The United Kingdom Autoimmune Hepatitis Cohort - a multi-centre national platform study for research and translational medicine

AIH is a rare, chronic inflammatory liver disease that can have serious consequences (cirrhosis and liver failure) if left untreated. Its diagnosis and management remain a challenge and patients often need lifelong treatment with high relapse rates on withdrawal of treatment. It affects up to 8,000 people in the UK. Despite well-established therapies, there are some patients who do not respond adequately to therapy or who suffer significant side effects from treatment. Patients with AIH also experience important symptoms, such as fatigue and mood disturbance, which can significantly impair quality of life. The impact on quality of life has not been adequately explored.

These problems have led to the inception of UK-AIH (a multi-centre national cohort study) that is funded by the NIHR Rare Diseases Translational Research Collaboration (RD-TRC) and is coordinated by Newcastle University and Newcastle upon Tyne Hospitals NHS Foundation Trust. It is an exciting unique collaborative project involving doctors, scientists, patients and industry.

The goal of UK-AIH is to understand why some patients with AIH do not respond to current treatments, to help identify better treatments, to demonstrate that those treatments help patients with AIH and ultimately improve clinical care across the UK for people with AIH.

The study began recruitment in March 2014 and has rapidly expanded to include 54 sites to date which are actively recruiting (see Figure 1).

Figure 1: UK Map showing UK-AIH centres (Green pins – recruiting centres)
A total of 1616 patients have been recruited to date (see Figure 2). This is subdivided into four subgroups:

a) Group 1: patients with new diagnosis of AIH recruited pre-treatment

b) Group 2A: complete responders to therapy

c) Group 2B: incomplete responders to therapy

d) Main Cohort: All other patients with clinical diagnosis of AIH that do not fit the inclusion/exclusion criteria for the 3 other subgroups.

The study’s patient-group representatives (Ann Brownlee and Penney Gray) have been actively involved from the beginning of the study and have produced a promotional article to encourage patients to participate in the study.

**Study outputs**

The study has successfully generated the following abstracts:

**Abstract 1:**

**Title:** BAFF is elevated in Autoimmune Hepatitis but does not determine disease phenotype

Reference: Journal of Hepatology 2016; 64(2): S440


Presented at International Liver Congress (ILC) European Association for the Study of Liver Diseases (EASL) meeting (April 2016, Barcelona, Spain).

74 patients’ serum BAFF levels from Group 2 (37 responders and 37 incomplete responders) were compared with 40 healthy controls. The findings showed a statistically significant difference in BAFF levels between the AIH patients and healthy controls. However, there was no significant difference in terms of disease phenotype (i.e. complete and incomplete responders). This may suggest that BAFF has an upstream role in disease aetiology and current treatments does not remove the fundamental
driver of disease. We are hopeful that this work will pave the way for studies of anti-BAFF-targeted therapy in AIH.

Figure 1. BAFF in AIH

Abstract 2:

Title: Understanding the Unmet Need in Autoimmune Hepatitis - the United Kingdom Autoimmune Hepatitis study (UKAIH)*

Reference: Hepatology 2016; 64: Poster Session IV: Abstract 1647: page 815A


(*Presidential Poster of Distinction)

Presented at the American Association for the Study of the Liver (AASLD) meeting Nov 2016, Boston, USA, and the British Association for the Study of Liver (BASL) conference (Sept 2016, Manchester, UK).

Data from 712 prevalent cases was analysed. The UKAIH cohort demonstrates there are some clear areas of unmet need in AIH that require better therapy. Over half of the patients (58%) are receiving steroids, of which 10% need high-dose maintenance steroids to maintain biochemical remission. This is resulting in 1 in 5 patients developing osteoporosis. Importantly, in the preceding year, 25% were not in biochemical remission in the preceding year and 20% required an increase in steroid therapy for a disease flare. The current treatment options are not controlling disease for all patients with over 10% of patients developing cirrhosis despite therapy.

Abstract 3:

Title: UKAIH - Highlighting the need for standardization of treatment in autoimmune hepatitis

Reference: Hepatology 2016; 64: Poster Session IV: Abstract 1663: page 823A

In the 660 patients on long-term therapy, 27 different combinations of treatment were reported. There is great variability and lack of uniformity in the treatment regimens of patients with AIH, reflecting underlying uncertainty regarding optimal treatment regimens. A significant proportion (38%) of patients are not achieving biochemical remission (normal ALT and/or IgG on recruitment) on their current therapy. This demonstrates the need for improved utilization of current treatments and the development of better therapies.

Abstract 4:

**Title:** Understanding the importance of pro- and anti-inflammatory cytokines in autoimmune hepatitis

Reference: Hepatology 2016; 64: Poster Session IV: Abstract 1651: page 817A


This pilot study explored the biological differences between patients in biochemical remission and those in whom AIH disease is poorly controlled in order to identify potential treatment targets. Panels of serum cytokines, chemokines, adhesion molecules and angiogenic factors were assessed in responders (Group 2A), non-responders (Group 2B) and healthy controls using the MSD Human Biomarker Assays V-PLEX panel.

Results were obtained on 116 patients with AIH (50 responders and 66 non-responders) and 30 healthy controls. Following correction for multiple testing, 9 out of 40 molecules were found to have significant inter-group differences (Kruskal-Wallis p<0.00125; 3/19 cytokine, 2/7 angiogenesis, 2/10 chemokine, 2/4 vascular adhesion molecules). For VEGF-D and IL-15, this principally reflected a difference between AIH and healthy controls unrelated to disease activity. Using a post-hoc analysis of responders vs non-responders, 7 markers were significantly different (after correcting for multiple testing) between responders and non-responders with all except VEGF-C and MDC showing elevation in non-responders. In conclusion, we have identified important molecular pathways which are associated with incomplete treatment response that represent plausible targets for second-line therapy. Significant TNF-a elevation was seen in incomplete responders and the potential of anti-TNF therapy should be systematically explored in AIH.

Abstract 5:

**Title:** Balance between exhausted regulatory T cells and CD161+ NK cells is crucial in acute AIH pathogenesis


Autoimmune hepatitis (AIH) immunopathogenesis is poorly understood especially in the treatment naïve stage. This has limited our ability to develop specific therapies. NK cells, key regulators of innate immunity, are abundant in the liver. We sought to characterize, for the first time, the role of NK cell dysregulation in acute AIH. **Method:** Flow cytometric peripheral blood immune subset profiles of a unique cohort of 14 treatment naïve Type 1 AIH patients from the UK-AIH consortium were investigated prospectively. Patients, all of whom met standard diagnostic criteria, were followed longitudinally from pre-treatment to 4 months. Immunohistochemistry staining of pre-treatment liver biopsies was performed for a subset. Cytokines in liver tissue were measured. **Results:** The frequencies of CD3negCD56+NKdim (median 18.3% vs. 6.4%; [p<0.05 Wilcoxon test]) and CD3negCD56+NKbright cells (2.23% vs. 0.5%; [p<0.05]) were significantly elevated pre-treatment compared with follow-up. Likewise, Treg were enriched pre-treatment (10.8% vs. 8.3%; [p=0.02]) and expressed an exhausted phenotype with significantly higher programmed cell death protein 1 (PD1) expression (45.5 vs. 43.1; [p<0.05]). The B cell frequency was lower in the treatment naïve state (22% vs. 31%), whereas there was no difference in the frequency of CD8 cells (40% vs. 36.6%). The expression levels of liver homing chemokine receptor CXCR3 were higher on circulating Treg (196 vs. 123; [p=0.08]) and NKdim cells (49.5 vs. 41.9; [p=0.2]) from pre-treatment and expression of the CXCR3 ligand, CXCL10, was observed on inflamed sinusoids. Interestingly, significantly higher levels of CD161 expression were noted on Treg (125.5 vs. 97.7; [p<0.05]) and NKdim population (308 vs. 223; [p<0.05]) pre-treatment, which declined at the follow-up. CD161 ligand, Lectin like transcript (LLT-1), expression was observed on the intrahepatic immune cells in pre-treatment liver biopsies. Additionally, Treg expressed a higher level of IL6 receptor (66.5 vs. 55; [p<0.05]) in the steroid naïve state compared to follow-up and significantly higher levels of the IL-6 cytokine were observed in supernatants of inflamed livers compared to normal livers (p<0.05). **Conclusion:** We demonstrated significant changes in the frequency and phenotype of innate NK cells and regulatory T cells in untreated acute AIH suggesting they may play a role in the underlying pathogenetic mechanism.

**Abstract 6:**

**Title:** Autoimmune Hepatitis patients with poor treatment response have a distinct liver transcriptome: implications for personalised therapy


Presented at the EASL meeting (April 2017, Amsterdam, Netherlands).


“Responders” and “non-responders” were identified using the UK-AIH platform and their pre-treatment, diagnostic liver biopsies retrieved. RNA was isolated from formalin-fixed paraffin-embedded biopsy curls and quantified. Transcriptomic analysis was performed using the Nanostring nCounter platform. 6 “responders” and 7 “non-responders” were included. In “non-responders”, 18 genes were significantly upregulated, as compared to “responders”, including chemokine and interleukin genes (p<0.05; fold change>1.5). 20 genes were, in contrast, significantly upregulated in “responders”, including several members of the complement family (p<0.05). Principle component analysis (PCA) demonstrated distinct and statistically significant clustering of the top 27 genes in the 2 groups suggesting significant transcriptional signatures associated with future response to therapy.
Conclusions: AIH patients who go on to respond and not respond to standard treatment have distinct and consistent molecular signatures in their liver tissue prior to therapy. This finding, if confirmed, will help us understand treatment non-response in AIH and develop more effective treatments. Furthermore, a clinical tool/companion diagnostic that enables identification of high risk patients at disease onset potentially opens the way to stratified therapy in this challenging disease.

Abstract 7:
Title: Exploring the Impact of Autoimmune Hepatitis on Health-Related Quality of Life*

Reference: To be confirmed.

Presented at the BASL conference (Sept 2017, Coventry, UK) and will be presented at the AASLD meeting (Oct 2017, Washington DC, USA).

(*Presidential Poster of Distinction)


We explored the impact of AIH on the HRQOL of 990 patients (39 hospitals) using the EQSDSL HRQOL tool [The EuroQol Group, 1990] and compared this to UK population norms (after mapping to EQSDSL index values using the crosswalk calculator). Our data shows evidence of HRQOL impairment in a large cohort of AIH patients compared to the general population. Furthermore, corticosteroid use is associated with decreased HRQoL, independent of remission status. This highlights the need for better corticosteroid-free therapy approaches and heralds future novel therapeutic trials in AIH.

Ongoing research projects

1. Nanostring Transcriptomics

2. Histology Review (central review by 2 lead pathologists for UK-AIH: Dina Tiniakos [Newcastle] and Stefan Hubscher [Birmingham])

3. Research projects in development include:
   - Gene expression analysis (in collaboration with Alberto Sanchez King’s College Hospital, London)
   - Genetics (collaboration with UK-PBC)
   - Proteomics

Appreciation

We are indebted to all our patient participants and collaborators involved in the UK-AIH study and want to thank them for their hard work and ongoing support.