

Best of EASL - Africa

8 October 2016, Addis Ababa, Ethiopia



Chris Kassianides, Chairman of the Gastro Foundation of South Africa, in conjunction with EASL put together a whole day symposium of Liver talks at the Gastroenterology Association of Ethiopia meeting in Addis Ababa, Ethiopia. The Faculty included International speakers Professor Massimo Pinzani, Director of the UCL Institute for Liver and Digestive Health; Professor Franco Negro from University of Geneva, Switzerland (Departments of Specialty Medicine, Pathology and Immunology) and Educational Councilor of EASL; and Dr Funmi Lesi from the University of Lagos and Lagos University Teaching Hospital in Nigeria. Local Faculty speakers from Addis Ababa were Drs Abate Bane, Hailemichael Desalegn, Rezene Gebru and Yohannes Berhanu; and the South African speakers were Mark Sonderup and Wendy Spearman from Cape Town.

The morning session started with Professor Negro discussing the important topic of "Screening, transmission, prevention and access to care: Strategies to combat liver diseases". His talk highlighted the global burden of Hepatitis B and C and emphasised the seroprevalance in sSA: overall estimated HBsAg seroprevalence of 8.83% and 3.2% for HCV (*Lancet 2016; 8;388(10053):1603*). However, failure to diagnose because of lack of awareness of the burden of liver disease and cost/limited availability of diagnostics prevents linkage to care which together with the cost/limited availability of antivirals significantly impacts on the long-term ability to eliminate viral hepatitis. The efficacy of nucleos/tide antivirals to prevent the complications of cirrhosis and reduce the risk of hepatocellular carcinoma in HBV-infected individuals is well documented. However, in order to eliminate HBV, it will be essential to prevent MTCT and early childhood acquisition of HBV.

Taiwan has demonstrated the efficacy of Universal HBV vaccination in reducing HBV seroprevalence from

9.8% in 1984 to 0.3% in 2009 in children <15 years and importantly in reducing the incidence of HCC in adolescents. The efficacy of infant HBV vaccination has similarly been demonstrated in The Gambia with HBsAg prevalence only 0.8% in vaccinated vs 12.4% in unvaccinated infants i.e 94% vaccine efficacy (*BMC Infectious Diseases 2014, 14:7*).

Globally, HBV vaccination of infants and neonates has already prevented 210 million new chronic infections by 2015 and will have averted 1.1 million deaths by 2030. However, without scale-up of existing interventions, modelling has shown that there will be a cumulative 63 million new cases of chronic infection and 17 million HBV-related deaths between 2015 and 2030 because of ongoing transmission in some regions and poor access to treatment for people already infected. A target of a 90% reduction in new chronic infections and 65% reduction in mortality could be achieved by scaling up the coverage of infant vaccination (to 90% of infants), birth-dose vaccination (to 80% of neonates), use of peripartum antivirals (to 80% of hepatitis B e antigen-positive mothers), and population-wide testing and treatment (to 80% of eligible people). These interventions would avert 7.3 million deaths between 2015 and 2030, including 1.5 million cases of cancer deaths. An elimination threshold for incidence of new chronic infections would be reached by 2090 worldwide. Scale-up of vaccination coverage, innovations in scalable options for prevention of mother-to-child transmission, and ambitious population-wide testing and treatment are needed to eliminate HBV as a major public health threat. Achievement of these targets could make a major contribution to one of the Sustainable Development Goals of combating hepatitis (*Lancet Infect Dis 2016, September 13*).

In The Gambia, where HBsAg prevalence is 8.8% in individuals >30 years; adult screening and treatment for HBV has an incremental cost-effectiveness ratio (ICER)



Best of EASL group



Dr Betty Musau and colleagues from Kenya

of \$540 per DALY averted, \$645 per life-year saved, and \$511 per QALY gained, compared with current practice. These ICERs are in line with willingness-to-pay levels of one times the country's gross domestic product per capita (\$487) per DALY averted, and remain robust over a wide range of epidemiological and cost parameter inputs. Adult community-based screening and treatment for HBV in The Gambia is likely to be a cost-effective intervention. Higher cost-effectiveness might be achievable with targeted facility-based screening, price reductions of drugs and diagnostics, and integration of HBV screening with other public health interventions (*Lancet Glob Health* 2016; 4: e568).

Three point-of-care tests (Determine, Vikia, and Espline) have been validated in the field in The Gambia with acceptable ranges of diagnostic accuracy. These tests may represent accurate, rapid, and inexpensive alternatives to serology testing for the screening of HBV infection in the field in sSA (*J Clin Microbiol* 2015;53:1156) and thereby increase diagnosis and linkage to care.

Hepatitis C is now curable in >90% individuals, but current prices of DAA regimens are variable and unaffordable globally. These prices threaten the sustainability of health systems in many countries and prevent large-scale provision of treatment. It is essential to implement a fairer pricing framework to deliver lower prices that take account of affordability. Without lower prices, countries are unlikely to be able to increase investment to minimise the burden of hepatitis C (*PLoS Med* 2016; 13(5): e1002032).

Dr Bane then presented "An approach to the patient with liver disease: the practical management" covering important basic concepts for Fellows in Gastroenterology and Hepatology to enable the development of an appropriate differential diagnosis when investigating a patient with liver disease.

NAFLD is the most common liver disorder in Western countries, affecting 17-46% of adults, with differences according to the diagnostic method, age, sex and ethnicity. Dr Desalegn discussed the "Standard evaluation of NAFLD", an increasingly important cause of liver-related and all-cause mortality in Africa. Obesity, an important driver of the metabolic syndrome and the development of NAFLD, is increasing in southern sSA with the highest incidence in South Africa where 13.5% of men and 42% of women are obese. NAFLD prevalence ranges from 20% (Nigeria); 50% in Sudanese patients with Type 2 Diabetes Mellitus and 16% in Egyptian schoolchildren.

This was followed by talks on new developments in NAFLD (Prof Negro) and Alcoholic liver disease (Prof Pinzani). Prof Negro presented the new EASL-EASD-EASO Clinical Practice Guidelines for the management and treatment of NAFLD (*Journal of Hepatology* 2016;64: 138). Non-alcoholic fatty liver disease (NAFLD) is very common in people with Type 2 Diabetes Mellitus and although estimates for the prevalence NAFLD vary according to age, obesity and ethnicity, some studies have indicated that up to 75%

of patients with Type 2 Diabetes Mellitus maybe affected. He addressed the role of genetics in NAFLD: Carriers of the *PNPLA3* I148M and the *TM6SF2* E167K variants have a higher liver fat content and increased risk of NASH (*Nat Gen* 2014;46:352). NAFLD due to these variants is not systematically associated with features of insulin resistance. Genotyping may be considered in selected patients and clinical studies, but is not recommended routinely. Interestingly, the *TM6SF2* EE genotype protects against NAFLD and increases the risk of CVD (*Hepatology* 2015;61:515-25). Although, NAFLD is a risk factor for HCC, which may also develop in the pre-cirrhotic stage; the risk is further increased by the presence of the *PNPLA3* rs738409 C>G polymorphisms. Cardiovascular complications frequently dictate the outcome of NAFLD and screening of the cardiovascular system is mandatory. Ultrasound liver is the preferred first-line diagnostic procedure for imaging of NAFLD, but liver biopsy is necessary to diagnose NASH. NASH patients with fibrosis associated with hypertension should receive closer monitoring because of a higher risk of disease progression. All individuals with Type 2 Diabetes Mellitus should be screened for NAFLD irrespective of ALT levels.



Massimo Pinzani, Chris Kassianides and Franco Negro

Management is aimed at lifestyle changes including dietary with energy restriction and exclusion of NAFLD-promoting components (processed food, and food and beverages high in added fructose). Increased physical activity, either aerobic exercise or resistance training, aiming for 7-10% weight loss in overweight/obese patients is recommended. Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis ($\geq F2$). There are no firm recommendations regarding choice or duration of therapy. Pioglitazone (most efficacy data, but off-label outside T2DM) or vitamin E (better safety and tolerability in the short-term) or their combination can be used for NASH.

Prof Pinzani then discussed "Pathogenesis, diagnosis and management of acute alcoholic hepatitis". Alcoholic hepatitis (AH) is a syndrome of jaundice and liver failure that occurs in a minority of heavy consumers of alcohol. The diagnosis is usually based on a history of heavy alcohol use, a suggestive liver profile with a reversed AST:ALT (2:1) ratio and elevated GGT; and exclusion of other liver diseases. Liver biopsy specimens, usually collected via the transjugular route, should be analyzed to confirm a diagnosis of AH in patients with an atypical history or presentation. Management involves nutritional resuscitation, either oral or enteral, aiming for 35-40 cal/kg/day and 1.2-1.5 g protein/kg/day; and assessing and treating complications of infection, GIT bleeding and hepatorenal syndrome. It is important to assess severity: Maddrey's Discriminant Function <32 or MELD <20 , for supportive therapy only. If Maddrey's Discriminant Function ≥ 32 or MELD ≥ 20 , provided there is no GIT bleeding or sepsis, consider prednisolone 40/mg/day, possibly in combination with N-acetyl cysteine for 7 days and then reassess: Lille score $<0,45$ (Day 7 Bilirubin), continue steroids for 28 days, but if Lille score $>0,45$, stop steroids. At present, only short-term increases in survival can be expected, no treatment has been found to increase patient survival beyond 3 months and the STOPAH trial raised the concern of increased mortality due to sepsis with steroid therapy. Abstinence is essential for long-term survival. Liver Transplantation improves survival in highly selected patients (*Gastro* 2016;150(8):1823)

The next session concentrated on Viral Hepatitis and HIV coinfections. Wendy Spearman discussed "HIV/HBV coinfection in sSA" and the associated increased risk of MTCT of HBV and more aggressive natural history of chronic hepatitis B. 70% of the global 36 million people with HIV live in sSA, corresponding to regions of high HBV endemicity (8.83% overall HBsAg seroprevalence). HIV/HBV co-infections tend to outnumber HIV/HCV co-infections and liver-related mortality is 2x higher in HBV/HIV than HCV/HIV co-infections. The 2016 WHO recommendations of "Test and Treat" with FDC (Tenofovir, Lamivudine/Emtricitabine and Efavirenz) regardless of immunological, virological or histological considerations simplifies management of HIV/HBV co-infections and improves all-cause and liver-related mortality.

Prof Negro discussed "Current and future approaches for the treatment of HBV". In 2016, the recommendations for treatment include the following individuals: Immune clearance or immune escape phase; Immune control phase (HBeAg-, HBV DNA $<2\ 000$ IU/mL, persistently normal ALT) in the setting of immunosuppressive therapy to prevent viral reactivation; Immune tolerant phase (HBeAg+, HBV DNA >6 log IU/mL, normal ALT) if family history of cirrhosis or HCC; and pregnant women if HBV DNA $>200\ 000$ IU/mL during the last trimester of pregnancy to prevent MTCT transmission (together with HBV birth dose vaccine $\pm$ HBIG). Long-term NUC therapy with Tenofovir or Entecavir is associated with fibrosis improvement, but treatment is usually life-long due to the persistence of intranuclear cccDNA. The risk of HCC, although reduced, persists due to persistence of integrated HBV DNA at sensitive sites and epigenetic changes (miR602, TFIID, miR148a). Future treatments are aimed at cure with drugs directed at various sites of the HBV life cycle: inhibiting HBV entry by targeting the entry receptor, sodium taurocholate co-transporting polypeptide (Myrcludex); targeting cccDNA (chromatin-modifying enzymes); targeting viral RNA via siRNA (ARC-520); inhibiting nucleocapsid assembly (Bay 41-4109, NVR 3-778) and inhibiting HBsAg release (REP 9AC, REP2139-CA). Immunomodulation therapies in



Juliet, Karin, Bini - Ethiopia

development include Toll-like receptor 7 agonists (GS-9620); Anti-PD-1 mAb (BMS-936559, CYT107) and therapeutic vaccines.

Prof Lesi discussed “HCV treatment options in Africa” and Prof Negro presented the “2016 EASL HCV Treatment Guidelines”. HCV is a public health threat with an estimated 19 million infections individuals being infected i.e nearly 11% of global infections. In Egypt, the estimated seroprevalence is 14.7%, affecting approximately 6.8 million individuals.

In sSA, incremental seroprevalence estimates vary: Southern Africa 0.72%; Eastern Africa 3%; Western Africa 4.14% and Central Africa 7.82%. Blood donors have the lowest documented prevalence at 1.78%, followed by pregnant women 2.51%, people living with HIV 3.57% and the general population 5.41%. In high-risk populations, Western Africa displayed the highest prevalence at 15.69%, whilst the greatest prevalence in the general population was observed in Central Africa and Southern Africa, with adult prevalence estimates of 16.26 and 6.40%, respectively.

The ideal approach to HCV screening in sSA remains unclear: population based, birth cohort or high-risk group screening. High HCV seroprevalences in Africa are frequently iatrogenic in origin: In Egypt, parenteral anti-schistosomal mass treatment programmes in the 1960s and 1970s; mass treatment campaigns against yaws, malaria, syphilis in Cameroon, Gabon, CAR and DRC; unsafe blood transfusions and traditional scarification practices. Despite the curative DAA therapeutic options, challenges facing the elimination of HCV in Africa include lack of robust epidemiological data to assess the burden of disease, lack of affordable and accurate POC diagnostics to diagnose infected individuals and link to care and the high costs and ongoing lack of availability of DAA therapy.

The 2016 EASL HCV Treatment Guidelines are the first to promote Universal access to therapy: All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV must be considered for therapy. Individuals who should be treated without delay include: Significant fibrosis or cirrhosis (METAVIR score F2, F3, F4), including decompensated cirrhosis; clinically significant extra-hepatic manifestations; HCV recurrence after liver transplantation and individuals at risk of transmitting HCV (active injection drug users, MSM with high-risk sexual practices, women of child-bearing age who wish to get pregnant, hemodialysis patients and prison inmates).

In Africa, access to pangenotypic DAA regimens such as Sofosbuvir/Daclastavir and Sofosbuvir/Velpatasvir will simplify management.

The session after lunch concentrated on the management of cirrhosis. Mark Sonderup gave an excellent overview of “An approach to a patient with cirrhosis”, linking the pathogenesis of portal hypertension to appropriate therapeutics for the management of ascites, variceal bleeding, SBP and hepatorenal syndrome. Prof Pinzani discussed the

important topic of “Non-invasive evaluation of patients with chronic liver disease”. Liver biopsy is the imperfect gold standard for the assessment of fibrosis as it only examines 1/50 000 of the liver, has risks, requires an experienced histopathologist for correct interpretation and has both inter- and intraobserver variation. Non-invasive markers including blood/serum tests and Elastography (FibroScan, MRE, ARFI) have a potential role in countries where access to biopsies and histopathologists are limited. An ideal serum biomarker would be able to predict early decompensation, ACLF and early HCC; and predict progression rate of cirrhosis. Serum markers maybe indirect (APRI, FIB-4, Fibrotest) or indirect (ECM components and enzymes). Fibroscan is able to distinguish between no fibrosis (F0) and advanced fibrosis/cirrhosis (F3/F4), but F1 and F2 remain a grey area where liver biopsies may still be necessary. The combination of serum biomarkers and fibroscan improves sensitivity and specificity. Other non-invasive measures include spleen parameters: Platelet count/spleen diameter ratio and Liver stiffness x spleen diameter/platelet count. More sophisticated methods in development include molecular imaging of collagen cross-linking and elastin content assessing irreversibility and the role of immunophenotypes and macrophage markers in assessing reversibility. The WHO recommended non-invasive test is APRI with a score >2 for cirrhosis, as the cost of Fibroscans is still a limiting factor in resource constrained countries.

Prof Pinzani then discussed “The need of a new pathophysiological classification of cirrhosis”. The underlying aetiology has a relevant impact on disease progression (fibrogenesis) and regression (fibrolysis).



Segun Ojo (Nigeria) and Marie-Jean Kouakou-Loues (Ivory Coast)



Fellow Yusuf Musa (Nigeria) and Chris Kassianides

Different aetiologies result in different patterns of fibrosis development and influence the prevailing pro-fibrogenic mechanisms. Inflammation is a key feature of fibrogenesis (viral hepatitis, autoimmune hepatitis). In certain aetiologies (ALD, NAFLD, Haemochromatosis), fibrogenesis may in part be independent of inflammation; with oxidative stress playing an important role. In the setting of chronic cholestasis, bile acids and bile acid receptors play a role in the regulation of inflammation; with oxidative stress and pro-inflammatory cholangiocytes leading to potential disturbances of the normal epithelial-mesenchymal equilibrium. It is also important to look beyond the development of cirrhosis – what are the factors that determine the progression to a decompensated state (*Am J Clin Pathol* 2012;137(1):5). Cirrhosis causes structural and functional changes in the mucosa of the small Intestine leading to increased intestinal permeability and increased Pathogen-Associated Molecular Patterns “PAMPs” (i.e. LPS) and bactDNA in the portal circulation. This contributes to a pro-inflammatory state in the liver and is clinically not only associated with increased risk of SBP, but also increased mortality.

In the final session, Prof Pinzani discussed “New trends in the screening, diagnosis and treatment of hepatocellular carcinoma”. HCC is the 5th most common cancer (700,000 new cases and 600,000 deaths in 2012) and the 2nd leading cancer-related cause of death worldwide, but treatment options remain limited with poor outcomes as HCC is still frequently diagnosed at intermediate or advanced disease stages, where curative

approaches are often not feasible. A molecular classification of HCC enables therapies directed at immune checkpoints and the microenvironment. Sorafenib remains the SOC for advanced disease, but overall survival benefit is only 3 months and has not been validated in HCC in Africa. New immunotherapies are in development for HCC: Ipilimumab and Tremelimumab targeting CTLA4 of the T cell co-stimulatory inhibitory pathway; Nivolumab and Pembrolizumab preventing interaction between PD-1 and PD-1 Ligand; and Bevacizumab targeting stellate cells and tumour-associated fibroblasts and macrophages via VEGF (*Nat Rev Clin Oncol* 2015;12(7):408).

The clinical case presentations from our colleagues in Ethiopia highlighted the need for access to affordable diagnostics, imaging and treatment modalities for the management of acute and chronic liver disease, if Africa is to achieve the post 2015 Sustainable Development Goal of Good Health and Well-being.

The development of a Sub-Saharan Association for Gastroenterology and Hepatology and the publication of management policies around crucial topics such as viral hepatitis and HCC together with educational programmes such as “Best of EASL in Africa” will enable us to move towards the WHO vision for the elimination of Viral Hepatitis by 2030 and SDG of Good Health and Well-being.

Wendy Spearman

Head: Division of Hepatology
University of Cape Town & Groote Schuur Hospital

Upcoming meeting

Liver Interest Group

Saturday 3 December 2016 - 08:30 – 13:00

Vineyard Hotel, Cape Town

“Liver Unusual”

- atypical aspects of liver disease
- less common problems
- case discussion
- AASLD update



**Please RSVP before 25 November 2016 - Enquiries: karin.fenton@uct.ac.za
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