Welcome to this review of GASTRO 2015 with a focus on hepatitis.

This year’s Australian Gastroenterology Week (AGW), the annual scientific meeting of the Gastroenterological Society of Australia (GESAA), was held in conjunction with the World Gastroenterology Organisation (WGO) in Brisbane from September 28th to October 2nd 2015.

This Review focuses on hepatitis-related presentations from the meeting. Selection and review of the research has been carried out independently by Dr Robert Cheng of Concord Hospital, Sydney, Australia. who attended the meeting. We hope you enjoy these selections, and as always, look forward to hearing your comments and feedback.

Kind Regards,

Dr Janette Tenne
Medical Research Advisor
janette.tenne@researchreview.com.au

INFLAMMATORY BOWEL DISEASE

Infliximab for the treatment of ipilimumab (anti CTLA-4) and nivolumab/pembrolizumab (anti PD-1) associated colitis

Authors: Sidhu M et al.

Summary: These authors conducted a retrospective review of the records of 19 subjects (11 male) from two centres who received treatment with ipilimumab, nivolumab or pembrolizumab between 2009 and 2015 and who subsequently developed immunotherapy-associated colitis. In ipilimumab-treated patients (n = 16) the time mean to onset of colitis was 72 days (8-146) and most had mild-moderately active disease (mean Mayo Endoscopic Score 1.78) of the distal colon. Mean time to symptom resolution was 61 days with corticosteroid monotherapy and 12 days following initiation of rescue infliximab in 9 corticosteroid non-responders (p = 0.0873). In subjects who received nivolumab or pembrolizumab monotherapy (n = 3) colitis was mild (mean Mayo Endoscopic Score 1) and left sided. Symptom resolution occurred after 36 days with both corticosteroids and rescue infliximab in this group.

Comment: Immuno therapy with anti CTLA-4 (ipilimumab) and anti PD-1 (pembrolizumab, nivolumab) agents is now the standard of care for metastatic melanoma and other malignancies. These two types of monoclonal antibodies act by immune-modulation of activated T cells and enhance host T cell response towards tumor clearance. Upregulation of T cells can produce deleterious effects on normal cells including colitis, hepatitis, thyroiditis, dermatitis and hypophysitis as previously reported in this journal. Immune-mediated colitis caused by these monoclonal antibodies can mimic inflammatory bowel disease and may progress to toxic megacolon requiring colectomy. This multi-centre series reported 19 patients with immune-mediated colitis of which 10 responded to infliximab as rescue therapy after failing high dose steroid induction. Infliximab (anti TNF-α monoclonal antibody) has emerged as an effective alternate treatment for patients with steroid-refractory immune-mediated colitis; however infliximab has also been implicated in drug-induced hepatitis as well as being efficacious for treating immune-mediated hepatitis. As more patients start to receive anti CTLA-4 and anti PD-1 agents a systematic prospective study may help clarify the role of TNF-α inhibitors in the treatment of immune-mediated colitis and hepatitis.


Abstract

THE LONG-AWAITED RESPONSE
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“According to EASL guidelines, long-term follow-up studies have shown that a sustained virological response (SVR) – defined as undetectable HCV RNA 12 weeks post-treatment – corresponds to a definitive cure in more than 99% of cases of hepatitis C. The concordance of SVR12 and SVR24 is 99%.”

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These authors conducted a retrospective analysis of all investigations in screening for Wilson’s disease and January 2004 and March 2014 in order to determine the value of these levels requested by the liver unit at a single tertiary centre between caeruloplasmin (n = 2,444) and α1-antitrypsin deficiency (PPV 1.8%). A single patient had a ZZ genotype and was diagnosed with α1-antitrypsin deficiency in this cohort retrospective series demonstrated that despite large quantities of serum caeruloplasmin and α1-antitrypsin being ordered, less than 3.1% (of caeruloplasmin) and 2.7% (of α1-antitrypsin) were observed. Low levels < 0.17 g/L) were observed in 76 subjects (3.1%); 21 underwent liver biopsy, hepatic copper quantification was carried out in 3, and Wilson’s disease diagnosed in 1 (PPV 1.4%). Abnormally low (< 0.9/L) α1-antitrypsin levels were observed in 88 subjects (2.7%). In those who received genotyping (n = 56) the most common genotypes were ZZ (41.8%) and MM (38.2%). A single patient had a ZZ genotype and was diagnosed with α1-antitrypsin deficiency (PPV 1.8%).

Comment: Wilson’s disease and α1-antitrypsin deficiency are rare metabolic liver disorders that remain difficult to diagnose. This large cohort retrospective series demonstrated that despite large quantities of serum caeruloplasmin and α1-antitrypsin being ordered, less than 3.1% (of caeruloplasmin) and 2.7% (of α1-antitrypsin) were abnormally low. Of those, the PPV of an abnormally low serum caeruloplasmin level for Wilson’s disease was only 1.4% and the PPV of a low α1-antitrypsin level for homozygote ZZ abnormality was only 1.8%. The authors concluded serum caeruloplasmin and α1-antitrypsin are low yield first-line investigations and should be limited to patients in whom initial liver screen is negative and clinical suspicion remains. Acute fulminant Wilson’s disease can often be a high morbidity and high mortality presentation; a cost-benefit analysis may help stimulate discussion on the utility of these screening tests in preventing disease-related complications.


Changes in the duodenal microbiota in chronic liver disease

Authors: Raj A et al.

Summary: The aim of this prospective cohort study was to characterise the duodenal microbiota of patients with CLD. Subjects, patients with CLD including chronic HCV/HBV, NAFLD and alcoholic liver disease (n = 41, 31 male, and controls (n = 27, 14 male) who were clinically and endoscopically free of mucosal GI disease, underwent upper endoscopy with duodenal biopsy in order that the mucosa-associated microbiota could be identified. Amongst patients with CLD the duodenal mucosa-associated microbiota showed greater similarities to others in the CLD group vs controls (p < 0.05). Despite greater intra-individual variation in the CLD group, CLD was associated with a reduction in species variety, a greater relative abundance of Firmicutes, and lower levels of Bacteroidetes. No effects of the metabolic syndrome, obesity status, proton pump inhibitor use or H. pylori status on the duodenal microbiota were observed.

Comment: Disruption of the gut microbiota, or dysbiosis, has been associated with pathological gastrointestinal conditions including colorectal cancer, inflammatory bowel disease, irritable bowel syndrome, obesity and type II diabetes. The relationship between chronic liver disease and dysbiosis has also become more topical in recent years. This pilot study showed duodenal microbiota of CLD patients were more likely to have reduced species diversity and their bacterial phylogeny appeared to cluster together more closely compared to normal controls. Exploration into the role of intestinal dysbiosis in CLD is important, as manipulating the gut microbiome to alter disease outcome has become a burgeoning research area. Probiotic supplementation and faecal transplantation are some of the therapies currently under investigation for luminal bowel disease, which may have health benefits for CLD patients. In examining the gut microbiome of CLD patients it is essential to account for individuals who have recently taken antimicrobials, non-acceptable antibiotics such as rifaximin, proton pump inhibitors and herbal medicines, as well as probiotic and probiotic formulations.


Abstract

Independent commentary by Dr Robert Cheng

Dr Cheng is a Gastroenterologist and Hepatologist at Concord Hospital, Sydney, Australia. Dr Cheng completed his undergraduate medical degree from the University of New South Wales and is a recipient of the National Health and Medical Research Council (NHMRC) research scholarship for his current doctoral thesis being completed at Centenary Institute, Royal Prince Alfred Hospital (University of Sydney), on the topic of genomic biomarkers of hepatocellular carcinoma. His other research interests include viral hepatitis, autoimmune and drug-induced hepatitis, and microvesicular mediators of inflammation and cirrhosis.

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Prevalence of elevated alanine transaminase in Australia and relationship to metabolic cofactors

Authors: Madagascar et al.

Summary: These Australian researchers examined relationships between elevated levels of ALT and metabolic cofactors in adult subjects (n=9,447) identified from a nationwide, population-based survey. Investigations included clinical assessment, anthropometric measurements and fasting phlebotomy. Factors significantly associated (p < 0.05 for all comparisons) with elevated ALT levels (found in 13.2 and 8.3% of males and females respectively) included younger age (43 vs 46 years), lower exercise activity, and greater BMI (30 vs 25 kg/m²), waist circumference (100 vs 91 cm), serum triglyceride levels (2.45 vs 1.23 mmol/L), apolipoprotein B (1.06 vs 0.95 g/L) and glucose (5.42 vs 5.06 mmol/L).

Comment: NAFLD is increasing in prevalence (estimated at 30–40%) and is the most common liver disorder in industrialised Western nations. NAFLD can progress to nonalcoholic steatohepatitis (NASH) cirrhosis, which is the third most common indication for liver transplantation. During the last ten years there was a substantial increase in the proportion of transplants performed for NASH cirrhosis, from 1.2% in 2001 to 9.7% in 2009. With such significant disease burden, accurate early screening for NAFLD would be invaluable. This Australian cohort study found ALT to be elevated in 13.2% of males and 8.9% of females in the community. On multivariate modelling male sex, younger age, higher triglycerides, glucose level, apolipoprotein B and waist circumference were found to be significant predictors of ALT elevation. This data reaffirms the prevalence of elevated ALT in Australia is among one of the highest reported in developed countries and it is strongly associated with several metabolic risk factors. More not specified is the underlying cause of NAFLD and more effective screening strategies for NAFLD will need to be developed and implemented on a public health and policymaking level.


Abstract

Survival benefits of multi-disciplinary team care in hepatocellular carcinoma at Liverpool Hospital, New South Wales, 2003–2013

Authors: Davison et al.

Summary: The authors of this retrospective review examined baseline characteristics of, and treatment outcomes for, patients with hepatocellular carcinoma (HCC) presenting to a single Australian hospital before (2003 to 2007), and after (2008 to 2013), the introduction of MDT care. A total of 177 cases (73.4% male, 19% male, 9% female) meeting these criteria were identified from a cohort of 715 CHB patients seen at a single Australian centre.

Comment: The management of HCC has evolved greatly over the past ten years, progressing from individual physician or surgeon care to MDT care. This single tertiary center audit produced robust data to support findings from other clinical series, demonstrating a MDT care model improved mean patient survival from 6.3 to 15.1 months with a higher rate of loco-regional therapy uptake. The overall prognosis of patients with HCC remains poor, and curative treatment continues to be restricted to transplant or liver resection. Nevertheless, this data is encouraging because it shows the MDT care model may lengthen mean survival with appropriate use of loco-regional therapy and, where tumor staging is within liver transplant criteria, MDT care can more effectively bridge the waiting time to transplantation.


Abstract

The TOSCAR study: sofosbuvir and daclatasvir therapy for decompensated HCV cirrhosis with MELD scores ≥ 15

Authors: McCaughan et al.

Summary: These authors reported interim results from the TOSCAR study in which patients with decompensated liver disease (MELD score ≥ 15) resulting from HCV infection were eligible for 24 weeks of interferon-free treatment with sofosbuvir and daclatasvir under a compassionate access programme. Baseline characteristics of the first 92 patients included mean MELD score of 17.4 (25% > 20) and Child Pugh Score of 9; ascites and encephalopathy were present in 76 and 65% of subjects respectively. The respective proportion with genotypes 1a, 1b and 3 were 39, 9 and 27%. Amongst patients with available end of treatment data 14/15 were HCV PCR negative; the 15th patient had had treatment interrupted by a surgical procedure and had also previously relapsed during sofosbuvir and ledipasvir therapy. Improvements of ≥ 2 points were observed in 8/15 patients for MELD score (all with baseline MELD < 20) and 4/15 for Child Pugh Score. MELD scores increased by ≥ 2 points in 4/15 patients.

Comment: With the advent of direct-acting antiviral therapy (DAA) for HCV, patients may expect to have SVR rates of greater than 95%. Genotype 3 infected HCV patients and decompensated cirrhotics have emerged as two difficult-to-treat populations. Previous data on GT1/3 patients with decompensated cirrhosis (mean MELD 11.9) have shown that 12-week therapy with either sofosbuvir/daclatasvir (SOF/DCV) or sofosbuvir/ledipasvir (SOF/LDV) combinations with or without ribavirin may achieve SVR12 rates of 70–80%. The TOSCAR study focused on HCV patients with significant hepatic decompensation (MELD ≥ 15). Preliminary results showed 93% (14/15) of patients were HCV PCR negative at the end of 24-week therapy (EDT) with SOF/DCV and 50% of these had improvements in MELD scores. TOSCAR follows an interesting cohort of HCV patients at the severe end of the decompensated liver disease spectrum and their long-term outcomes may help define optimal DAA therapy for this difficult-to-treat cohort.


Abstract

Predicators of clinical response: results from a large, randomized controlled study with tenofovir disopirox fumarate plus peginterferon alfa-2A combination for chronic hepatitis B

Authors: Strasser et al.

Summary: This randomised, controlled, 4-arm study examined predictors of response to treatment with tenofovir disopirox fumarate (TDF) and peginterferon alfa-2A (PEG) in patients with chronic hepatitis B (CHB). Subjects without advanced disease received TDF + PEG x 48 weeks (Arm A), TDF + PEG x 16 weeks then TDF x 32 weeks (Arm B), continuous TDF (Arm C) or placebo (Arm D). Reported outcomes were HBV surface antigen (log10 IU/mL) and HBV DNA (log10 IU/mL) kinetics and their associations with baseline and on-treatment variables.

Comment: Previous studies on combined pegylated interferon and oral nucleotide analogue therapy for chronic HBV focused on low rates of HBV DNA loss and HBV sAg seroconversion, but there was paucity of data on on-treatment HBV DNA and sAg viral kinetics. In recent years abundant data have emerged demonstrating that quantitative sAg levels may be used to predict HBV treatment response. In this prospective multicentre trial, combined TDF and PEG for 48 weeks produced greater HBV sAg decline than either TDF or PEG monotherapy. Higher baseline HBV sAg levels appear to impact adversely on on-treatment HBV DNA response. HBV sAg decline at week 12 had very high negative predictive value (>95%) of HBV sAg positivity at week 72. HBV sAg quantitation appears to be a useful tool for response-guided therapy in TDF+PEG combination treatment; however sAg quantitation is currently not standard management protocol in many parts of the world and restricted access may limit on-treatment quantitative monitoring of sAg levels to tertiary referral centers.


Abstract

The natural history of immune escape hepatitis B infection without biochemical flare: treat now or wait

Authors: Lewis et al.

Summary: These authors studied the natural history of, and treatment predictors for, patients with chronic hepatitis B (CHB) who presented in the immune escape phase without biochemical flare (HBV e antigen [eAg] negative, viral load > 2,000 IU/mL and ALT < .5 IU/L) (“Phase 4a”). A total of 97 subjects (mean age 45.1 years, 27.8% male, 71.7% Chinese ethnicity) meeting these criteria were identified from a cohort of 715 CHB patients seen at a single Australian centre.

Comment: Management of CHB patients in the immune escape phase, with negative eAg status and high viral load but normal ALT, has become an area of less defined treatment landscape. Guidelines suggest antiviral therapy is indicated when liver biopsy demonstrates evidence of hepatic necroinflammation or early fibrosis, but in the era of transient elastography, significantly fewer liver biopsies are now performed in patients in immune escape. This study followed 97 CHB patients in immune escape with normal ALT for a period of 12 months and found that 5% commenced antiviral therapy (due to clear indications of cirrhosis or elevated ALT), 30% regressed to immune control, 10% progressed to immune escape with ALT elevation, and a majority of 45% of patients continued to remain in a state of high viral load with normal ALT. Although a conclusion was made to adopt a watchful waiting strategy, the long-term outcome for this group of CHB patients in immune escape and normal ALT is less clear beyond one-year follow-up. For the purpose of cirrhosis and hepatocellular carcinoma (HCC) prevention, liver biopsy may still be a useful tool for selecting out patients at higher risk of progression and may fulfill criteria for commencing antiviral therapy, particularly for those with additional risk factors such as metabolic syndrome, fatty liver disease, positive alcohol intake and family history of HCC.

Does thyroid dysfunction predict sustained virological response in triple therapy regimes with protease inhibitors in hepatitis C genotype 1 patients?

Authors: Uchila R et al.

Summary: This retrospective cohort analysis investigated associations between thyroid dysfunction (TD) and SVR in patients with genotype 1 HCV treated with triple therapy (pegylated interferon and ribavirin plus protease inhibitor, n = 88) and compared them to an age and gender-matched control cohort who received pegylated interferon and ribavirin alone (n = 362). Amongst the total group SVR rates were 72 vs 50% for patients with and without TD respectively (p = 0.0018). TD rates were 16% in patients treated with triple therapy and 9/14 (64%) of these achieved SVR. Respective figures for controls were 12% and 33/44 (75%). Triple therapy-treated subjects developed TD significantly earlier than controls: 18 vs 25 weeks respectively (p = 0.03).

Comment: Thyroid dysfunction has been reported to occur in 10-15% of patients on pegylated interferon-based HCV antiviral therapy. The development of autoimmune phenomenon in patients on interferon has been recognised as a clinical predictor of SVR in previous studies, possibly because the systemic immunogenic effects of interferon may serve as a surrogate predictor of enhanced host immune response to viral clearance. This retrospective analysis of 450 genotype 1 HCV patients showed thyroid dysfunction continues to predict higher SVR rates in the era of interferon-based direct-acting antiviral (DAA) triple therapy, and that thyroid dysfunction occurred significantly earlier in the DAA-based group compared with the interferon-ribavirin therapy group. The immune modulating effects of interferon are fascinating from a translational research perspective, and while HCV antiviral therapy has moved into an interferon-free era, continued research into the host immune system response to interferon may still benefit other viral hepatitis patient groups.


MicroRNAs as potential serum biomarkers of fibrosis progression and hepatocellular carcinoma development in chronic hepatitis C

Authors: Wei A et al.

Summary/comment: MicroRNAs (miRNA) are short noncoding RNA molecules that regulate gene expression by binding to messenger RNA (mRNA). In recent years miRNA have been the subject of intensive research and have been found to implicate cellular injury, inflammation, carcinogenesis and autoimmunity. This prospective study found that in the serum of 36 hepatitis C patients, there were statistically significant differential expressions of at least two miRNA (miRNA-493-3p and miRNA-4731-3p) between patients with and without hepatocellular carcinoma in the context of cirrhosis. They concluded that a panel of circulating miRNA could be developed as biomarkers for liver fibrosis and hepatocarcinogenesis. An interesting and novel area, this investigation into circulating miRNA may benefit from expansion of its cohort size and inclusion of patients with non-hepatitis C related liver disease. There are important diagnostic and therapeutic implications for miRNA research, as demonstrated by the recent development of anti-miR-122 for treating hepatitis C.

Reference: Poster Presentation