NHS BLOOD AND TRANSPLANT

LIVER ADVISORY GROUP

UK LAG proposal

Early Access, Pan-Genotypic, active treatment proposal for utilisation of Sofosbuvir containing antiviral HCV regimen in HCV patients listed for Liver Transplant in the UK

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Full Title: Early Access, Pan-genotypic use of Sofosbuvir (SOF) in combination Ribavarin (RBV) with/ without pegylated interferon (PEG-IFN), for Chronic HCV patients on the UK transplant waiting list undergoing orthotopic liver transplantation (LT).[Combination therapy with Sof/ Ledispavir (LDV-GS5885) for HCV G1 without interferon when available/ filed]

Context: HCV recurrence impacts significantly on patient and graft survival, leading to HCV outcomes being suboptimal in comparison to other liver disease indications for LT. Licenced Antiviral therapy, including pegylated interferon, is poorly tolerated in this group of patients pre-LT due to risk of decompensation, sepsis and death.

New DAA therapies such as sofosbuvir, (DAAs- Directly Acting Antivirals), in combination with or without pegylated interferon/ ribavirin, are likely to be licenced in Q1 2014 but not available till post NICE evaluation. Thus, this group of patients, with end-stage liver disease and the complications of HCV may be significantly disadvantaged. Abrogating/ curing HCV prior to transplantation, or more likely, preventing re-infection of the graft with HCV would optimise donor utilisation, improve immediate and medium- term management for patients post LT and avoid the need for antiviral therapy post transplantation, which in itself is often associated with significant morbidity and risk with low post-LT SVR (cure) rates. On a broader scale, early access for this population allows the optimal transplant management for best outcomes for the limited donor organ poor available within the UK

Groups for Inclusion:	HCV monoinfection
	HCV/HIV co-infection
	HCV and hepatocellular carcinoma (HCC)
	Primary and re-transplant patients
Exclusion:	Creat clearance <30ml/min. [Patients on dialysis, ie liver-kidney, need clarifying: Liver –Kidney as dosing not yet delineated]
	Non-NHS entitled patients
Study Centres:	Seven transplant centres in the UK and Ireland

Potential number of subjects: NHSBT Data on the waiting list currently 14.09.13

57 HCV mono-infected

48 HCV and HCC

3 HCV and HIV co-infected

Study Timelines: Post licensing of Sofosbuvir, provision through NHSE after endorsement of LAG/ NHSBT

Conversion to Sofosbuvir and Ledispavir fixed dose combination for HCV G1 after filing for licencing (May 2014)

Medication: Peg-IFN and RBV as per standard dosing. RBV to be taken with food at a total daily oral dose 1000-1200mg (1000mg for patients <75kg – 1200mg for those individuals >75kg)

Commitment from Gilead to allow compassionate access to sofosbuvir/ledipasvir combination when licence filed and for those who are intolerant/ treatment failure, and those with debilitating serious disease or life threatening disease who cannot be treated with the authorised medicinal product

NHS England funding prior to NICE need clarity (outwith this proposal)

Target Population: UK patients with Chronic HCV (pan-genotypic) fulfilling standard orthotopic liver transplant listing criteria

Duration of treatment: 24 weeks pre-transplant rollover to 48 weeks till LT

[+/- 24 weeks post-transplant?]

Primary Objectives of study: HCV RNA recurrence in liver graft post liver transplantation

Primary Safety endpoints: Proportion of patients discontinued (pre-LT)

Death (pre-/ post-LT) and graft loss

Secondary Objectives of study:

RNA negativity at transplant

To determine if the administration of this regimen to HCV-infected subjects pre-transplant can establish SVR pre-transplant

To determine if the administration of this regimen to HCV-infected subjects pre-transplant can prevent post-transplantation recurrence at 12 weeks post-transplant (SVR12- defined as <lower limit of quantification [LLOQ])

To determine on treatment therapeutic efficacy as measured by change of Child –Pugh Turcotte (CTP) score/ MELD during treatment and follow-up

To determine therapeutic efficacy as measured by change of UKELD/ MELD score during treatment and follow-up

To evaluate the safety and tolerability of a SOF containing regimen in a real life clinical cohort

To determine reduction in resource utilisation pre and post transplantation

To evaluate the kinetics of circulating HCV RNA during and after treatment

Design Open label, multicentre, real life multi-centre active-therapy study

Assessments:

Each Transplant centre to nominate Hepatology consultant responsible at each centre for patient care and timely data collection

Discretion of centre to treat patients without Peg-IFN if Platelets < 60,000/mm^3; albumin < 35 g/L; or Conjugated bilirubin >1.5 x ULN

Discretion of centre to treat compensated HCV with primary indication being liver cancer (HCC) with 12 weeks Peg-IFN/ SOF/ RBV if treatment naïve, albumin >35, plts>100, bilirubin normal

Standard delisting criteria (eg if progression of HCC) likewise centre discretion regarding 'salvage' or improvement and delisting. However, currently, there is no data on improvement in HCV and delisting/ deferral of LT must be taken on with caution

Central viral labs?

Standard clinical worksheets and data collection. Data repository through NHSBT?

?Biobank possibility HCV UK (d/w Prof Irving) / Stop HCV (d/w E Barnes)

Baseline: Indication – primary or secondary LT/ HCV RNA viral load/ genotype/ subtype/ previous treatment history/ UKELD/ MELD/ concomitant medication/ Blood group/ IL-28B status/ date listed/ centre/ HCC interventions/ QOL/ pregnancy test

4 weekly: AEs/ admissions/ adherence/ UKELD/MELD/ HCV RNA/ QOL/ serial pregnancy

Discontinuation if increase in HCV RNA on treatment – virological failure

Patients who are on Sofosbuvir and for whom a donor graft becomes available, should stop study drug and will be followed post LT. weekly HCV-RNA and documentation of complications (ACR/ biliary complications/ Primary graft failure/ episodes of sepsis/ CMV)

Donor details (DCD vs DBD, split, CIT, steatosis) data to be collected. Surgical complications likewise – standardised definitions

SVR 12 – post LT – as per pre-LT

SVR 24 – post LT - as per pre-LT

Other points:

Cost risk –sharing of DAA- Sof to be delineated with NHSE

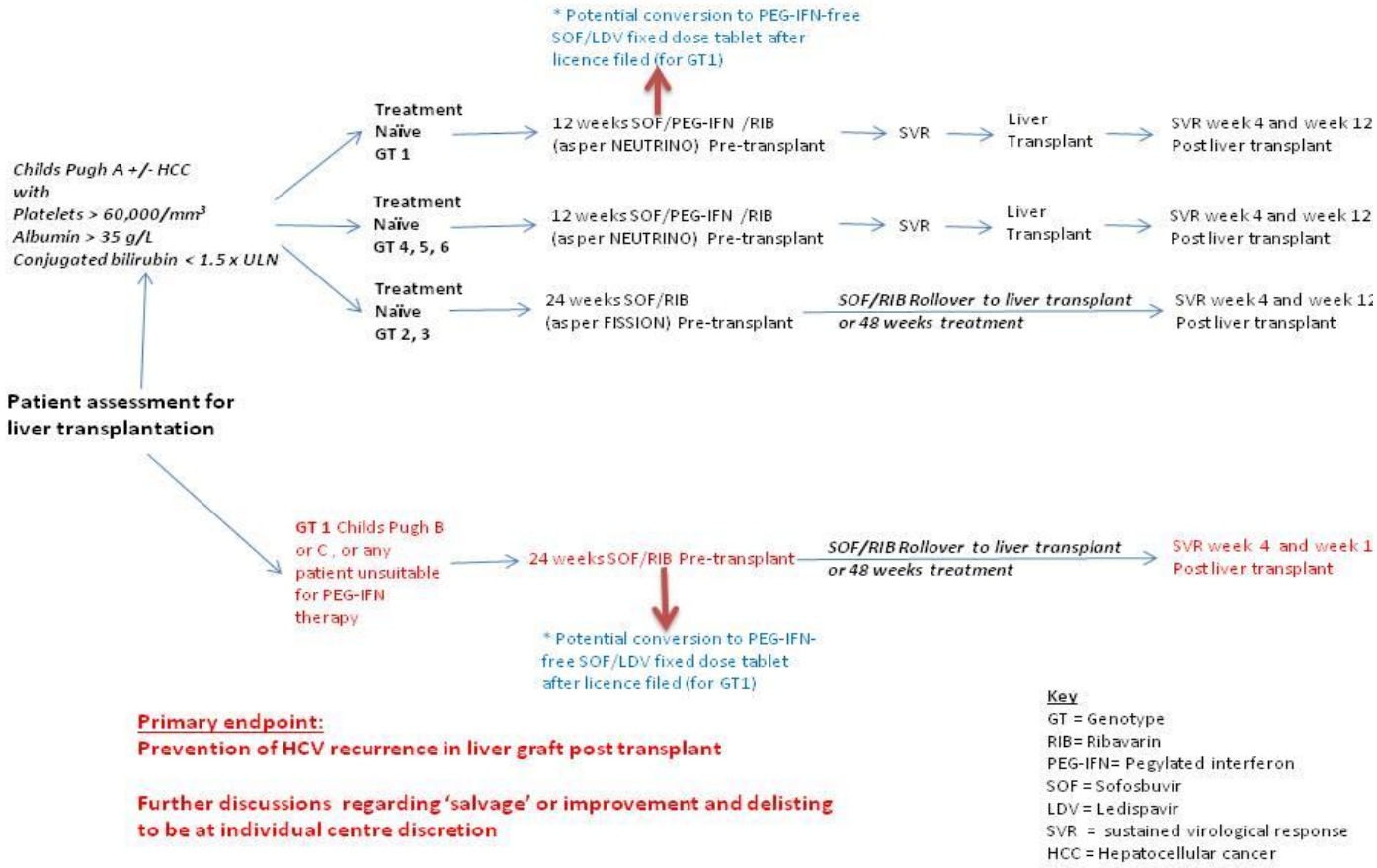
Resource for data collection via NHSBT or through a nominated lead centre?

Opportunity for 'substudy' – biomarkers of regeneration/ immunological/ viral resistance modelled on French ATU

Patient group endorsement and advocacy

29.09.13

Figure 1: Schematic of Proposal



Primary endpoint:
Prevention of HCV recurrence in liver graft post transplant

Further discussions regarding 'salvage' or improvement and delisting to be at individual centre discretion

Key
GT = Genotype
RIB= Ribavarin
PEG-IFN= Pegylated interferon
SOF = Sofosbuvir
LDV = Ledispavir
SVR = sustained virological response
HCC = Hepatocellular cancer