

2017

Variation in the use of corticosteroids for the treatment of acute severe alcoholic hepatitis in the post-STOPAH era: results of a UK national survey

Dhanda, Ashwin

<http://hdl.handle.net/10026.1/12626>

10.1016/s0168-8278(17)31024-3

All content in PEARL is protected by copyright law. Author manuscripts are made available in accordance with publisher policies. Please cite only the published version using the details provided on the item record or document. In the absence of an open licence (e.g. Creative Commons), permissions for further reuse of content should be sought from the publisher or author.

reference showed a dose effect of alcohol on the HR of death: 2.36 ($p = 0.052$) for 1–29 g/day, 3.2 ($p = 0.003$) for 30–49 g/day, 3.51 ($p < 0.0001$) for 50–99 g/day and 5.61 ($p < 0.0001$) for ≥ 100 g/day. The baseline MELD score was not predictive of long-term outcome while Lille score ($p = 0.02$) and alcohol relapse ($p < 0.0001$) were independent prognostic factors.

Conclusions: This study shows that new therapeutic development for severe AH must target liver injury for short term and alcohol consumption for long term. Thus, health agencies can endorse future study design adapted to the time-frame of factors influencing mortality. With this in mind, drugs targeting mechanisms involved in liver injury should only be tested for the short-term period.

FRI-300

Disease spectrum of alcoholic liver disease in Beijing 302 hospital from 2002 to 2013: a large tertiary referral hospital experience from 7,422 patients

A. Huang¹, B. Chang¹, Y. Sun¹, H. Lin¹, B. Li¹, G. Teng¹, Z.-S. Zou¹. ¹The Center for Non-Infectious Liver Diseases, Beijing 302 Hospital, Beijing, China

E-mail: huangangwin@aliyun.com

Background and Aims: Alcohol consumption in China has substantially increased over the last three decades and the number of patients with alcoholic liver disease (ALD) is rising at an alarming rate. However, accurate and representative data on time trends in its hospitalization rates are not available. The aim of this study is to assess the current status and burden of ALD in China by analyzing the data from a large tertiary referral hospital, Beijing 302 Hospital.

Methods: Data were retrospectively recorded from patients diagnosed as ALD in Beijing 302 Hospital from 2002 to 2013. The disease spectrum and biochemical parameters of each patient were collected.

Results: The patients with ALD accounted for 3.93% (7,422) of all patients (188,902) with liver diseases between 2002 and 2013. The number of patients hospitalized with ALD increased from 110 in 2002 to 1,672 in 2013. The ratio of patients hospitalized with ALD to all patients hospitalized with liver diseases was rising almost continuously and increased from 1.68% in 2002 to 4.59% in 2013. Most patients with ALD were male. Age distribution of ALD hospitalization showed that the highest rate was in 40- to 49-year-old group in subjects. Notably, the annual proportion of severe alcoholic hepatitis (SAH) increased 2.43 times from 2002 to 2013. We found the highest levels of MCV, the AST/ALT ratio, TBIL, INR, and ALP in SAH patients, while serum levels of HGB, ALB, and CHE were significantly decreased in SAH group. Among these ALD, the SAH patient population has the worst prognosis. Alcoholic cirrhosis (ALC) is the most common ALD, and annual admissions for ALC increased significantly during the analyzed period.

Conclusions: The number of hospitalized patients with ALD and the annual hospitalization rate of ALD were increasing continuously in Beijing 302 hospital from 2002 to 2013. More attention should be paid to develop population-based effective strategy to control ALD.

Disclosure of Interest: None Declared.

FRI-301

MAIT cell dysfunctions correlate with markers of intestinal integrity in ALD patients

A. Riva^{1,2}, V. Patel³, K. Mehta¹, C. Lopez³, G. Wright⁴, S. Tarff⁴, A. Evans⁵, D. Shawcross⁶, J. Ryan⁶, R. Williams^{1,2}, S. Chokshi^{1,2}.

¹Institute of Hepatology London, Foundation for Liver Research; ²Division of Transplantation, Immunology and Mucosal Biology, Faculty of Life Sciences and Medicine, King's College London; ³Department of Biomedical Sciences, University of Westminster, London; ⁴Basildon and Thurrock University Hospital, Basildon; ⁵Department of Gastroenterology, Royal Berkshire Hospital, Reading; ⁶Institute of Liver Sciences, King's College London, London, United Kingdom

E-mail: a.riva@researchinliver.org.uk

Background and Aims: Mucosa-associated invariant T cells (MAIT) reside in the gut, liver and systemic circulation and are a key component of the host immunity. We have previously shown that the immunocompromised state in ALD is associated with systemic depletion of MAIT which display defective antibacterial responses induced by contact with stool. Here we present new evidence indicating that MAIT alterations correlate directly with markers of gut mucosal integrity and bacterial translocation in ALD.

Methods: We measured plasma levels of intestinal fatty acid binding protein (FABP2) and D-lactate (DL), surrogate markers of mucosal damage and live bacteria translocation, in ALD patients with alcohol related cirrhosis (ARC, $n = 9$), alcohol abusers with varying degrees of fibrosis (FibroScan) (AA, $n = 35$), severe alcoholic hepatitis (SAH, $n = 12$) and healthy controls (Ctrl, $n = 13$). We investigated correlations with MAIT phenotype and functions (CD69/HLA-DR, PD1/TIM3/LAG3, IFN γ /TNF α /IL17, CD107a/Perforin/GranzymeB) and clinical/ demographic information.

Results: DL was significantly higher in ARC compared to controls ($p = 0.001$), even higher in patients with SAH ($p < 0.001$), and correlated with markers of disease severity across groups (Child-Pugh: $r = 0.601$, $p = 0.008$; MELD score: $r = 0.750$, $p < 0.001$). Interestingly, in AA patients DL also correlated with CAP scores (Controlled Attenuation Parameter, surrogate marker of liver steatosis: $r = 0.372$, $p = 0.030$). DL levels were associated with MAIT activation (CD69: $r = 0.686$, $p = 0.007$) and hyperexpression of immunoinhibitory receptors (PD1: $r = 0.595$, $p = 0.032$; LAG3: $r = 0.608$, $p = 0.028$) in patients overall. Further to this, in SAH patients DL correlated with cytotoxic potential of MAIT ($r = 0.985$, $p = 0.015$). FABP2 was comparable overall between ALD and controls but patients had significantly higher variability ($p < 0.025$). Within the ARC group, 4 subjects had strongly elevated FABP2 ($p = 0.014$) and in this group MAIT were similar to those seen in SAH, with altered activation levels ($p = 0.031$), hyperexpression of immune-inhibitory receptor LAG3 ($p = 0.021$) and more cytotoxic ($p = 0.021$).

Conclusions: In conclusion, increased intestinal mucosal damage and bacterial translocation seem to discriminate between ARC and SAH patients and are directly associated with altered MAIT cells, with activation/inhibition imbalance but enhanced cytotoxic capacity, suggesting they may be driving inflammation, immune mediated tissue damage and susceptibility to bacterial infection in ALD.

FRI-302

Variation in the use of corticosteroids for the treatment of acute severe alcoholic hepatitis in the post-STOPAH era: results of a UK national survey

A. Dhanda^{1,2}, S. Atkinson³, M. Thursz³. ¹Institute of Translational and Stratified Medicine, Plymouth University Peninsula Schools of Medicine and Dentistry; ²South West Liver Unit, Plymouth Hospitals NHS Trust, Plymouth; ³Faculty of Medicine, Imperial College London, London, United Kingdom

E-mail: ashwin.dhanda@nhs.net

Background and Aims: There remains much uncertainty in the optimal management of patients with acute severe alcoholic hepatitis (SAH). Recent evidence from the STOPAH clinical trial suggests a modest short-term survival benefit with corticosteroid treatment but a significantly increased risk of mortality with infection prompting clinicians to use corticosteroids more cautiously. We aimed to document the current variation in clinical management of these patients in the UK and determine whether the results of the STOPAH trial have changed practice.

Methods: An anonymised online survey of gastroenterologists, hepatologists and trainees in the UK was conducted which was distributed via the British Association for the Study of the Liver and the British Society of Gastroenterology. Data was analysed descriptively.

Results: There were 129 respondents including 52 hepatologists, 23 gastroenterologists with an interest in hepatology and 33

POSTER PRESENTATIONS

trainees/fellows. 36% worked in acute hospitals with level 2 hepatology services, 22% in hospitals with hepatology services, 20% in district general hospitals and 22% in transplant centres. Corticosteroids remain the most common pharmacological therapy either used alone (72%) or in combination with pentoxifylline (3%) or N-acetylcysteine (8%). No pharmacological therapy was used in 16%. The majority (74%) intended to complete 28 days of treatment with corticosteroid but 92% applied steroid discontinuation rules either based on the Lille score (40%), early change in bilirubin (23%) or a combination of other factors (37%). 76% felt that the STOPAH trial had altered their practice either by changing their choice of treatment (68%) or by discontinuing corticosteroids in patients with infection (26%). However, no respondent was satisfied with the current management options for SAH and suggested clinical trials of novel therapy (73%), improved access to alcohol liaison services (57%), development of an updated clinical guideline (51%) and improved methods to determine corticosteroid responsiveness (48%) as strategies to improve care.

Conclusions: Corticosteroids remain the most popular pharmacological therapy for SAH. However, there is wide variation in practice in the UK regarding length of treatment course and discontinuation rules reflecting the uncertainty of how to measure clinical corticosteroid response. There is a need to improve methods of patient stratification to enable accurate selection of patients who derive the most benefit from corticosteroids.

FRI-303

Intermediate (CD14⁺⁺CD16⁺) monocytes from patients with acute severe alcoholic hepatitis are activated and functionally similar to classical (CD14⁺⁺CD16⁻) monocytes

A. Dhanda^{1,2,3}, E. Williams³, E. Yates¹, P. Collins⁴, R. Lee³, M. Cramp^{1,2}.
¹Institute of Translational and Stratified Medicine, Plymouth University Peninsula Schools of Medicine and Dentistry; ²South West Liver Unit, Plymouth Hospitals NHS Trust, Plymouth; ³School of Clinical Sciences, University of Bristol; ⁴Department of Liver Medicine, University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom
E-mail: ashwin.dhanda@nhs.net

Background and Aims: Monocytes respond to pathogenic and inflammatory signals to coordinate the immune response. They are important in acute severe alcoholic hepatitis (AAH) in which infection often contributes to severe liver inflammation. Three phenotypically distinct monocyte subsets have been described: classical (CD14⁺⁺CD16⁻), intermediate (CD14⁺⁺CD16⁺) and non-classical (CD14⁺CD16⁺⁺). Enrichment of intermediate monocytes has been demonstrated in many inflammatory conditions which we have previously confirmed in AAH. However, their functional phenotype has not been fully characterised. We aimed to investigate monocyte subset function in terms of phagocytosis, monocyte oxidative burst (MOB) and T cell interaction in patients with AAH in comparison to healthy controls (HC).

Methods: Peripheral blood mononuclear cells were isolated from 10 patients with AAH (recent onset jaundice in a heavy alcohol drinker; DF > 32; AST:ALT > 1.5) and 6 HCs. Monocyte subsets and memory CD4⁺ T cells were isolated by flow cytometry. MOB was determined by oxidation of dihydrorhodamine to rhodamine123 over 10 minutes which was quantified in each subset by flow cytometry. Phagocytosis was determined by cellular uptake of fluorescent latex beads. Memory CD4⁺ T cells were co-cultured for 5 days with each monocyte subset and T cell phenotype determined by flow cytometry.

Results: Intermediate monocytes are expanded in patients with AAH compared to HCs (24% v 9%; p < 0.001). Phagocytic capacity of classical and intermediate monocytes from patients with AAH was similar and significantly greater than HCs (62% v 44% for classical; p = 0.02 and 59% v 20% for intermediate; p < 0.001). MOB was similar between classical and intermediate monocytes from AAH patients (62% and 56% rhodamine123 positive respectively). Memory T cell

proliferation was greater in co-cultures with intermediate monocytes from AAH patients than HCs (73% v 50%; p = 0.03) but proliferation, IL-17 and IFN γ expression were similar in co-cultures with each monocyte subset in patients with AAH.

Conclusions: Intermediate monocytes are functionally activated with higher capacity for phagocytosis and ability to drive T cell proliferation in AAH patients than in HCs. In patients with AAH classical and intermediate monocyte subsets have a similar functional phenotype. These in vitro surrogates of monocyte function suggest that in the context of severe inflammation the expanded pool of circulating intermediate monocytes is primed to clear pathogens and perpetuate the immune response.

FRI-304

No consensus among nutritional assessment tools for identification of malnutrition in patients with alcoholic liver disease

C.R. Kalal¹, J. Benjamin², V. Shashthry², Y. Joshi², S. Sarin². ¹Hepatology; ²Clinical Nutrition, Institute of Liver and Biliary Sciences, Delhi, India
E-mail: dr.chetankalal@gmail.com

Background and Aims: Malnutrition is a major concern in alcoholic cirrhosis (AC) which needs urgent attention. Prevalence of malnutrition varies with the methods used for assessment. Gamut of methods ranging from traditional like anthropometry, functional status and composite scores, to reference methods like bioelectrical impedance analysis and radiological imaging are available for defining malnutrition. Aims: To assess nutritional status of patients with AC using various methods.

Methods: 147 consecutive pts with AC, from Jun 2013 to Aug 2015 underwent complete nutritional workup using anthropometry [triceps skin fold (TSF) by Harpenden's calliper; mid arm muscle circumference (MAMC)] hand grip strength (HGS) by electronic dynamometer, Royal Free Hospital-Subjective Global Assessment (RFH-SGA), Phase angle (PA) by multifrequency TANITA & skeletal muscle index (SMI) by single slice L3 CT image by Slice-Omatic software. Dietary intake using 24 hr dietary recall along with semi-quantitative food frequency method. Energy requirements (ER) were estimated using Harris Benedict equation. Protein requirements (PR) were assessed as 1.2 gm/Kg IBW. Demographic, clinical, and biochemical data were also collected. The cut-offs for defining malnutrition by TSF (12.5 mm), MAMC (24.5 cm), HGS (37.5 Kg), PA (5.4°) were taken from literature while that of SMI (36.5 cm²/m²) was from our own ethnic data of healthy controls (2SD below the mean; unpublished data)

Results: In total 147 AC [M-100%; age- 44.08 ± 9; BMI- 18.45 ± 6.85; Child A:B:C-14%:38%:48%, disease duration 8 (1-40 mo), alcohol intake 112 ± 30 gm] were studied. Mean intake of proximate principles was calorie 1,588.94 ± 566.68 Kcal (69.6% of EER), protein 57.6 ± 25.2 (73% of PR) carbohydrates 263.3 ± 20, fat 32.7 ± 4.2; erroneous dietary restrictions were practiced by 91.5% patients. Mean values of TSF, MAMC, HGS, PA, and SMI were 11.73 ± 5.52 mm; 21.38 ± 2.8 cm; 25.37 ± 6.98 Kg; 4.97 ± 1.3°; and 46.2 ± 10.4 cm²/m² viz. Prevalence of malnutrition as n (%) was: TSF-92 (62.6%); MAMC-137 (93.2%); HG-141 (95.9%); RFH-SGA-123 (83.6%), PA-102 (69.4%) and SMI-23 (15.6%).

Conclusions: Prevalence of malnutrition and dietary inadequacy is high in patients with ALD; however nutritional assessment tools do not uniformly identify patients as malnourished. Traditional as well as modern methods (TSF, MAMC, RFH-SGA, and PA) using western cut-offs may overestimate malnutrition while the reference method (SMI) using ethnic cut-offs challenge these values. Hence there is an urgent need for ethnic cut-offs for all methods to obtain uniformity.