UK-PBC Newsletter

IS005 / SEPTEMBER 2017

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Message from Professor Dave Jones

Summer is here and UK-PBC goes from strength to strength. Thanks to everyone for their hard work in recruiting to the cohort and delivering the science that we do. Thanks also to all the patients and patient groups who make this happen.

Following on from the FDA and EMA approval of OCA, we now have NICE approval in the UK (with the application being supported by UK-PBC data). We have just recently had NHS approval, therefore stratified therapy in PBC (the goal of UK-PBC) has reached the clinic in the UK - a major achievement!

The trials programme for ever better disease treatments continues with Gilead, Genfit, Cymabay and Novartis, and all are very active. A real highlight however has been the success of GSK 2330672 (an ileal bile acid uptake inhibitor) for the treatment of pruritus. This study was published in the Lancet and the drug is being taken forward by GSK. None of this would have been possible without the UK-PBC platform. All these advances are incorporated in the EASL PBC Guidelines, the development of which was led by UK-PBC investigators.

In my last update I mentioned the award of European Reference Network status for liver disease, with the network being led by UK-PBC. This is great news for European hepatology and for patients in Europe with rare liver disease, as it will help with dissemination of best practice in treatment across Europe. The network went "live" on 1st April of this year so watch this space.

Finally some news about the future. Working with colleagues from UK-AIH and UK-PSC we have been shortlisted for a new MRC Stratified Medicine programme covering the whole of autoimmune liver disease. In simple terms we want to bring the UK-PBC approach of close working with patients, industry and clinicians across Europe to bear on solving all the remaining problems in AILD. Lets keep our fingers crossed!!

Professor David Jones, Newcastle University

UK-PBC Genetics Study

We are delighted to announce that the UK-PBC Genetics Study recruited its **6000th** participant in July! This is an amazing achievement and reflects the great efforts of all of our collaborators who have been working so hard to identify new potential participants and invite them onto the study.

We have seen an impressive level of recruitment so far this year: over 493 reply slips have been returned to the study office since January and we have already received a completed consent form from 263 of these patients. It takes an average of 3 weeks for a recruitment pack to be returned as a signed consent form so this total is sure to continue to increase.

It has been especially encouraging this year to hear that many of our collaborators are following up invitations which do not result in a reply slip being returned. Sometimes a courtesy call is all that is needed to turn an invitation into a consent so we would encourage everyone to look over their invitations and see whether there is any way we can bring these missing patients into the study. Of course everyone has the right to choose not to participate, but it would be a shame if a patient was to miss out on an opportunity to join the study because of a mislaid reply slip or a simple query about the study that could be easily resolved with a friendly chat.

Whilst it's great to have all these new participants joining the study, the really important task is completing the questionnaires so that we have data to analyse. Happily, great progress continues to be made here too with an amazing 94% of clinician questionnaire events having been completed. To put it another way, this is 16,878 questionnaires worth of data, an incredible number! There are however 1000 questionnaires on the database still awaiting completion. Most collaborating centres only have a couple of questionnaires to complete and so we would ask that everyone makes a concerted effort to spend an hour or so over the next couple of weeks completing the last few questionnaires for their hospital and answering any outstanding queries.

Our most sincere thanks to everyone in our collaborating centres for all of your hard work in helping to make the UK-PBC Genetics Study such a success. If you have any questions relating to recruitment of participants or questionnaires, please contact Steve (spf36@medschl.cam.ac.uk) who will be more than happy to help.

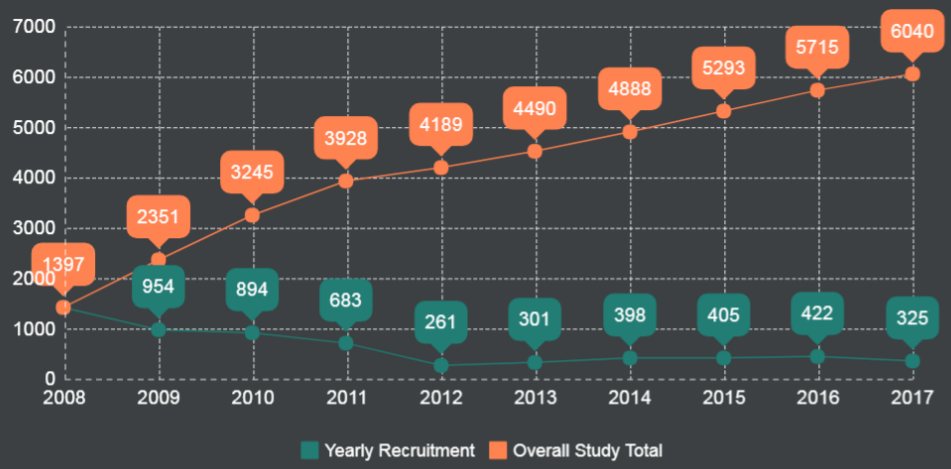
Top 20 Recruiting Sites

Trust	No. Of Participants Recruited	% Questionnaires Complete
University Hospitals Birmingham NHS Foundation Trust	357	86.9
Newcastle upon Tyne Hospitals NHS Foundation Trust	340	93.2
Cambridge University Hospitals NHS Foundation Trust	264	99.5
King's College Hospital NHS Foundation Trust	201	96.4
Leeds Teaching Hospitals NHS Trust	190	96.8
Sheffield Teaching Hospitals NHS Foundation Trust	143	83.2
NHS Lothian	130	94.1
Oxford University Hospitals NHS Trust	129	99.2
Royal Free London NHS Foundation Trust	122	94.0
Nottingham University Hospitals NHS Trust	121	99.2
Hull And East Yorkshire Hospitals NHS Trust	103	98.4
County Durham and Darlington NHS Foundation Trust	93	99.3
North Cumbria University Hospitals NHS Foundation Trust	85	100.0
Plymouth Hospitals NHS Trust	84	99.2
NHS Greater Glasgow and Clyde	83	94.0
Royal Liverpool And Broadgreen University Hospitals NHS Trust	81	97.9
University Hospital Southampton NHS Foundation Trust	81	98.4
York Teaching Hospital NHS Foundation Trust	79	100.0
Derby Hospitals NHS Foundation Trust	77	94.4
City Hospitals Sunderland NHS Foundation Trust	72	99.1

RECRUITMENT

REPORT

RECRUITMENT OVER TIME

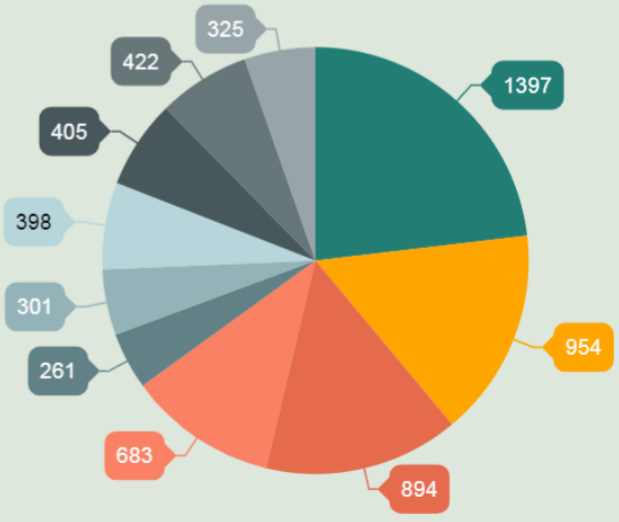


DATA CORRECT ON: 11th August 2017

TOTAL RECRUITMENT

6040

BREAKDOWN BY YEAR



2008 (23.13%) 2009 (15.79%) 2010 (14.80%) 2011 (11.31%)
2012 (4.32%) 2013 (4.98%) 2014 (6.59%) 2015 (6.71%)
2016 (6.99%) 2017 (5.38%)

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The UK-PBC Nested Cohort Study

Recruitment into the UK-PBC Nested Cohort Study is now nearing 400. This rapid increase is due to excellent interest and engagement from participants and hard work by staff, especially Research Nurses.

Thanks to an increase in total recruitment we have recently been granted a 6 month extension to use the remaining Study funding. This is fantastic news and will ensure the potential of the Study is maximised and the best possible quality of research produced.

Over the past year we have increased the number of active research sites from five to eight which has been a significant contributing factor in the recruitment increase. These eight sites are The Freeman Hospital in Newcastle-upon-Tyne, St James's University Hospital in Leeds, The Queen Elizabeth Hospital in Birmingham, Queen's Medical Centre in Nottingham, Norfolk and Norwich University Hospital in Norwich, Addenbrooke's Hospital in Cambridge, Royal Free Hospital in London and St Mary's Hospital also in London.

It is anticipated that recruitment will draw to a close towards Christmas 2017. We will then use the remaining time to conduct the bulk of the sample and statistical analysis. In the meantime, however, we will begin analysis of participant DNA in collaboration with the Sanger Institute in Cambridge. This will allow us to see whether UK-PBC Nested Cohort Study patients also carry the genes indicated as being significant in pre-disposing people to PBC.

Finally, the UK-PBC Nested Cohort Study research team would like to say a big thank you to all of those who have contributed to the Study as staff and participants. For those who would like more information or to discuss their eligibility to participate in the UK-PBC Nested Cohort Study please contact Jonathan Badrock, the Project Manager, on 01223 789088 or jb2069@medschl.cam.ac.uk.

DO YOU HAVE ACCESS TO THE UK-PBC CLINICAL DATABASE?

DO YOU HAVE ACCESS TO THE INVITATION APP?

If not, please contact Steve Flack (spf36@medschl.cam.ac.uk)

Work Strand 2 Update

As part of UK-PBC, we have evaluated fatigue and cognitive impairment in cholestatic liver disease. In vivo experiments modelling cholestatic liver disease have yielded interesting results plus/minus bile acid agonists with bile duct dysfunction massively upregulated with injury. Profiling of bile acids in different tissues by Imperial College London is providing an insight into how cholestasis might affect cognition/fatigue.

Another part of the project involving immunohistochemical staining of a myriad of different markers is nearing completion. Retrospective paraffin-embedded tissue including core biopsies and explants have been organised from different centres including Newcastle, Leeds, Nottingham, Sheffield, Cambridge and Birmingham for analysis. This combined with the transcriptomic profile via the Nanostring™ multi-analyte platform (over 700 mRNA targets) will enable a full cellular profile from archival tissue as well as nested prospective cohort cases.

In terms of in vitro investigations, we have furthered our understanding of biliary epithelium stressors including reactive oxygen species and the unfolded protein response. Multiple stressors have been determined to stimulate secretion of cytokines/chemokines that directly affect migration of immune T cell infiltrate. To understand interactions between stressed epithelium and activated T cells have been modelled in a co-culture system that appears to correlate with what we see in human tissue biopsies.

Work Strand 3 Update

Current trials in PBC

We have successfully been screening the UK-PBC database for a number of clinical trials now, and made great contributions in making trials easier to recruit onto. Interest around this trials platform is growing and we are now getting requests from other pharmaceutical companies to help do the same.

- **Intercept Pharmaceuticals** (https://clinicaltrials.gov/show/NCT02308111)
- **Novartis Pharmaceuticals** (https://clinicaltrials.gov/show/NCT02516605)
- **GlaxoSmithKline; GSK** (https://clinicaltrials.gov/show/NCT02966834)
- **Gilead** (https://clinicaltrials.gov/show/NCT02943447)

CymaBay MBX8025 (Seladelpar)

CymaBay Therapeutics announced positive interim results from its ongoing low-dose Phase 2 study of seladelpar in patients with PBC. A planned interim analysis of the first 24 patients enrolled in these two dose groups demonstrated after 12 weeks of treatment a significant ALP reduction from baseline of 39% and 45% for the 5 mg and 10 mg groups, respectively. On seladelpar, 45% of patients in the 5 mg and 82% of patients in the 10 mg dose groups had ALP values < 1.67 times the upper limit of normal (ULN).

“The data emerging from this study are impressive and support our hypothesis that lower doses of seladelpar than previously studied retain strong efficacy without raising a concern with transaminase elevations. We also see that seladelpar activity is not associated with drug-induced itch, an important benefit for patients with PBC. If these results are maintained over longer periods, we think that seladelpar could offer patients significant advantages over existing treatments,” said Professor Gideon Hirschfield in the CymaBay press release.

You can read the full press release by visiting: http://ir.cymabay.com/press-releases

RUNNING A TRIAL AND NEED HELP IDENTIFYING PBC PATIENTS?

If you are running a trial that is recruiting PBC patient and wish to see if UK-PBC can help identify patients, then please contact the UK-PBC Clinical Trials Project Manager, Zohur Miah, (zohur.miah@uhb.nhs.uk).

PBC Clinical Guidelines Poster Presentation at BSG

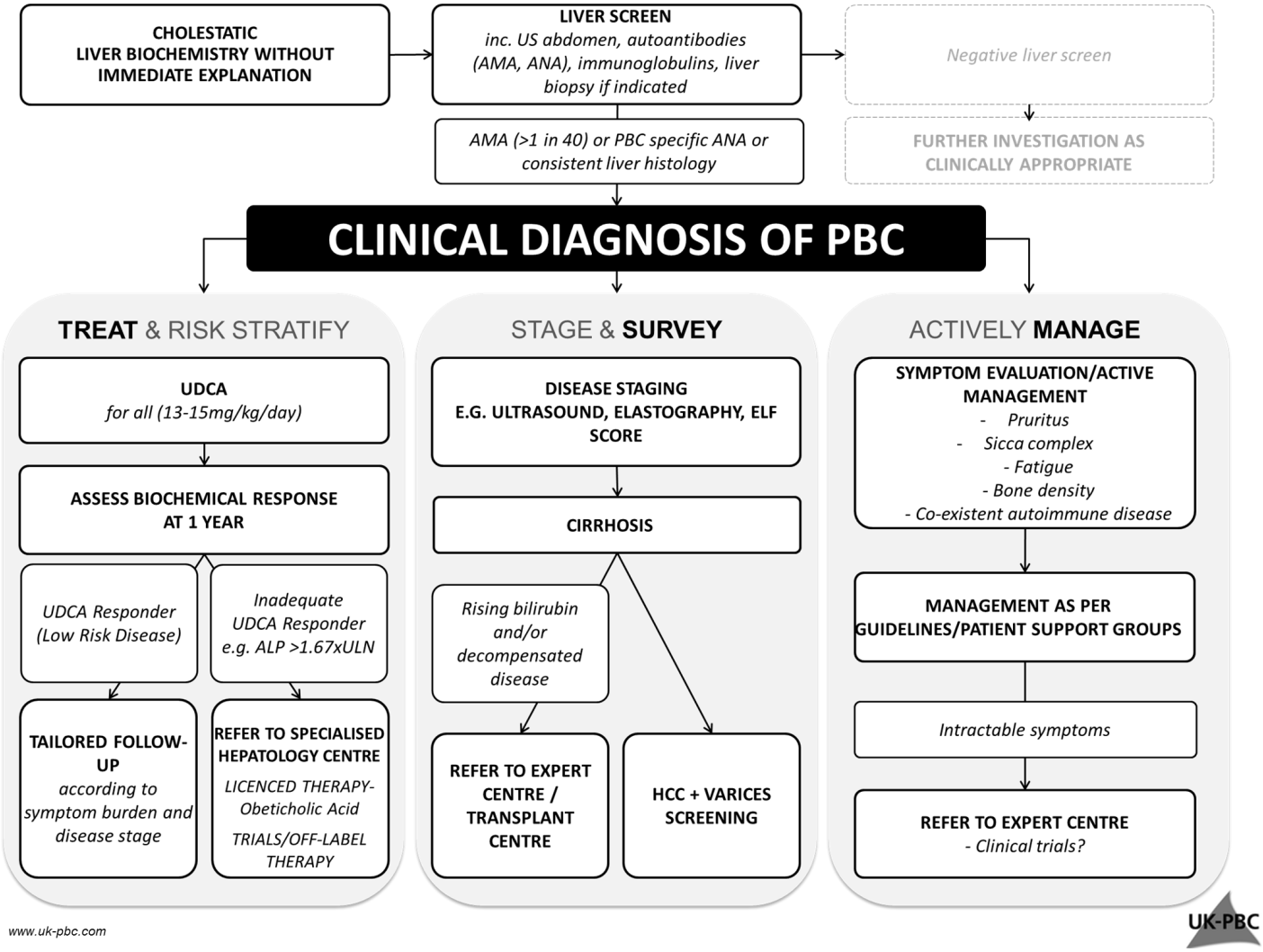
We are still working towards submitting the British Society of Gastroenterology/UK-PBC Clinical Practice Guidelines which we previously mentioned in the last update.

The guidelines, which are predominantly targeted towards those Gastroenterologists and Hepatologists leading the care of patients with PBC, usually in secondary care, but may also be of value to primary care physicians, nurses and even patients, was exhibited at the BSG Annual Meeting 2017, which took place at Manchester Central.

We are now in the final stages and preparing for submission, and hope to have something published on the BSG and UK-PBC website shortly.

The Clinical Care Pathway, which is part of the Clinical Practice Guidelines and is show below, can be accessed from the UK-PBC now by clicking the following link: http://www.uk-pbc.com/resources/tools/care-pathway/

A interactive version of this Care Pathway will be made available on the UK-PBC website shortly after the guidelines have been approved and published.



Publications

EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis

Journal of Hepatology

European Association for the Study of the Liver

These clinical practice guidelines summarise the evidence for the importance of a structured, life-long and individualised, approach to the care of patients with PBC, providing a framework to help clinicians diagnose and effectively manage patients. The full paper can be read here: https://www.ncbi.nlm.nih.gov/pubmed/28427765

Phenotyping and auto-antibody production by liver-infiltrating B cells in primary sclerosing cholangitis and primary biliary cholangitis

Journal of Autoimmunity

Chung BK, Guevel BT, Reynolds GM, Gupta Udatha DB, Henriksen EK, Stamataki Z, Hirschfield GM, Karlsen TH, Liaskou E

Authors compared antibody-secreting B cells (ASCs) in PSC and PBC liver explants to determine if liver-infiltrating ASCs represent an opportune and novel source of disease-relevant auto-antibodies. The full paper can be read here: https://www.ncbi.nlm.nih.gov/pubmed/27784538

Seladelpar (MBX-8025), a selective PPAR-δ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study

The Lancet Gastroenterology & Hepatology

Jones DE, Boudes PF, Swain MG, Bowlus CL, Galambos MR, Bacon BR, Doerffel Y, Gitlin N, Gordon SC, Odin JA, Sheridan D, Wörns MA, Clark V, Corless L, Hartmann H, Jonas ME, Kremer AE, Mells GF, Buggisch P, Freilich BL, Levy, C, Vierling, JM, Bernstein, DE, Hartleb M, Janczewska E, Rochling F, Shah H, Shiffman ML, Smith JH, Choi YJ, Steinberg A, Varga M, Chera H, Martin R, McWherter CA, Hirschfield, GM

Key international PBC experts evaluated the anti-cholestatic effects and safety of seladelpar (MBX-8025) in patients with PBC, who had an inadequate response to ursodeoxycholic acid. The full paper can be read here: http://www.thelancet.com/journals/langas/article/PIIS2468-1253(17)30246-7/fulltext

VISIT THE UK-PBC WEBSITE FOR LATEST PUBLICATIONS:

HTTP://WWW.UK-PBC.COM/RESOURCES/PUBLICATIONS/

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