UK-AIH Update

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Aims

- Evaluate current treatment practice and outcomes
- Determine the unmet needs of patients
- Develop and implement improved treatment approaches
- Create platform for recruitment to future trials

UK-AIH Mark 1

- Funded by NIHR RD-TRC
- 56 sites
- Group 1
  - People with suspected AIH
  - Recruited pre-treatment and ideally pre-biopsy
- Group 2A – complete responders to therapy
- Group 2B - non-responders to therapy
- Main cohort – everyone else (inc overlap syndromes)

Group 1 (n ~ 120)

- Baseline data and samples:
  - Liver tissue
  - Serum, EDTA and Tempus RNA
  - PBMCs at baseline (& 4 and 12 months post-treatment following amendment)
  - Questionnaires: QoL, fatigue, cognitive symptoms, anxiety, depression and adherence
- Follow-up data and blood samples during treatment
  - 2 weeks, 4 weeks, 4 months, 8 months and 12 months
- Annual clinical update from treating clinician
  - Biochemical response, complications and treatment
- Consent to “call back” for future studies

UK-AIH Mark 2

- Funded by LIVErNorth (national patient support group)

- Removed groups 2A and 2B
  - everyone apart from new diagnoses in main cohort

- Data collection using NHS Digital and Patient View
  - To observe for clinical end points as ongoing prospective cohort study
  - Existing cohort reconsented

Main cohort (n~2300)

- Data collected at point of study entry
  - Demographics
  - Biochemical status and immunology (at diagnosis and now)
  - Treatment regimen
  - Serum, EDTA and Tempus RNA
  - Digitised histology slides

- NHS Digital and Patient View

- Consent to “call back” for future studies

UK-AIH Mark 3

- Changes due to
  - Lack of funding
  - COVID pressures on research activity

- Funded by LIVErNorth

- Building national cohort of adult AIH patients
  - Newcastle as research centre and other units as PIC sites
  - REDCAP
  - Option for completely electronic process
    - Expression of interest, consent, single page CDF

Outputs

Impact of AIH and its treatment on health utility

- 990 participants
- Validated HRQOL tools inc EQ-5D-5L
  - compared with UK population norms and PBC controls
- HRQOL significantly impaired in AIH
- Steroids significantly associated with impaired HRQOL even after controlling remission status

HEPATOLOGY

AASLD

HEPATOLOGY, VOL. 68, NO. 4, 2018

AUTOIMMUNE, CHOLESTATIC AND BILIARY DISEASE

The Impact of Autoimmune Hepatitis and Its Treatment on Health Utility

Lin Lee Wong,[1,2*] Holly F Fisher,[3*] Deborah D Stocken,[4] Stephen Rice,[3] Amardeep Khanna,[1,2] Michael A Heneghan,[5] Ye Htun Oo,[6] George Mells,[7] Stuart Kendrick,[8] Jessica Katharine Dyson,[1,2**] and David E. J. Jones[1**]

UK-AIH

Inequity of care provision and outcome disparity

- N = 1249
- 635 cared for in transplant units and 614 under non-transplant centres
- Key findings
  - 29 treatment regimens were reported
  - 55% have ongoing corticosteroids
  - 59% biochemical remission rate
- Remission rates higher in transplant centres (62 vs 55%, P = 0.028)
- ≤20 yrs at diagnosis more likely to become cirrhotic

UK-AIH

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WILEY APT Alimentary Pharmacology & Therapeutics

Inequity of care provision and outcome disparity in autoimmune hepatitis in the United Kingdom

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European multicenter validation of autoantibodies against huntingtin-interacting protein 1-related protein for the diagnosis of autoimmune hepatitis in adults

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1 INTRODUCTION

Autoantibodies are major components for the diagnosis of autoimmune hepatitis (AIH). Currently, common auto-antibody testing is hampered by lack of either high specificity or sensitivity. We discovered antibodies against huntingtin-interacting protein 1-related protein (HIP1R) in AIH single center cohorts with a better specificity and overall accuracy compared to antinuclear antibodies (ANA)[1]. We now validated anti-HIP1R antibody testing in a large European multicenter AIH cohort.

2 AIM

The aim was to validate the diagnostic performance of our anti-HIP1R assay to distinguish between AIH and non-AIH-liver disease (non-AIH-LD) in an international multicenter cohort.

3 METHOD

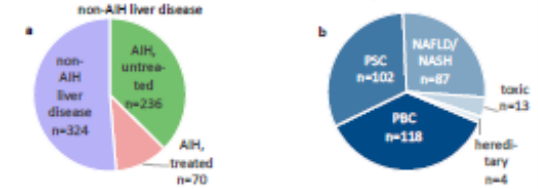
IgG antibodies against HIP1R were measured via ELISA in cryo-conserved serum samples. Anti-HIP1R antibody concentrations were measured semi-quantitatively (arbitrary units) and normalized to a set of 5 reference sera/plasma with very low/ low/ medium/ high/ very high optical densities in the ELISA. Intercenter variability was compensated by normalization to the center background of treated AIH and non-AIH-LD. Statistical analysis was performed using SPSS Statistics (Version 25, IBM). Graphs were designed using Graph Pad Prism 6 and Microsoft Power Point (Version 16.23).
Sensitivities and specificities were compared with the McNemar test within those patients with AIH or those with non-AIH liver diseases.

4 RESULTS

Table 1: Patient characteristics

	AIH, untreated	AIH, treated	non-AIH liver disease
female gender	72.9 %	74.3 %	55.8 %
median age [yrs] (range)	53 (18 - 87) n = 236	55 (19 - 83) n = 70	51 (22 - 76) n = 321
median ALT [x ULN] (range)	7.0 (0.3 - 61.5) n = 187	0.8 (0.1 – 24.7) n = 57	1.0 (0.2 – 57.1) n = 289
median IgG [x ULN] (range)	1.4 (0.5 - 4.8) n = 180	0.9 (0.4 – 10.2) n = 57	0.8 (0.2 – 2.4) n = 141

Figure 1: a) Distribution of samples in european multicenter cohort
b) Ethiologies and distribution of liver disease in the group of non-AIH liver disease



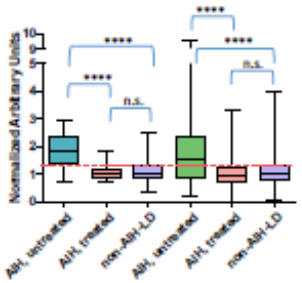


Figure 2: Concentrations of anti-HIP1R antibodies in untreated AIH compared to treated AIH and non-AIH liver disease; Single Center training cohort is shown as reference to original data (published at ILC 2018 before[1]). Statistical analysis was performed using one-way ANOVA with Tukey's test. **** equals p < 0.0001, n.s. = not significant.

Figure 3: Comparison of anti-HIP1R concentrations of untreated AIH samples of participating centers

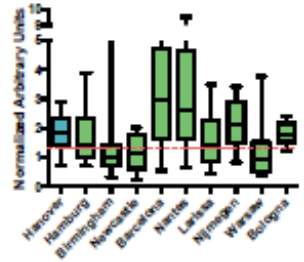


Figure 4: Concentrations of anti-HIP1R in different non-AIH liver diseases compared to untreated AIH (european multicenter cohort)

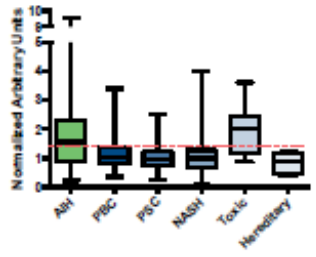
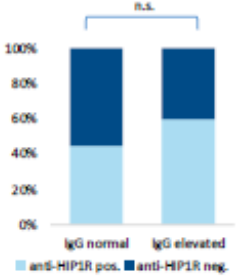


Table 2: Statistical analysis of anti-HIP1R compared to ANA, SMA and a combined marker of either ANA and/or SMA and/or anti-HIP1R in european multicenter cohort; significance compared to anti-HIP1R antibodies; *** equals p < 0.001 (McNemar Test)

	anti-HIP1R	ANA	SMA	ANA+/SMA+/ HIP1R
sensitivity	57.2 % (CI: 50.6 – 63.6 %)	72.9 %*** (CI: 66.7 – 78.5 %)	66.9 % (CI: 60.6 – 72.9 %)	97 %*** (CI: 94.0 – 98.8 %)
specificity	77.5 % (CI: 72.5 – 81.9 %)	59.0 %*** (CI: 53.4 – 64.4 %)	72.8 % (CI: 67.7 – 77.1 %)	36.4 %*** (CI: 31.2 – 41.9 %)
accuracy	68.9 % (CI: 64.9 – 72.7 %)	64.8 % (CI: 60.7 – 68.8 %)	70.4 % (CI: 66.4 – 77.1 %)	62.0 % (CI: 57.8 – 62.0 %)

Figure 5: Sensitivity of anti-HIP1R antibodies in AIH with diagnostic and non-diagnostic conventionell autoantibodies

Figure 6: Sensitivity of anti-HIP1R antibodies in AIH with normal IgG compared to elevated IgG



5 CONCLUSIONS

- We could validate the higher specificity of the anti-HIP1R assay to diagnose AIH compared to ANA. The higher specificity compared to SMA and higher overall accuracy of anti-HIP1R compared to ANA and SMA, as found in our single center cohort, could not be validated in this retrospective multicenter cohort.
- Anti-HIP1R can serve as additional non-invasive marker in diagnosing AIH
- Anti-HIP1R is easier, faster and cheaper to determine while being less observer dependent using ELISA and clearly defined cut-off values than conventional immunofluorecent staining
- Detection of anti-HIP1R antibodies can help to improve the diagnostic work up of liver diseases, when conventional autoantibodies are not elevated to diagnostic levels

6 ACKNOWLEDGEMENTS

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7 REFERENCES

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ORIGINAL ARTICLE

Quantification of polyreactive immunoglobulin G facilitates the diagnosis of autoimmune hepatitis

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- Promising marker to improve diagnostic workup
- Higher specificity for AIH compared to conventional autoantibodies

UK-AIH

B-cell activating factor is elevated in Autoimmune Hepatitis but does not determine disease phenotype

On behalf of the UK-AIH Consortium

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EASL The Home of Hepatology
THE INTERNATIONAL LIVER CONGRESS™ 2016
APRIL 13-17, BARCELONA, SPAIN

Newcastle University

Rare Diseases Translational Research Collaboration
NHS National Institute for Health Research

UK-AIH

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

BACKGROUND

Autoimmune hepatitis (AIH) is an inflammatory liver disease with a prevalence of approximately 17 per 100,000 population in Northern Europe.[1] Despite well-established evidence-based therapies, unmet need persists in AIH with some patients having inadequate response to therapy and significant treatment side-effects.

The United Kingdom AIH Cohort (UK-AIH) was established in 2014 with the aim of understanding the mechanistic basis of AIH and providing a platform for therapeutic advance. [2] Study entry is open to all patients under secondary medical care with a clinical diagnosis of AIH.

B-cell activating factor (BAFF), a member of the tumour necrosis factor (TNF) superfamily, has previously been shown to be elevated in patients with AIH compared with healthy subjects and those with acute hepatitis or chronic hepatitis C. Corticosteroid treatment was shown to result in marked reduction in serum BAFF levels in AIH patients.[3]

OBJECTIVES

The aim of this work was to assess the role of BAFF in disease phenotype and whether it may be an avenue for therapeutic development.

MATERIALS & METHODS

UK-AIH includes a subset of prevalent patients, who have been diagnosed and treated for AIH for at least 12 months.

Serum BAFF was tested using a Human BAFF Quantikine™ ELISA system (R&D Systems). Statistics were performed using Graphpad Prism and unpaired t-tests and one-way ANOVA testing as appropriate.

RESULTS

AIH patients were stratified into 2 groups:

1. "Responders" – complete responders to therapy as defined by biochemical response (normal ALT and IgG) who are not requiring steroid treatment although can be on other immunosuppression
2. "Non-responders" - incomplete responders to therapy as defined by abnormal biochemistry despite treatment or requiring high dose steroids (≥ prednisolone 10mg or budesonide 6mg) to achieve normal results

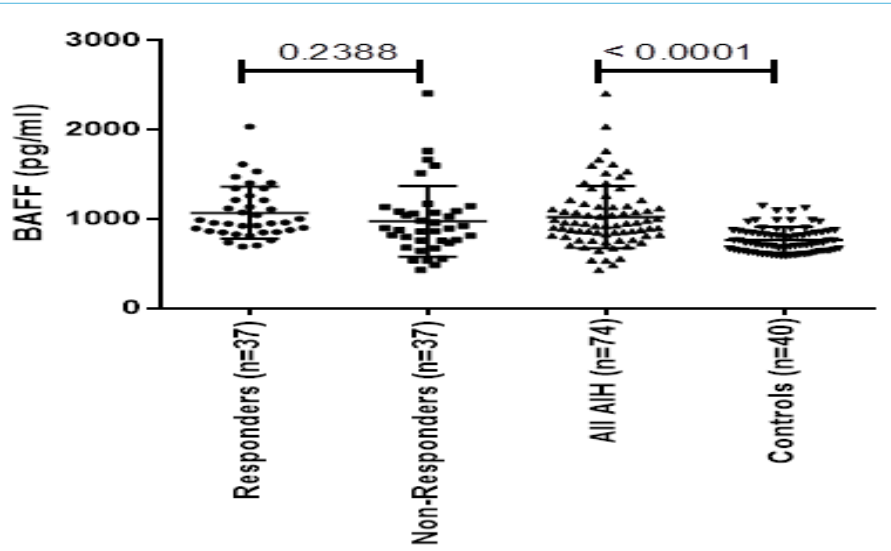
Results were obtained on 74 patients with AIH (37 responders and 37 non-responders to treatment) and 40 healthy controls. The healthy controls were were gender- and age-matched (p=0.3818) to the AIH patient cohort.

There was a statistically significant difference in BAFF levels between the overall cohort of AIH patients (1022 ± 40.66pg/ml) and healthy controls (766.8 ± 16.71) [p<0.0001].

However, there was no significant difference in terms of disease phenotype:

- 1070 ± 47.99 in responders
- 973.5 ± 65.36 in non-responders
- p=0.2388

There was also no statistically significant difference between BAFF levels between the overall AIH cohort and the sub-groups as defined by treatment response (p=0.4966).



SUMMARY

Serum BAFF levels are elevated in patients with autoimmune hepatitis (AIH) as compared to healthy controls.

However, there does not appear to be a significant difference in serum BAFF levels between groups of AIH patients according to their response to treatment (complete or incomplete biochemical response).

CONCLUSIONS

Elevated serum BAFF is clearly a feature of AIH. It appears that steroids/current immunosuppressants (eg azathioprine) control the downstream inflammatory consequences of AIH but do not change the fundamental biology of the disease. This may explain why patients remain at risk of disease flares.

BAFF may have an upstream role in disease pathogenesis. We therefore need therapies that address the underlying mechanism (ie B-cell therapies). The role of BAFF requires further investigation and work is ongoing using the UK-AIH cohort to examine serum BAFF in new diagnosis, treatment-naïve patients with AIH.

REFERENCES

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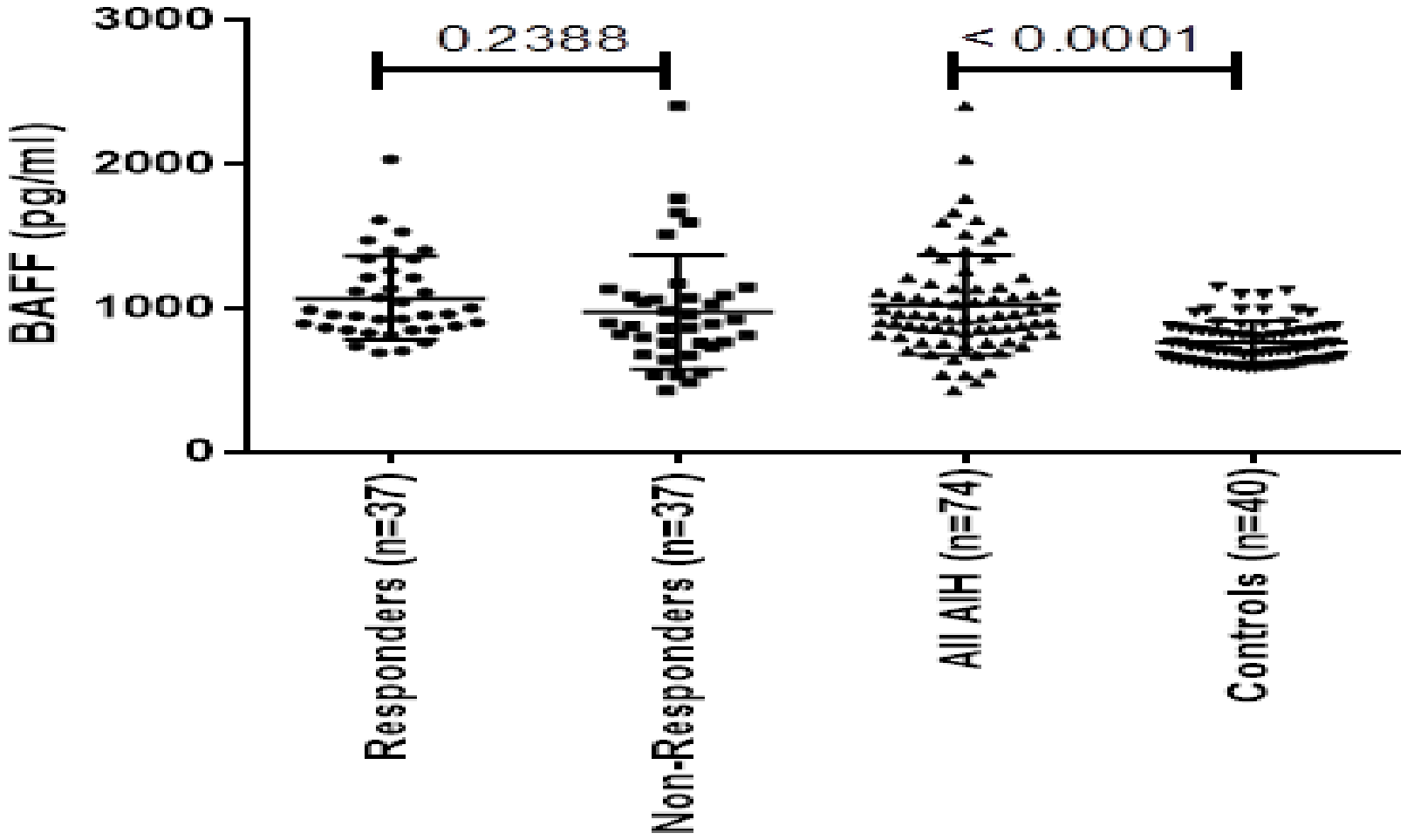
[2] http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=17556

[3] Migita et al. Elevated serum BAFF levels in patients with autoimmune hepatitis. Human immunology 2007; 68.7: 586-591

B-cell activating factor elevated in AIH but does not determine disease phenotype

- EASL abstract



UK-AIH

Utility of azathioprine metabolites in AIH

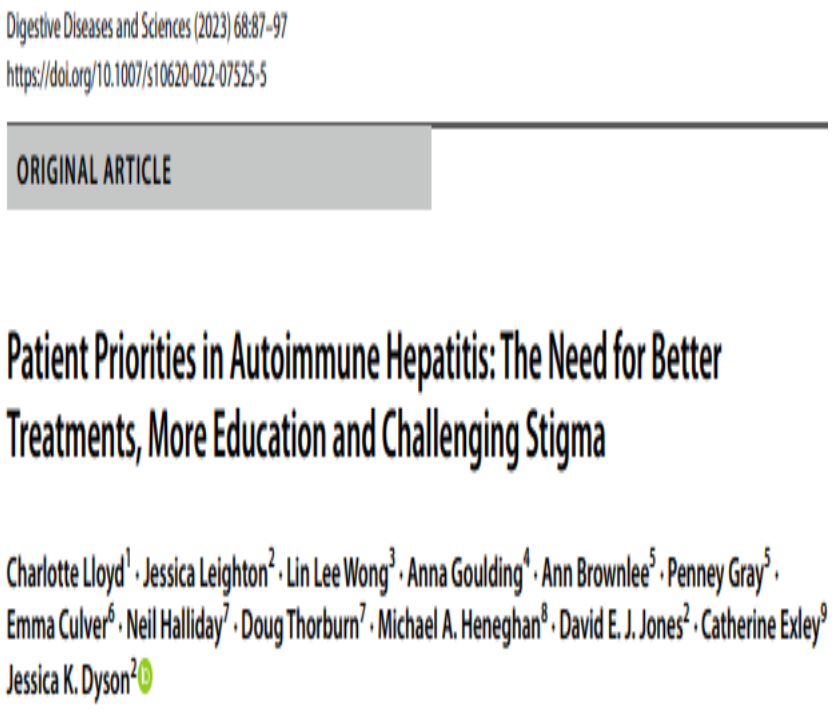
- Pilot study
  - measure levels of dTG in DNA of AZA-treated AIH using novel LC-MS/MS technique
  - ? correlate with clinical response

- 28 Group 2A and 30 Group 2B
  - average ratio of dTGDNA:dA - group 2A 97.5 vs group 2B 81.8 ($P>0.05$)
  - normal vs abnormal ALT ($P>0.05$)

- No correlation between levels of dTG in DNA with disease-response or azathioprine dosage
- Submitted for publication

Patient priorities in AIH

- Anonymised patient survey – 270 responses
  - Led by Charlotte Lloyd (MRes), input from AIH Support/LIVErNorth
- Identified:
  - lack of support networks
  - need for patient empowerment
  - ongoing stigma
  - willingness to participate in trials
- Patients want:
  - better therapies to slow disease progression
  - to avoid steroids and minimise side-effects


Digestive Diseases and Sciences (2023) 68:87–97
https://doi.org/10.1007/s10620-022-07525-5

ORIGINAL ARTICLE

Patient Priorities in Autoimmune Hepatitis: The Need for Better Treatments, More Education and Challenging Stigma

Charlotte Lloyd[1] · Jessica Leighton[2] · Lin Lee Wong[3] · Anna Goulding[4] · Ann Brownlee[5] · Penney Gray[5] · Emma Culver[6] · Neil Halliday[7] · Doug Thorburn[7] · Michael A. Heneghan[8] · David E. J. Jones[2] · Catherine Exley[9] · Jessica K. Dyson[2]

Ongoing projects/collaborations

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

Ben Millar1, Lin Lee Wong2,3, Kile Green1, Anastasia Resteu1, Stuart Kendrick4, David EJ Jones2,3, Jessica K Dyson2,3, on behalf of the UK-AIH Consortium
1 Newcastle University, UK 2 NIHR Biomedical Resource Centre, Newcastle, 3 Liver Unit, Freeman Hospital, UK 4 GlaxoSmithKline (GSK), Research & Development, UK

ACKNOWLEDGEMENTS - We would like to thank all members of the UK-AIH consortium

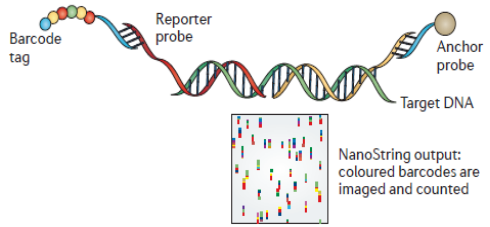
INTRODUCTION

Autoimmune hepatitis (AIH) is a heterogeneous, chronic inflammatory liver disease which can progress rapidly to cirrhosis if under-treated. Data from UK-AIH (a nationwide multi-centre study of over 1000 patients) highlights significant unmet therapy need, including 40% of patients not achieving biochemical remission and 13% developing cirrhosis despite therapy.

UK-AIH includes a subset of prevalent patients, who have been diagnosed/treated for at least 1 year, divided into "responders" with complete biochemical response without long term steroids and "non-responders" with abnormal biochemistry despite treatment or high dose steroids being required to achieve normal biochemistry.

METHODS

- "Responder" and "non-responder" patients from the Newcastle cohort were identified using the UK-AIH platform and their pre-treatment, diagnostic biopsies retrieved.
- RNA was isolated from formalin-fixed paraffin-embedded (FFPE) biopsy curls (2 x 10 microns) using the AllPrep FFPE RNA extraction (Qiagen, UK)
- Transcriptomic analysis was performed using Nanostring nCounter platform analyzing 770 gene targets in a PanCancer Immune profiling panel with statistics performed using R software for multivariate analysis.



Goodwin et al. (2016) Nature Reviews Genetics

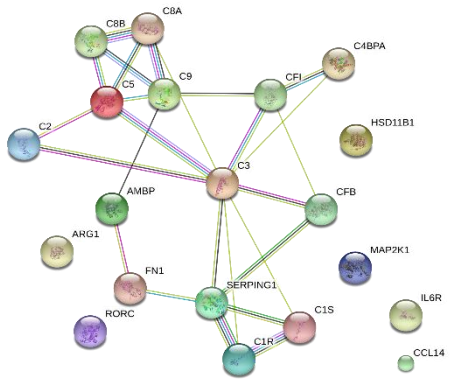


Figure 3: Network of 20 genes differentially upregulated in responders (Group 2A) compared to non-responders (Group 2B). Responders demonstrate increased expression of complement-associated genes (depicted by the above node network using String online software). All genes above were selected for significance ($p<0.05$) and a fold change of at least 1.5

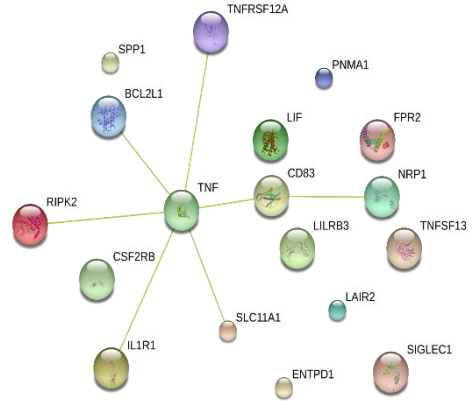


Figure 4: Network of 18 genes differentially upregulated in non-responders (Group 2B) compared to responders (Group 2A). Non-responders demonstrate increased expression of chemokine and interleukin genes (depicted by the above node network using String online software). All genes above were selected for significance ($p<0.05$) and a fold change of at least 1.5

AIMS

The aim of this feasibility study was to examine if pre-treatment diagnostic liver biopsies can be used to identify high-risk patients at disease outset, improve our mechanistic understanding of incomplete therapy response and point the way to future stratified therapy.

RESULTS

6 "responders" (median age 67 years, range 40-75) and 7 "non-responders" (median 54 years, range 22-69) were included. All biopsies were taken pre-treatment.

Principle component analysis (PCA) of all 770 genes demonstrated overlap between "responders" and "non-responders" (Figure 1).

However, PCA demonstrated distinct and statistically significant clustering of the top 27 genes in the 2 groups suggesting significant transcriptional signatures associated with future response and non-response to therapy (Figure 2).

In "responders", 20 genes were significantly upregulated (Figure 3), including several members of the complement family ($p<0.05$).

In the "non-responders", 18 genes were significantly upregulated (Figure 4), including chemokine and interleukin genes ($p<0.05$; fold change>1.5).

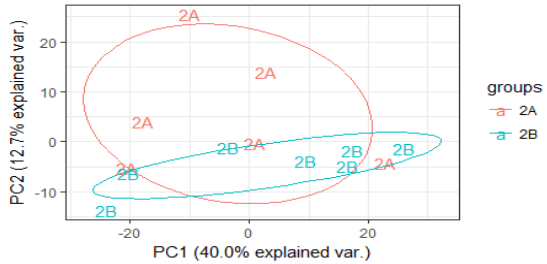


Figure 1: Principal component analysis (PCA) of all 770 genes in immune profiling panel in responders (Group 2A) and non-responders (Group 2B). Multivariate analysis of all genes shows overlap between these patient groups with R programming software

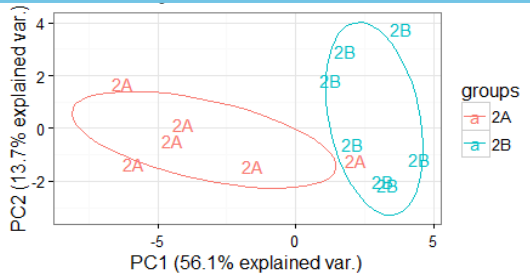


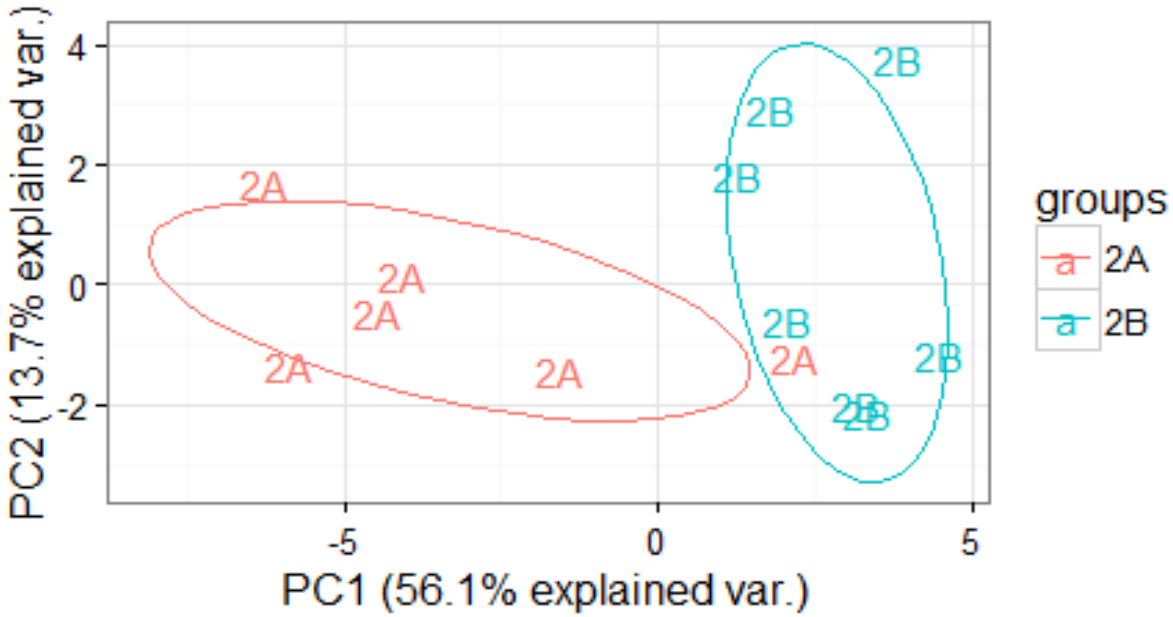
Figure 2: PCA of the top 27 genes in immune profiling panel in responders (Group 2A) and non-responders (Group 2B). Multivariate analysis of all genes shows distinct molecular signatures in the 2 patient groups.

CONCLUSIONS

AIH patients who go on to respond or 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 to understand the mechanism of non-response and develop more effective treatments. A clinical tool/companion diagnostic that allows us to identify high risk patients at disease onset potentially opens up the way to stratified therapy in this challenging disease.

Poor treatment response has distinct pre-treatment liver transcriptome

- RNA isolated from FFPE diagnostic biopsy curls
- Nanostring nCounter platform analyzing 770 gene targets
- 6 “responders” and 7 “non-responders”
- Distinct molecular signatures in the 2 groups



Collaboration with Norfolk and Norwich/Imperial

- Can nanostring transcriptomics from pre-treatment diagnostic liver biopsies can be used to identify high-risk patients at diagnosis

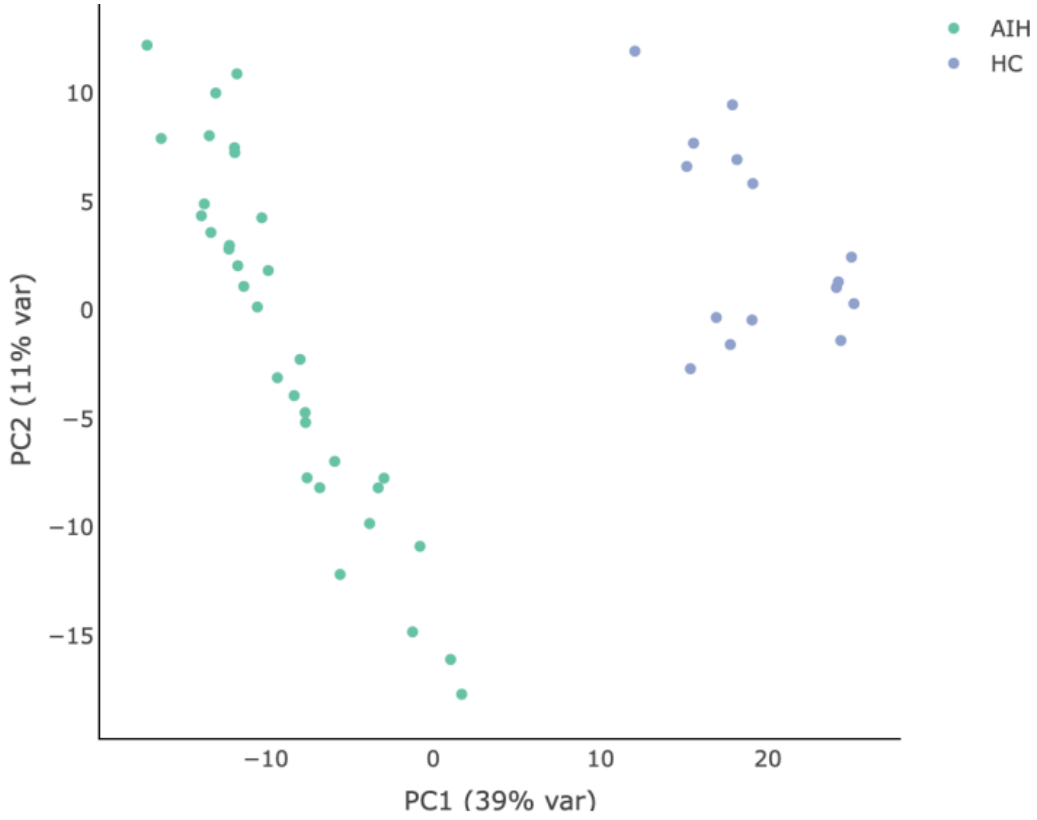
- Low risk (LR) - ALL of:
  - ALT/IgG normal
  - no steroids/flares/progression to cirrhosis
  - aza or MMF/MA only

- High risk (HR) - ANY or ALL of:
  - prednisolone >5mg or budesonide >3mg daily
  - flares/progression to cirrhosis/transplant
  - abnormal ALT and/or IgG
  - on tacro or other immune suppression

UK-AIH

Preliminary findings (courtesy of John Thomas)

- Identified genes that distinguish AIH vs HCs
- Less accurate high vs low/intermediate risk
- Few DEGs in biopsies overlapped with peripheral blood DEGs
- Larger cohort under development



UK-AIH

Using cohort to aid trial recruitment

- Pre-screening for Novartis AMBER/VAY trial
- 114 potential participants identified
- UK-AIH centres asked to pre-screen
- Potential participants approached & referred to trial centre

Novartis proteomics

- Identify biomarkers to aid disease classification and predict outcome

- Identify protein markers in serum that predict:
  - AIH vs healthy controls
  - presence of individual histological hallmark criteria
  - disease progression and unfavourable clinical endpoints

- Using treatment naïve group 1 patients with longitudinal data and prevalent patients

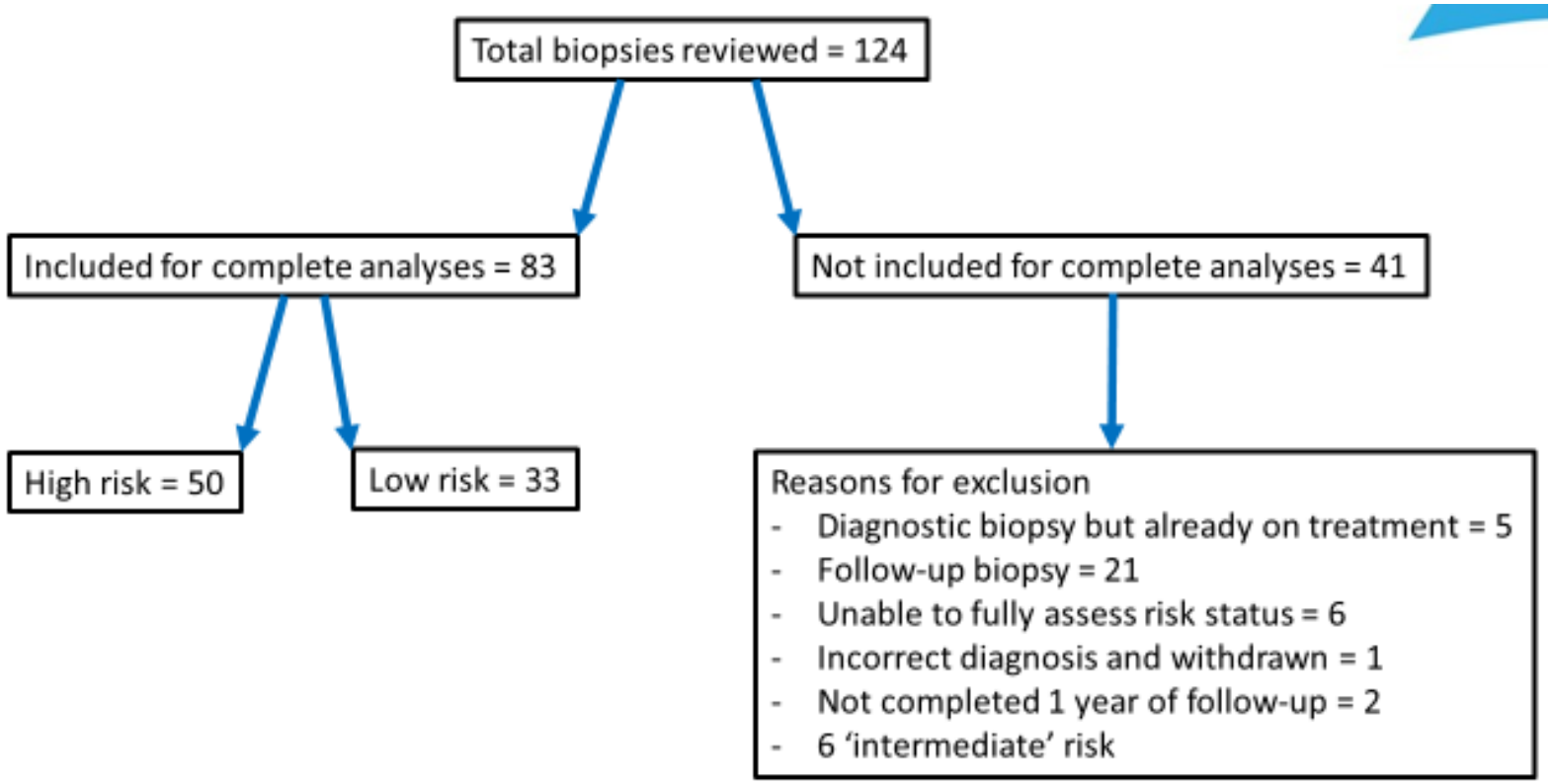
- Healthy controls provided by JKD

Role of serum/tissue IgG4 in predicting disease severity and treatment response in AIH

- Led by Emma Culver
- IgG4 antibodies often associated with a more severe and aggressive phenotype
- Project:
  - measure IgG subclasses and IgE in serum
  - detect cytokines driving class-switch to IgG4 and promoting fibrosis
  - examine liver specimens to document morphology and immunostain for IgG subclasses
  - correlate findings with clinical parameters
- Samples/data provided

Histology assessment

- All diagnostic, pre-treatment liver biopsies
- ‘Low’ versus ‘high’
- Central reporting by Stefan Hubscher and Dina Tiniakos



Histology preliminary findings

- Not significant
  - Interface hepatitis, p=0.171
  - Confluent necrosis, p=0.376
  - Necroinflammatory foci, p=0.819
  - Portal inflammation, p=0.377
  - Advanced fibrosis, p=0.631

- mHAI - Minimal/mild versus moderate/severe, p=0.031

  i.e. higher mHAI significantly associated with high risk disease

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

On behalf of the UK-AIH Consortium

J Dyson[1,2], J Palmer[3], LL Wong[3], S Kendrick[4], D Jones[1,3]

[1] Liver Unit, Freeman Hospital, [2] NIHR Newcastle Biomedical Research Centre, [3] Institute of Cellular Medicine, Newcastle University, [4] GSK Research & Development

INTRODUCTION

There have been few therapeutic advances in autoimmune hepatitis (AIH) for decades. The United Kingdom AIH (UK-AIH) Cohort aims to understand the mechanistic basis of risk in AIH and explore novel therapeutic approaches. This pilot study explored the biological differences between patients in biochemical remission and those in whom disease is poorly controlled in order to identify potential treatment targets.

METHODS

UK-AIH includes a subset of prevalent patients, who have been diagnosed and treated for at least 12 months, divided into 2 groups:

1. "Responders" - complete biochemical response (normal ALT and IgG) and not requiring steroids
2. "Non-responders" - abnormal biochemistry despite treatment or requiring high dose steroids to achieve normal biochemistry

Panels of serum cytokines, chemokines, vascular adhesion molecules and angiogenic factors were assessed in responders, non-responders and healthy controls using the MSD Human Biomarker Assays V-PLEX panel.

RESULTS

Results were obtained on 30 healthy controls and 116 patients with AIH:

- 50 responders
- 66 non-responders

Following correction for multiple testing:

- 9 of 40 molecules were found to have significant inter-group differences
  Kruskal-Wallis $p<0.00125$
- 3/19 cytokines
- 2/7 angiogenesis factors
- 2/10 chemokines
- 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
- All except VEGF-C and MDC showed elevation in non-responders.

TABLE 1. MARKERS SHOWING SIGNIFICANT DIFFERENCE BETWEEN TREATMENT RESPONDRS AND NON-RESPONDERS

Parameter (pg/mL)	Control, median [range]	Responder, median [range]	Non-Responder, median [range]	Responder vs Non-Responder Corrected p value
CYTOKINES				
Interleukin 10 (IL-10)	0.29 [0.05-1.21]	0.54 [0.17-8.46]	1.06 [0.25-5.53]	<0.0001
Tumour necrosis factor α (TNF-α)	1.84 [0.83-3.96]	2.42 [1.43-5.15]	2.93 [1.32-88.9]	0.0085
CHEMOKINES				
Interferon-γ inducible protein 10 (IP-10)	159.0 [48.1-356.0]	212.0 [94.5-1039.0]	317.9 [53.2-2212.0]	0.0013
Macrophage derived chemokine (MDC)	1400.0 [865.8-3809.0]	1391.0 [706.1-2618.0]	1087.0 [299.9-2152.0]	<0.0001
ANGIOGENIC FACTORS				
Vascular endothelial growth factor-C (VEGF-C)	585.3 [256.1-1249.0]	512.3 [166.5-980.5]	410.7 [76.9-1187.0]	0.0096
SOLUBLE ADHESION MOLECULES				
Intercellular adhesion molecule-1 (ICAM-1)	3.48×10^5 [$2.38\text{-}5.21 \times 10^5$]	4.08×10^5 [$2.18\text{-}8.01 \times 10^5$]	5.65×10^5 [$3.14\text{-}28.15 \times 10^5$]	<0.0001
Vascular cell adhesion molecule-1 (VCAM-1)	4.21×10^5 [$2.91\text{-}6.36 \times 10^5$]	5.21×10^5 [$3.13\text{-}10.5 \times 10^5$]	6.86×10^5 [$3.14\text{-}28.1 \times 10^5$]	<0.0001

CONCLUSIONS

Using a novel approach to disease stratification, we have identified important molecular pathways which are associated with incomplete treatment response. This opens the way for stratified therapy in AIH. Significant TNF-α elevation was seen in incomplete responders and the potential of anti-TNF therapy should be systematically explored in AIH.

Understanding importance of pro- and anti-inflammatory cytokines in AIH

- MSD V-PLEX - 40 assays: cytokines, chemokines, vascular adhesion molecules and angiogenic factors

- 30 healthy controls
- 116 AIH patients
  - 50 responders
  - 66 non-responders

- 7/40 had significant inter-group differences
- Validation cohort under analysis

Parameter (pg/mL)	Responder vs Non-Responder Corrected p value
CYTOKINES	
Interleukin 10 (IL-10)	<0.0001
Tumour necrosis factor α (TNF-α)	0.0085
CHEMOKINES	
Interferon-γ inducible protein 10 (IP-10)	0.0013
Macrophage derived chemokine (MDC)	<0.0001
ANGIOGENIC FACTORS	
Vascular endothelial growth factor-C (VEGF-C)	0.0096
SOLUBLE ADHESION MOLECULES	
Intercellular adhesion molecule-1 (ICAM-1)	<0.0001
Vascular cell adhesion molecule-1 (VCAM-1)	<0.0001

Other ongoing projects

- Vitamin D – role in treatment response

- Safety and efficacy of budesonide versus prednisolone
  - EME application, led by Neil Halliday

- Transcriptomics on Tempus RNA samples (led by Alberto Sanchez from King's)

- Can senescence spread between organs (led by Tom Bird, Glasgow)
  - mouse models of genetically induced liver senescence and measuring systemic effects
  - fulminant AIH from Edinburgh (Ken Simpson)
  - UK-AIH: milder presentations to correlate pre-treatment ALT with renal function

Thank you

Any questions?

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