Wilson's SIG meeting 20.11.20 via Zoom

Present: Bill Griffiths, Barbara Hoeroldt, Chris Harrington, James Dooley, Val Wheater, Rupert Purchase, Adrian Bomford, Aftab Ala, Aidan Ryan, Anil Dhawan, Andy Holt, Carys Lippiatt, David Nicholl, Deirdre Kelly, Emmanouil Tsochatzis, Evangeline Wassmer, Godfrey Gillett, Harpreet Dhaliwal, Indra Van Mourik, Jan Coebergh, Jay Patel, Jeanette Aston, Jeremy Cosgrove, Joanna Moore, Karolina Stepien, Lin Lee Wong, Mary Bythell, Mike Samuel, Maggie Burrows, Michelle Camarata, Miranda Durkie, Tom Marjot, Tala Valliani, Nicola Ho Yen, Oliver Bandmann, Osob Mohamed, Paul Cook, Paul Worth, Peter Beresford, Sam Shribman, Sital Shah, Tammy Hedderly, Tom Warner, Maria Bonacini, Paul Selby

Apologies: Rosa Miquel, Steve Masson, Graeme Alexander, Neil McDougall

Minutes of 29.11.19 meeting approved as accurate.

Matters arising:
•NHSE Specialist Centres updated re North Bristol, Oxford and Nottingham
•Centre Expertise spreadsheet - updated and added to BASL website - will send to Oliver Bandmann for inclusion in the ABN website.
•Clinical stds document for Centres of Excellence - updated (v1.3) and added to BASL website
•HPB CRG - not pursued/COVID
•PHE - review today's meeting
•'BMJ review – 'potentially BJGP case/letter (Sam Shribman liaising with potential patient's GP)
•'Consensus 'document – today's meeting 'guidance'/'guidelines'
•Lab questionnaire resent by Chris Harrington - review today's meeting
•DBS role update - access for carefully selected patients is available, ABN will continue to discuss
•Nottingham linking with PHE - in progress

Meeting Agenda

Guidance/Guidelines

It was agreed that the SIG should produce as a minimum a document which could be variously labelled a 'guidance document' (BSG terminology), 'position paper' or 'consensus statement'. This needs to be published across the specialties, chiefly Gastroenterology/Hepatology and Neurology though Psychiatry should be considered also. Example journals are Frontline Gastroenterology and Practical Neurology. There was some debate about whether we should be aiming 'higher' with the caveat that this would morph into formal detailed guidelines and might be harder to publish across specialties. Example journals on the Hepatology side include Lancet GastroHep and Gut. Another option is a general journal although felt unlikely BMJ would publish. The children section needs to be distinct but could be combined with adult across the document. The patient voice needs to be heard through both children/adolescent and adult sections. The document should be designed to get the basics right and to streamline diagnosis, treatment and monitoring. It should serve as a practical guide for clinicians and answer common questions. Bill G put up some slides showing example content. Val Wheater proposed Oliver Bandmann as lead for the adult section.

Chris Harrington showed the questionnaire results for diagnosis and monitoring which had examples of common ground but a few areas of ambiguity for which further consensus would be desirable eg on/off treatment 24 hour urinary copper, utility of serum copper ?useful for over treatment, spot urine copper testing. Some work to be done in relation to reference ranges, inter-lab variation - suggested that 'spare' samples or samples from CROWD study could be used for this purpose, with necessary consent.

Actions:

- *Chris H to go back to centres where there was missing information in the questionnaire and once complete to circulate the summary information round the SIG.*
- *Bill G to request interest from SIG members to form a working group(s) for guidance production, this will need representation from all relevant specialties, adult and children, including devolved nation input.*

PHE

Osob Mohamed presented the most recent data from the WD National Registry project. 470 WD patients identified, 82 deceased = 372 alive. Approx 60% obtained through 'linkage' data eg HES, mortality data. 47 Trusts approached, 27 responded. 44 Trusts have no data sharing agreement as yet, but in progress. The SIG congratulated PHE on the impressive number of cases ascertained nationally. A specific data collection relates to transplanted WD patients over the past two decades. 84 identified with median age of 23 years - liver status at listing, geographical location, mortality and re-transplantation rates presented. Aftab A suggested that going back to the transplant centres/NHSBT might firm up the accuracy of the data here (limits of HES/ICD10 re actual liver status). Further work includes registering additional data sources eg trace labs, Blueteq and ultimately primary care diagnosis. Data sources all have their own limitations but the more sources the better. Case confirmation remains a vital aspect especially in relation to brain disease.

Mary Bythell described the hierarchy within which NCARDRS sits (under the National Disease Registration Service NDRS). A consultation is occurring to do with moving NDRS to NHS Digital. To firm up the WD registry going forwards, submissions to the NDRS Project Panel include the overarching WD project and, for the first time, cohort linkage to the cancer registry (NCRAS). NCARDRS is taking on alpha-1 antitrypsin deficiency now also (Tamir Raschid). The exemplar is the RECORDER group for rheumatological disease - 160,000 patients and a 5 year NIHR fellowship, with PHE undertaking a COVID related analysis. The ambition is an overarching rare liver disease project plan but would require a significant personal commitment to drive. Brain disease in WD could be interrogated further as PHE has the legal basis to capture the necessary data. The group discussed 'two way data sharing' with PHE as a promising way forward eg where consent is built in such as with the CROWD cohort.

CROWD update

Sam Shribman argued that biomarkers in neuro WD are an unmet need. Outcomes can still be poor and standard markers don't correlate with severity. With gene therapy trials starting, brain markers are needed. It is possible to measure proteins produced by neurones and glia in the plasma and the hypothesis is that these might correlate with aspects of neuro WD. 40 patients were phenotyped, 23 with neuro disease of which 5 were 'active' as opposed to 'stable' (mean disease duration 23 years). 24 hour urine coppers were significantly higher in active vs stable patients. Plasma Neurofilament light (Nfl) was significantly higher in neuro vs hepatic disease. Within neuro disease it segregated active vs stable disease and correlated with disease severity (UWDRS-N subscore). This work has just been published in Movement Disorders. Future work will examine serial measurement in patients and report on quantitative neuroimaging analysis. The SIG congratulated Sam and his co-workers on their successful work here. Deirdre Kelly suggested 1) samples could be contributed - they would need freezing quickly but can then be stored 2) studying children would be ideal.

EASL/AASLD abstracts

Tom Marjot presented 6 abstract from the recent international liver meetings. There were 2 abstracts on Trientine (both K Weiss group) - first a pharmacokinetic study in healthy volunteers showing the difference in plasma concentration between equivalent doses of the di and tetra HCL formulations reaffirming the '0.6' dose conversion factor. The second demonstrated that in WD individual exposure varies according to severity of liver disease, and correlates with AST - potential for overtreatment. Abstract no 3 was a French retrospective

study of 14 patients who underwent single daily dosing - there was a 21% 'failure' rate by 3.5 years but no patient came to harm and would appear 'safe'. Abstract no 4 (Innsbruck) showed specific differences in MR

imaging between neurological (basal ganglia) and hepatic (white matter) WD, furthermore that subcortical atrophy can be present in hepatic WD reaffirming the need for prompt treatment. Abstract no 5 (Michigan) showed worse outcome for hospital admissions in WD patients who have additional alcohol related liver diagnoses. Abstract no 6 studied mitochondrial dysfunction in WD patients and in a mouse model, findings consistent with copper related damage. Oliver B reaffirmed the major therapeutic implications of this and previous work on mitochondrial dysfunction in WD and that mitochondrial rescue agents might be the answer for neurological worsening on conventional therapy - there is an urgent need for trials in this area. Methanobactin has been shown to be effective in a rat model (J Clin Invest 2016).

Clinical Trials

Aftab Ala updated the SIG on current and future clinical trials/studies:

- CHELATE - completed, awaiting evaluation. Teta4HCL vs D pen, non inferiority/safety phase 3 study.
- ALXN1840 (bis-choline TTM) - phase 2 open label 12 m copper/molybdenum balance study currently recruiting.
- WD registry - ongoing prospective study between US and Europe, both repository and clinical aspects
- UNITED study - UNIVAR phase 4, Cufence pharmacokinetics/dynamics, fixed vs response guide dosing in 50 patients, about to open.
- ALXN1840-WD-205 - in set up, phase 2 study involving liver biopsy to assess ultrastructural changes and liver copper concentrations.
- Proposed Royal Surrey/Kings study of once daily Trientine using a cross over design randomising to once vs twice daily. NB Orphalan (was GMP Orphan) considering a once daily formulation of Cuprior. General SIG support based on clinician experiences of patients remaining stable on once daily chelator dosing. Godfrey G suggested urine copper excretion worth considering as a marker. James D raised issue of what constitutes an 'empty stomach' when designing studies. Follow up may need to be longer in order to fully exclude treatment failures.

Gene therapy - 2 studies planned:

1) VIVET's phase 1/2 study of VTX801 in US/Europe, FDA approved as of 18.11.20.
2) ULTRAGENYX phase 3 study of UX701

Regarding gene therapy not clear if patients would remain on their existing treatment.

Actions:

- *Aftab A to continue to develop once daily study design.*
- *All - centres to review which studies they might be interested in.*
- *WDSG to consider updating website with a research section.*

Children - Lessons from cases / management

Tammy Hedderly presented 3 cases which highlighted some delays in diagnosis, the importance of investigating abnormal LFT, a possible link with autism, MRI brain can often be normal in spite of clinical brain disease, and excellent response to trientine. Common themes are compliance, adolescent transition and input from neuropsychology, neuropsychiatry and clinical psychology.

Anil D described treatment of children with WD at Kings - experience with zinc limited to four children two of whom switched and the other two had abnormal LFT at last review, experience is that it is not a good option for hepatic WD and NCC levels are variable. Penicillamine needs to be given slowly and starting with a low dose. 16 patients on trientine all did well. In fulminant WD, encephalopathy is not used but would transplant with a Wilson Index score of 11 or above, use penicillamine below 11 and add a lunchtime dose of zinc if score 8-10. The Wilson Index has been reviewed against a more recent cohort (2005-2018) — for non-transplanted ALF takes on average up to a year to settle clinically on chelator therapy. 24 hour urinary coppers are carried out 'on' treatment as too difficult logistically for 'off' treatment and the data reveals a mean of 8 umol/24 hrs after 1 year and 6 umol/24 hrs after 5 years. If levels rise then suspect compliance problem and monitor more frequently (3m vs 6m). Kings use a multidisciplinary approach with therapists, psychologist (32% have depression/anxiety), hepatology/neurology and report a lower rate of transplantation cf other centres. Will be publishing experience shortly.

There followed a discussion in relation to 'heterozygotes' - Anil D reported 15% of heterozygotes have low Cp levels. Important to decide WD Y/N and if Y then treat.

Trientine formulations

Rupert Purchase presented the available brands (from Univar, GMP Orphan now Orphalan, Tillomed). A summary table had been circulated prior the meeting (courtesy of Aftab A). Cuprior is calculated to need 60% of the base salt cf Univar formulations due to greater bioavailability although of note there is a lack of peer-reviewed published data. From November 2020, Univar are replacing their 300 mg trientine dihydrochloride capsules named 'Trientine Dihydrochloride' with the same product but with the brand name, 'Cufence'. For regulatory reasons, Cufence is labelled with the amount of trientine free base in each capsule (200 mg) equivalent to 300 mg trientine dihydrochloride. Each capsule still contains 300 mg trientine dihydrochloride, but the Patient Leaflet for this product states 'Cufence 200 mg hard capsules'. The transition from 300 mg Trientine Dihydrochloride capsules to Cufence 200 mg capsules may cause confusion among pharmacists and patients. Tillomed manufacturer associated with previous FDA warnings. Godfrey Gillett suggested the SIG liaises with the NHS Business Services Authority (NHSBSA) given there are now competing formulations.

Action: Bill G to take forward GG's suggestion on behalf of SIG. Clinicians advised to inform patients of the difference between Cufence and the previous Univar capsules during the transition period.

Genetic testing for WD

Miranda Durkie described 5 tenets related to National testing now and going forward - 7 Genomic Laboratory Hubs, National Genetic Testing directory, Whole Genome Sequencing (WGS), Clinical services, Genomics England. For ATP7B sequencing there will be 2 testing centres Yorkshire/NE (Sheffield/Leeds/Newcastle) and London (Kings/GSTT/St Georges) serving respective parts of England. Testing and reporting processes are unified across the centres. The clinical indication ID for ATP7B single gene sequencing is R172. Turn around 6 weeks for diagnosis, 2 weeks for familial mutations. Neurology needs adding as a requesting specialty on the web page. ATP7B is also within 10 different exome panels which should lead to increased diagnosis. Publications can be added to the webpages and opportunities for research collaborations. Was due to start 1.4.20 but COVID led to delay, 96% tests ready, awaiting finance sign off. Will be moving to WGS soon. Reminder to refer parents of index cases to confirm compound heterozygosity.

Trientine / NHSE

Paul Selby (Cambridge lead hepatology pharmacist) described the need for Specialist Centres to create pathways for new and existing patients, to ensure access to trientine prescribing by spoke Trusts via the Blueteq system and annual review in the Specialist Centre. NHSE will not do this for you! Cambridge has produced a shared care guideline (SCG) incorporating a pathway algorithm which others may wish to adopt for their

region. With COVID remote reviews have become the norm eg video consultation, which should facilitate the process between hub and spoke.

Actions:

- *PS/BG to feed back to NHSE regarding suggested 'best practice'.*
- *BG will circulate the SCG with the minutes to the SIG.*

AOB

A discussion about COVID and WD - Tom Marjot who published an international registry of COVID in liver disease patients reported that 3 had WD, 1 of whom died. Mary Bythell indicated that PHE could link WD to COVID.

Graeme Alexander has been in discussion with Pharma about and educational video for WD which individuals could contribute to - the SIG welcomed this initiative.

The WDSG website has been updated with a professional makeover.

Slides from speakers will be requested to go up on the BASL website.

Thank you from BG to all who attended today (45 participants at one point which is an excellent number)

Date of next meeting: TBA