"Primary Sclerosing Cholangitis associated with Inflammatory Bowel Disease: Analysis of intestinal outcome after liver transplantation" - LIVIBD

Abstract. Primary Sclerosing Cholangitis (PSC) is a cholestatic liver disease characterised by chronic inflammation and intra- and extra-hepatic bile ducts strictures. It is frequently associated with an Inflammatory Bowel Disease (IBD) and in particular with Ulcerative Colitis (UC). This liver disease cannot be neither prevented nor its natural history can be modified by medical therapy. For this reason, the only curative strategy in advanced disease is orthotopic liver transplantation (OLT). The management of the IBD before and after OLT can be challenging. Moreover, the natural history of IBD after liver transplantation remains ill-defined and current data are limited. The aims of the multicentre, retrospective, observational case-control study we propose are, at first, the evaluation of the differences in terms of progression and outcome of intestinal disease between a group of transplanted and a group of non-transplanted IBD/PSC patients; secondary outcomes are the potential risk factors that could influence of the IBD course in transplanted group, including the role of immunosuppressive drugs.

Background and rationale

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease which is characterised by chronic inflammation, strictures in intra- and more often extra-hepatic ducts and a frequent association with an inflammatory bowel disease (IBD), particularly with ulcerative colitis (UC); in almost 50% of PSC patients the diagnosis of IBD precedes the diagnosis of PSC, but after 10 years of follow up, IBD is diagnosed in 80% of PSC patients[1]. This means that between 3-6% of all IBD patients have or will eventually develop this condition. Nowadays there isn't any medical treatment able to prevent or modify the natural history towards liver cirrhosis and failure, that is why orthotopic liver transplantation (OLT) is the only viable solution towards patients presenting advanced disease[2]. About 46% of all patients presenting PSC in Europe have already been transplanted, making it the most frequent cause for OLT in IBD patients with approximately 2% of all European IBD cases undergoing the procedure, of whom 20-50% will eventually undergo to a re-transplant (re-OLT) due to the hepatic disease recurrence[3]. Management of IBD before and after liver transplant for PSC can be challenging, as there are no formal guidelines: the natural history of IBD after liver transplantation remains ill defined, and currently there is limited data about the outcome of intestinal disease after the procedure[4,5,6]. A study by Dvorchik et al.[4] suggests that OLT and subsequent immunosuppressive therapy can accelerate to three times the natural progression of the IBD, showing an increased need for colectomies in OLT UC patients. A recent meta-analysis by Singh et al.[2] that included 609 IBD patient from 14 clinical studies, investigated the clinical outcome of intestinal disease after a mean 4.8 year from OLT: one third (31%) showed signs of improvement versus an almost same quote (30%) of patient with worsen IBD activity. A recent case-control study[7] analyses the IBD outcome and the role of immunosuppressive drugs in a group of 41 IBD/PCS patients who underwent to OLT against a group of 42 matched IBD patients without OLT; the Authors observed a rate of 23.2% of relapses in the OLT group (against 22.7% of the non-OLT group) and a rate of remissions of 53.6% (27.4% in the control group) after a follow up of 14.5 years. Because of the lack of data and their contradictions, it is important to investigate the outcome of the inflammatory bowel disease after liver transplantation and the risk factors associated.

Study design and patient population

- Observational, multicentre, case-control retrospective, spontaneous study
- Patients included in the study should be affected both by PSC and IBD (already diagnosed before OLT)
- Exclusion criteria are: absence of a clinical follow up documentation, patients who received IBD diagnosis after the OLT, patients without an IBD diagnosis supported by colonoscopic and histologic

sampling, patients without instrumental findings highly suggestive for PSC, OLT for diseases different from PSC, patients with colectomy for IBD before the start of the follow up

- Primary outcome is the different need for biologic therapy or bowel resection for medically refractory IBD or hospitalization for IBD relapse during the follow-up between OLT and non-OLT patients.
  The follow up start 1 one year after first OLT in OLT patients (we consider 1 year a reasonable time frame to re-establish from the transplant). In non-OLT patients the follow-up will start from the diagnosis of coexistence of IBD and PSC.
  A minimum follow-up is not need using the Kaplan-Meier survival curve analysis. The follow up will finish at the time of escalation of IBD-related medical therapy or colectomy for medically refractory IBD or at the last follow up visit.
  The follow up end if there is the need for biologic therapy (such as anti–tumor necrosis factor [anti-TNF] agents or vedolizumab or ustekinumab)) or bowel resection for medically refractory IBD[8] or a hospitalization for IBD relapse or at the last follow up visit

- Risk factors for escalation of IBD-related medical therapy or colectomy will be evaluated in the OLT-IBS-PSC group about smoking habits, disease activity before OLT, duration of illness, age at diagnosis..., different immunosuppressive drugs used after liver transplantation

- Secondary outcome: rate of colonic dysplasia, CRC, solid tumours will be compared with the same method of the primary outcome

Materials and Methods

Data collection

For all included patients, physicians will perform a retrospective collection of hospital records. Data collected include gender, family history of both IBD and PSC, smoke habit, age at IBD and PSC diagnosis, type and localization of IBD, medical therapy history, presence of intestinal dysplasia or CRC, solid tumours within the end of follow-up.

To calculate the sample size, we accepted a Type I error – alpha = 0.05, a Type II error – beta = 0.2. We calculated the sample size on the primary outcome starting from our pilot study in which an unfavourable IBD course was found in 63% of transplanted patients versus 31% of non-transplanted patients, with a ration of sample sizes between two group of 1. We chose, in a precautionary manner, to hypothesise a 56% of unfavourable IBD in OLT patients, and a 38% of unfavourable IBD in non-OLT patients: the total sample size resulted 240.

At least two hundred and fifty patients (50 in our centre, 20 for each of at least 10 satellite centres) will be included. The deadline will be on 30/06/2019. All centres will be free to include the PSC-IBD patients with or without an OLT in every ratio (i.e., if a centre has only PSC-IBD patients that did not undergo to OLT that centre could include all patients without an OLT history).

Ethical considerations

All patients receive a written information and sign the consent to clinical data collection and the privacy statement form. Shared database will be anonymous. The study followed the principles of the Declaration of Helsinki.

Statistical Analysis

The comparison in primary and secondary outcomes in the two group will be performed using the Kaplan-Meier survival curve analysis.

The influence of risk factors on the outcome will be analysed with Cox proportional-hazards regression multivariate analysis.

P <0.05 is considered statistically significant. The statistical analysis will be performed by using MedCalc software (version 14.8.1).

Phases of the study

Once approved by the Ethic Committee of the coordinator centre and satellite centres, the data collection can be started. A shared database will be. After the deadline of 30/06/2019, available data will undergo to statistical analysis, as already described above.

Expected results

The aims of the study proposed are the evaluation of the natural history of the Inflammatory Bowel Disease after Orthotopic Liver Transplant for Primary Sclerosing Cholangitis and the risk factors predicting a worse outcome, because data are lacking. In the clinical practice, this study may contribute to extend the knowledge about this disease and to influence the management of this particular population of patients.

Bibliographic References

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Appendix Shared database

Center	N
Patient ID	N
General characteristics of the population	
Date of Birth	dd/mm/yyyy
Gender	M = Male F = Female
Date of first follow up visit	Dd/mm/yyyy
Age at the time of Analysis	n
IBD	MC / UC / IBDU
Date diagnosis IBD	mm/yyyy
Date diagnosis PSC	mm/yyyy
Age at the diagnosis of IBD	years
Age at the diagnosis of PSC	years
Difference between age of diagnosis IBD and PSC	years
Active smoking	Yes / No
Years of smoking (both active smokers and ex)	n
OLT	Yes/No
Age at OLT	n
Date OLT	Dd/mm/yyyy
Re OLT (Re-transplantation)	Numbers of re-OLT
Date Re-OLT (1°)	Dd/mm/yyyy
Date Re-OLT (2°)	Dd/mm/yyyy
Date Re-OLT (3°)	Dd/mm/yyyy
Cause reOLT	xx
Duration of IBD at OLT (years)	n
Duration of PSC at OLT (years)	N
Family history positive for IBD	Yes/No
Family History positive for PSC	Yes/No
Perianal disease	1=Yes 0=No
ANCA	0= Negative 1=Positive
Montreal classification at the start of follow up	CD: A1, A2, A3; L1, L2, L3, + L4; B1, B2, B3, (p) UC: E1, E2, E3
Clinical activity of the intestinal disease at last visit pre-OLT	0 = Remission / Mild Activity 1= Moderate /Severe / Systemic steroid in the last three months
Bowel resection	Yes/no
Reason of bowel resection	Refractory IBD / dysplasia or CRC
Date of bowel resection	Dd/mm/yyyy
Biologic therapy (such as anti–tumor necrosis factor [anti-TNF] agents or vedolizumab or ustekinumab)	Drug/No
Date of escalation	Dd/mm/yyyy
OLT immunosuppressive therapy during follow up	Tacrolimus, Mycophenolate mofetil, Thiopurines, Cyclosporine
Hospitalization due to disease relapse	Yes/No
Complications developed	
Colonic dysplasia	0 = LGD 1= HGD 2 = undefined 3 = no

Colorectal Cancer	No / Yes
Lymphoma	1=Yes 0=No
Cholangiocarcinoma	1=Yes 0=No
Hepatocellular Carcinoma	1=Yes 0=No
Other tumours	Xxx
Date diagnosis of colonic dysplasia or CRC	Dd/mm/yyyy
Date diagnosis of CRC	Dd/mm/yyyy
Date diagnosis of Lymphoma	Dd/mm/yyyy
Date diagnosis of solid tumor	Dd/mm/yyyy
Death	1=Yes 0=No
Cause of Death	Xxx
Date of Death	Dd/mm/yyyy
Date of last follow up visit	Dd/mm/yyyy