on HCAs in Switzerland.

The primary endpoint is to conduct a national analysis of the epidemiology, diagnoses and clinical manifestation of HCA to provide a comprehensive description of HCA's characteristics in Switzerland. Histological, immunohistochemical and radiologic features will also be collected.

Second, our interest will be focused on the treatment and evolution of HCA. The proportion of biopsies performed and the reasons for non-biopsy will be studied as well as the type of treatment and follow-up.

PATIENTS AND METHODS

All patients diagnosed with HCA in Switzerland will be eligible. Any patient refusing the reuse of his clinical data will be excluded.

Regarding the retrospective component of the present registry, we will include any patient diagnosed since January 1, 2018.

This study is a multicenter project including ideally at least the seven Swiss reference hospitals in Hepatology (GE, VD, BE, ZH, BS, SG, TI). All centers will be individually

contacted and invited to participate to the study. In case of positive response, they will be asked to transmit coded information to Prof. Christine Sempoux, Dre Montserrat Fraga and Dre Sophie Kasmi.

Data collection will include demographic aspects (age, sex, origin), clinical characteristics (mode of presentation, BMI, diabetes, oral contraception, other drugs, alcohol intake, smoking, pre-existing chronic liver pathology, chronic viral hepatitis, glycogenosis, immunosuppression, and other potential relevant comorbidities). Biological data will include liver function tests and inflammatory parameters (white blood cells, C reactive protein, sedimentation rate). The number of years of oral contraceptive use and the number of pregnancies for women will be included. If available, radiological and histological data including the number of nodules, the size of the largest nodule, the non-tumoral liver characteristics (steatosis, steatohepatitis, fibrosis, vascular liver disease…) and the immunohistochemical and molecular profile for sub-classification of HCA if available.

For retrospective inclusions, if the HCA has not been sub-classified, or if the subclassification is unclear, blank slides should be provided to IPA-CHUV for additional immunohistochemistry. If necessary central revision might be organized.

For prospective inclusions of newly diagnosed HCA, an additional formalin-fixed paraffin-embedded sample containing both tumoral and non tumoral tissue will be taken from the surgical sample and sent for bio-banking.

The coding work will be done, following the usual rules for coding, by Dre Sophie Kasmi under the supervision of Prof. Christine Sempoux and Dre Montserrat Fraga. The data will be copied onto an Excel spreadsheet by coding them using a neutral and study-specific number. No patient identity will appear in the table. Each patient will be assigned an ID number that will be attached to his or her name in a Word document (containing the allocation code). This document will then be submitted to the research project management, who will ensure correct coding prior to analysis.

A study protocol will be submitted to the Ethics Committee of the Canton de Vaud (CER-VD) and will be extended to each referral committee depending on the participating centers.

EXPECTED SIGNIFICANCE

This study will provide the first detailed understanding of the landscape of HCA epidemiology in Switzerland. This registry will provide the data for carrying out future research projects on HCA across Switzerland.

BUDGET AND PUBLICATIONS

Initially, there will be no funding for this study.
Support by SASL will be requested upon approval by its scientific committee.

PROJECT TIMELINE

June 2021: Submission of a short protocol to SASL council for approval and assignement of a SASL study number.

July to September 2021: Redaction of detailed protocol and submission to the CER-VD as well as to each referral committee depending on the participating centers.

January 2022: Start of the registry and beginning of inclusions.

REFERENCES

1. Nault J-C, Couchy G, Balabaud C, Morcrette G, Caruso S, Blanc J-F, et al. Molecular Classification of Hepatocellular Adenoma Associates With Risk Factors, Bleeding, and Malignant Transformation. Gastroenterology. 2017 Mar;152(4):880–894.e6.

2. Bioulac-Sage P, Sempoux C, Balabaud C. Hepatocellular adenoma: Classification, variants and clinical relevance. Semin Diagn Pathol. 2017 Mar;34(2):112–25.

3. Blanc JF, Frulio N, Chiche L, Sempoux C, Annet L, Hubert C, et al. Hepatocellular adenoma management: Call for shared guidelines and multidisciplinary approach. Clin Res Hepatol Gastroenterol. 2015 Apr;39(2):180–7.

4. Nault J-C, Paradis V, Cherqui D, Vilgrain V, Zucman-Rossi J. Molecular classification of hepatocellular adenoma in clinical practice. J Hepatol. 2017 Nov;67(5):1074–83.

5. Bioulac-Sage P, Sempoux C, Frulio N, Le Bail B, Blanc JF, Castain C, et al. Snapshot summary of diagnosis and management of hepatocellular adenoma subtypes. Clin Res Hepatol Gastroenterol. 2019 Feb;43(1):12–9.

6. Thomeer MG, Broker M, Verheij J, Doukas M, Terkivatan T, Bijdevaate D, et al. Hepatocellular adenoma: when and how to treat? Update of current evidence. Ther Adv Gastroenterol. 2016 Nov;9(6):898–912.

7. Sempoux C, Paradis V, Komuta M, Wee A, Calderaro J, Balabaud C, Quaglia A, Bioulac-Sage P. Hepatocellular nodules expressing markers of hepatocellular adenomas in Budd-Chiari syndrome and other rare hepatic vascular disorders.J Hepatol. 2015 Nov;63(5):1173-80.