Portal Hypertension Special Interest Group (SIG) Inaugural Meeting

Medical School, University of Birmingham

1st May 2019

Report prepared by Dr Dhiraj Tripathi and Steering Committee

Contents

1. Introduction

The meeting was attended by 40 participants. Industry sponsors were Gore Medical and Sequana Medical. Dr Tripathi also thanked Samantha Jones, BASL Senior Administrator for her assistance in organising the meeting.

The SIG was introduced to all participants by Dr Tripathi who was appointed by BASL to lead the SIG for the first year. The purpose and aims of the SIG was described with relevance to the BASL terms of reference for all SIGs. The Portal Hypertension SIG was established to facilitate collaborations in clinical and translational research, and to provide a platform to nurture discussion in best management of patients in this complex and rapidly evolving area. The SIG is linked to Cirrhosis and its Complications CRN topic area. Portal Hypertension is a very active research area with recent NIHR HTA funding of 3 randomised controlled trials which have the potential to the largest ever clinical trials in cirrhosis. Translational research has been boosted by studies on non-invasive assessment of portal hypertension, and exciting new drugs. The SIG also aims to encourage debate on the best management of patients with regards to medical and radiological therapies.

Members of the steering committee were introduced:

Dr Dhiraj Tripathi (Chair), University Hospitals Birmingham
Prof Jonathan Fallowfield, University of Edinburgh
Prof Peter Hayes, University of Edinburgh
Dr Joanna Leithead, Addenbrookes Hospital, Cambridge
Dr Raj Mookerjee, University College London
Dr David Patch, University College London
Dr Vikram Sharma, Royal London Hospital
Prof Adrian Stanley, Glasgow Royal Infirmary
Dr Emmanouil Tsochatzis, University College London
Dr Abhishek Chauhan, University Hospitals Birmingham (trainee representative)
Ms Mandy Lomax (patient representative)

Membership for the SIG has increased from 73 to 195 members in the last 6 months.

A description of presentations and summary of the discussions is presented thus. Slides for most presentations have been uploaded to the BASL website.

2. Active research studies

a. CALIBRE – Dr Tripathi (Chief Investigator) and Dr Ahmed (Senior Trial Manager) presented an overview of this NIHR HTA funded trial:

i. Trial Design: A multicentre randomised controlled, open-label, self-evident two-arm trial with internal pilot.
ii. Aim: To investigate the clinical and cost-effectiveness of carvedilol versus variceal band ligation in patients with cirrhosis and medium to large oesophageal varices that have not bled
iii. Sample size 2630 – CALIBRE is largest ever Phase III trial in cirrhosis:
iv. NIHR HTA funded - £2.3m: Sponsor University of Birmingham over 75 months
v. Recruitment over 4 years nationally: All acute NHS trusts and health boards in UK potentially eligible
vi. Primary end point: Any variceal bleeding within 1 year of randomisation. Full protocol has been published: https://bmjopengastro.bmj.com/content/6/1/e000290
vii. Trail progress: recruitment began in January 2019 as part of 12 month pilot with 26 sites open in England, Wales and Scotland. Total of 51 sites contacted and 32 SIVs completed. 34 patients recruited. Recruitment and number of sites opened ahead of projections. At the end of the 12 month pilot a minimum of 20 sites should be open, 240 patients recruited.

At present CALIBRE team are looking for more sites as funding allows for up to 66 sites. There was much national support for this pragmatic trial. A member of the group asked about the need for longer follow up for the secondary outcomes. Dr Tripathi informed the group that consent process includes long term follow beyond one year by tracking patients using NHS number of equivalent. Dr Ahmed also highlighted the importance of seeking CRN research nurse support using the ACROSS platform.

b. BOPPP – Dr Patel (Chief Investigator) presented an overview of this NIHR HTA funded trial:

i. Trial Design: Multi-centre, phase IV, triple blinded (participant, investigator, analyst), prospective RCT
ii. Purpose: To determine if carvedilol reduces rate of variceal haemorrhage (VH) in patients with cirrhosis and small oesophageal varices without red signs(OV)
iii. Primary objective(s): To determine the clinical and cost effectiveness of the reduction in VH in patients treated with carvedilol vs placebo after 3 years.
iv. Secondary objectives: all-cause mortality, increase in OV size, hospitalisation with decompensation, MELD score increase, development of overt hepatic encephalopathy (HE), ascites, jaundice,

renal impairment, HCC, myocardial infarction, liver transplantation. NSBB optimisation in 1o care

v. Target population & setting: 1,200 cirrhotic patients with small OV to be recruited across 20 UK NHS sites, each f/u for 3 years
vi. Primary Endpoints: Time to first variceal haemorrhage, cost-utility of NSBB over trial follow up to 3 years.
vii. Key exclusions criteria: isolated gastric varices, rectal varices, duodenal varices. Already on a beta-blocker. CTIMP in last 3 months. Child's C cirrhosis.
viii. Pilot phases: Phase 1 to assess recruitment and retention March 2020. Phase 2 to assess placebo variceal bleeding rate (must be ≥4% annually).
ix. Trial progress: Regulatory approvals received. TSC/DMC meeting held. Currently making some amendments to protocol and also adding 1 page introduction to BOPPP and CALIBRE for all potentially eligible patients – CALIBRE and BOPPP complementary not competitive. Plan pan-London investigators meeting 24 May 2019. Aim 1st patient recruited in June 2019. So far 21 sites contacted with PIs identified.

There was discussion about the uncertainty of bleeding rate in light of emerging data suggesting it is low in patients with small varices and compensated cirrhosis and prevention of decompensation is more important (PREDESCI trial). However, this is based on small numbers.

A real potential issue could be intraobserver variability in differentiating small varices from no varices. Dr Patel informed the group that photographs should be taken where possible although this may not capture the real time assessment with regards to flattening on air insufflation.

c. ASEPTIC – Dr O'Brien (Chief Investigator) presented an overview of this NIHR HTA funded multicentre RCT. His group also lead the ATTIRE trial:

i. Research question: To determine the efficacy of antibiotic prophylaxis for adults with cirrhosis & ascites but no previous spontaneous bacterial peritonitis (SBP) to prevent development of SBP, "primary prophylaxis".
ii. Methods: A multicentre placebo controlled randomised doubled blind trial to assess efficacy, cost-effectiveness and safety of cotrimoxazole for 2 years to prevent SBP in 548 participants with cirrhosis, ascites and a low ascitic fluid (AF) protein count (<1.5g/dl) from 30 NHS sites. The *primary outcome* will be event free survival with time to first incidence of SBP compared between arms. *Sample size calculation* used 90% power and 2-sided 5% significance level with 20% loss-to follow- up. *Secondary outcomes* include mortality, AMR & CDAD incidence and cost effectiveness. Patients will be stratified by liver disease severity and active alcohol use. Patients >18 years with cirrhosis, ascites and low AF protein count will be eligible. They will have 3 monthly follow-up visits to collect medication, bloods. A case report form (CRF) will document SBP

admissions. Patients will stop treatment if ascites resolves, undergo transplant or complete 2 years follow-up. A detailed statistical analysis plan will be approved before analysis of unblinded data, including health economics, quality of life & serious adverse events.

iii. Timelines for delivery: 6 month setup for protocol development, CRFs and organising contracts with sites. Recruitment will be 24 months with anticipated recruitment rate of 1 patient per site per month with a staggered initiation of 30 sites over 12 months. A 9 month GO/NO GO internal pilot will demonstrate deliverability based on anticipated recruitment. Estimated recruitment of 320 patients from first 15 sites & 230 from the second 15 giving 548 participants required to demonstrate a 55% relative reduction in cumulative event probabilities of SBP. Treatment duration is 24 months. Close out, cleaning, analysis & dissemination will be 6 months

iv. Anticipated impact and dissemination: This will be the largest study of SBP prophylaxis ever and if successful we will update international guidance.

ASEPTIC is presently at set up stage. Sites recruiting well for ATTIRE will be selected.

d. Vascular liver disease:

This is a niche area with a lack of high level evidence. Collaborative studies with a multidisciplinary approach are key to advancing knowledge. Dr Tripathi informed the group of VALDIG (Vascular Liver Diseases Interest Group) which is an international collaborative group led by Prof Garica-Pagan and Prof Valla with support from EASL. Some members of the SIG are already part of this group. There have been a number of high impact publications which have resulted from VALDIG collaborations including the EASL Guidelines on Vascular Liver Disease. Dr Tripathi encouraged members with interest in vascular liver disease to consider joining VALDIG.

The following presentations were delivered:

i. Dr Patch presented an overview of vascular liver disease with case presentations. There is a lack of good quality evidence and paucity of guidelines (no Grade 1a level evidence on treatment). There are no published RCTs for BCS with just 13 RCTs on PVT. A case of acute PVT with cardiac thrombus treated with thrombolysis was presented. Case demonstrates the risks of bleeding as confirmed in the literature. Another case of extensive splanchnic vein thrombosis successfully treated with catheter directed thrombolysis was presented. The final case had PVT on a background of antiphospholipid syndrome successfully treated with pharmaco-mechanical clot dissolution and TIPSS. The cases illustrate the need for MDT involvement in all decisions and a protocol. It is

important to note that therapeutic options for PVT and cavernoma is limited.

ii. Dr Chen presented an overview of splanchnic vein thrombosis (SVT) and myeloproliferative neoplasms (MPNs). He shared some data and presented a case. The data shows that most patients had a de novo presentation of SVT without prior MPN diagnosis. JAK2 positivity is more common with BCS than PVT. Peripheral blood counts are often normal in patients presenting with SVT and JAK2 +ve and additional studies such as red cell mass may be necessary e.g. masked polycythaemia rubra vera. JAK2 allele burden often low. BCS and EHPVO have differences at a molecular level with high frequency of additional myeloid mutations detected by next generation sequencing. A diagnostic algorithm provided guidance on the role of bone marrow biopsy. There is a clear recommendation for anticoagulation in all and cytoreductive therapy (raised counts) in patients with MPN-SVT. The role of cytoreductive therapy in those with normal counts is not clear.

3. Patient and public involvement and engagement (PPIE)

a. Laura Chapman (BRC PPIE Manager), delivered a presentation providing an overview of PPIE. Key messages included that PPIE can happen in all parts of the research cycle. Involvement refers to those using services, carers and researchers. There was also discussion on the benefits of the patient experience, which adds value, insight, recognition and legitimacy.
b. Mandy Lomax gave a personal account of her journey in the health care system. She was very grateful for the specialist care she received and how this saved her life. She identified with the hepatological and haematological aspects of vascular liver disease and thanked Dr Patch and Dr Chen for their talks.

4. Clinical guidelines

a. TIPSS – BSG Guideline in collaboration with BASL and BSIR

Dr Tripathi on behalf of the Guidelines Development Group (GDG) chaired by David Patch presented an overview and summary of the current progress with this guideline. It is the 1st ever UK Guideline on TIPSS and is aimed at referring teams. All BSG guidelines are NICE accredited. GRADE system is used for appraising evidence and formulating recommendations. GDG includes hepatologists (tertiary and secondary care), patient representation, and nursing representation. It is very timely given the emerging high level data on TIPSS. The areas covered include patient selection, procedural details, complications, indications, service delivery and development, and research agenda. There has been good

progress over the last year with a complete first draft being prepared and due to be submitted to BSG CSSC for internal review next month.

b. Ascites guideline – BSG

Dr Wilkes on behalf of the GDG chaired by Prof Guru Aithal presented an overview and summary of the current progress with this guideline. This is an update of the previous BSG guidance on ascites. The key areas covered are diagnostic tests, diet and diuretics, paracentesis, albumin, TIPSS and SBP. It was noted there will be some overlap with the BSG TIPSS guideline, and Prof Stanley from the TIPSS GDG is in close communication with Prof Aithal to ensure harmonisation of the recommendations. Dr Tripathi noted that the ALFA pump is not included and this is something that will be considered in light of recent NICE guidance discussed below.

5. Service development

a. Alfapump

i. Dr Tripathi presented an overview of NICE Interventional procedures guidance [IPG631]: Subcutaneous automated low-flow pump implantation for refractory ascites caused by cirrhosis. Dr Tripathi is a member of NICE Interventional Procedures Advisory Committee (IPAC) and is clinical lead for this NICE guidance. The ALFA pump is manufactured by Sequana Medical and is a novel method of treating refractory ascites with a small battery operated pump implanted surgically. The procedure is often considered for patients not suitable for a TIPSS. IPG631 was originally published in 2014, when it was recommended that the procedure should only be used in the *context of research*. Further evidence including a RCT and registry data prompted a further review in 2018. This resulted in the procedure being recommended for use with *special arrangements*. The committee noted the high incidence of device failure, risk of acute kidney injury, and potential need for albumin.

ii. Dr Mookerjee presented data from the only RCT of ALFA pump versus large volume paracentesis (Bureau C. Adebayo D, Chalret de Rieu M et al. (2017) Alfapump system vs.large volume paracentesis for refractory ascites: A multicenter randomized controlled study. Journal of Hepatology 67: 940–49). Seven EU sites (including 2 in UK) participated and recruited 60 patients. The primary outcome (median time to LVP) was 15 days in control group versus >6 months in the ALFA pump group ($p<0.001$). Median number of LVPs per month is reduced from 1.0 in control group to zero in ALFA pump group. Improvement in nutrition and

HRQOL were also noted. There was no difference in overall survival and infections. However more AKI was noted with the ALFA pump

The discussion focused on 3 main areas:

1. Re-interventions: It was noted that there has been significant improvement in device design to reduce risk of complications and device failure.
2. Acute kidney injury: The role of albumin infusions as for LVP would seem logical. It is likely this will reduce risks of AKI, but further study is necessary to inform us on the optimal regimen and clinical effects.
3. An assessment of costs-effectiveness is clearly necessary. NICE IPAC does assess this. NICE guidance does not mandate that the NHS must fund this procedure. Given the cost most procedures are done privately. An individual funding request would seem the only method of applying for funding within the NHS.

Dr Mookerjee proposed a trial of LVP versus ALFA pump assessing cost effectiveness and QUALY. Potential funding streams could be NIHR HTA. This needs further development but there was general support from the group.

b. TIPSS service

i. Dr Patch presented the results of a national survey on TIPSS service courtesy of Professor Cramp, BASL President. The data focused on finished consultant episodes (FCE) from 2006-2018. The vast majority of TIPSS were referred from other sites, in keeping with a hub and spoke model. It was noted that there was an increase in FCE in the order of 75% in this time period with a recent decrease in proportion of emergencies. Most units were performing 11-20 procedures per year, although 25% performed 1-10 procedures per year.

ii. Dr Tripathi presented emerging data on early or pre-emptive TIPSS. Since the 2010 RCT of early TIPSS there have been two further RCT's from China and UK. The results of the Chinese study were presented at International Liver Congress 2019 which confirmed the findings of the 2010 study, showing better survival in the early TIPSS arm than standard of care. All sub groups had improved transplant free survival. There is debate regarding high risk criteria used to select patients, in particular active bleeding, since the data does not consistently show that these patients benefit. The UK RCT (NCT02377141) is due to be presented at the BSG Annual Meeting in June 2019. Prof Hayes mentioned that there are major logical and resource challenges with implementation of early TIPSS in the UK and other parts of EU. A recent French audit showed that early

TIPSS uptake was low, with less than 7% of potentially eligible patients being offered early TIPSS.

iii. Dr Travis presented a view of the current TIPSS service, including advice for those wishing to set up a TIPSS service.

Discussion focused on providing a service and what this means. 24/7 or a more tapered service. Clearly there is a need to ensure provision for training and mentoring. A sensitive area is that of competence, and it is challenging defining this. All agreed that mandating a minimum number of cases per year per site was not necessary in uncomplicated cases, although there is evidence from a US study recommending a minimum of 20 per year to ensure optimal outcomes. The adoption of early TIPSS could have major service implications, but all agreed on the need to review the data from the recent evidence, in particular the UK RCT when the results are presented.

There was also much support for a national *TIPSS registry* to prospectively collect data. This would require funding and an option is to approach the specialist societies. The BSG TIPSS guideline is likely to make a strong recommendation for a registry.

6. Research in development

a. BEAMing and other MRI studies

Dr Palaniyappan presented a proposal for the Beta-blocker Efficacy Assessment using MRI in Guiding Therapy of Varices (BEAMinG) study. This is led by Prof Aithal whose Nottingham group have previously shown MRI measures to correlate with HVPG. The aim is to compare changes in splanchnic haemodynamic and structural MRI measures with changes in HVPG in patients with cirrhosis and varices treated with carvedilol. The study will help understand the mechanism of action of carvedilol by evaluating the changes in splanchnic and collateral flow, cardiac function, and liver T1. The study could help select haemodynamic non-responders to carvedilol using non-invasive methods, who would then be offered alterative treatment thus improving clinical outcome. Initial work will focus on harmonisation of the Nottingham MRI protocol validated as a surrogate for HVPG across research centres. Patients in the CALIBRE trial randomised to carvedilol are potentially eligible and will undergo baseline HVPG and MRI, then carvedilol therapy, followed by repeat HVPG and MRI after 4-12 weeks. Patients who decline to participate in CALIBRE can also be considered if a clinical decision was made to start carvedilol. Nottingham in collaboration with Derby, Edinburgh, UCL, and Birmingham have submitted a first stage application in response to a NIHR EME Researcher led call.

Dr Mookerjee emphasised the importance of assessing flow not just pressure when assessing efficacy of therapies in decompensated cirrhosis. He presented preliminary rodent data using phase contrast MRI and arterial spin labelling showing reduction in PV flow in sham and cirrhotic bile duct ligated animals after terlipressin. There is an ongoing study at RFH assessing liver haemodynamics and cardiac protocol for patients pre and post NSBB funded by Academy of Med Schi.

b. CALIBRE substudies

Dr Mookerjee presented a proposal for a CALIBRE sub study. There has been a lot interest in the role of non-selective beta-blockers (NSBB) in patients with advanced liver disease and refractory ascites. Growing evidence suggest NSBB can be beneficial with positive effects on gut barrier function (bacterial translocation), immune system and inflammatory response. These effects in turn could lower the risk of variceal bleeding and other complications of cirrhosis. Dr Mookerjee in collaboration with CALIBRE team submitted a Stage 2 NIHR EME application entitled "*Mechanistic evaluation of changes in inflammatory responses with carvedilol therapy compared to non-pharmacological intervention for portal hypertension, and the relation to changes in bleeding and cirrhosis complication risks, for patients enrolled into the CALIBRE study*". This was involved biobanking samples of patients randomised to the CALIBRE study at baseline and at 6 months and analysis of makers of infection, inflammation and endothelial function. Sadly the application was rejected and the feedback was that the proposal was hypothesis generating as opposed to hypothesis testing?

Dr Mookerjee is proposing to re-submit to EME for the same call in August 2019 focusing on patients at high risk of decompensation (CLIF-C AD > 50), where SIRS is a key driver. The question being whether carvedilol decreases the onset of ACLF through reduction of systemic inflammation. The high event rate of ACLF in this group has to be balanced against the few de novo patients and limited centres. Dr Mookerjee will discuss further with the CALIBRE team as it may be possible to get some data on potential number of candidates from current CALIBRE recruitment.

c. Liver HOPE

Dr Mookerjee (PI for RFC site) presented LIVEROPE which is HORIZON 2020 EU Program funded (5.6M Euro). It is a multi-centre, double-blind, placebo RCT to evaluate the efficacy of simvastatin plus rifaximin over 12m in halting the progression of decompensated cirrhosis as assessed by the time to first incidence of ACLF during treatment period. The aim is to recruit 240 patients across 7 centres. Key secondary end points include time to Tx Free survival; severity of ACLF and/or frequency of hospital admissions secondary to decompensation events; biological markers incl.

microbiome changes, neurohormones and SIRS/cytokines; QUALY; HE; and frailty scores. An ancillary study of haemodynamics (systemic, liver non-invasive and cardiac) is part of the protocol and includes systemic.

Discussion focused on optimising recruitment as only one site has opened in UK (RFH) and efficacy trial has started late.

d. Relaxin, biomarkers in AKI/HRS

Prof Fallowfield presented studies in relaxin, biomarkers in AKI/HRS. AKI is cirrhosis affects 50% of hospitalised patients and HRS can have dismal prognosis. Diagnosis and therapies are challenging.

There has been increasing interest in biomarkers of AKI in urine, blood and imaging to accurately predict prognosis and treatment response. These include:

- Chief Scientist Office (CSO) Catalytic Grant (Ref: CGA/16/45): 'Prognostic Biomarkers for Acute Kidney Injury in Liver Cirrhosis' n=53; n=53; pKIM-1, FeNa, uL-FABP, uPCR, uKIM-1 on admission
- Edinburgh and Lothians Health Foundation Research Grant (Ref: SO7074): 'Superior markers of renal dysfunction in patients admitted for liver transplant assessment could improve both short and long term outcomes' (n=?; pre-transplant biofluid biomarkers, renal MRI, impedance cardiography, aortic pulse wave velocity, retinal optical coherence tomography)
- A further study on MRI (contrast MRI and arterial spin labelling) to phenotype AKI/monitor terlipressin response was not funded and may be resubmitted to NIHR EME.

Prof Fallowfied's group have shown serelaxin (recombinant human relaxin-2) to have anti-fibrotic and favourable vasoactive effects in preclinical studies. Whether improved renal haemodynamics translates to better renal function is not clear. Serelaxin has been shown to reduce portal pressure in a Phase II trial sponsored by Novartis. However, a Novartis funded trial (Serelaxin To Lower Portal Pressure (STOPP)) was terminated as Novartis have closed all global serelaxin programmes and stopped making the drug. No alternative source of serelaxin is available at this time.

7. Future meetings

1. Steering committee meeting – proposed at time of BASL annual meeting in September 2019.
2. Meeting for all SIG members – proposed in November 2019 with venue to be confirmed.