Advances in Inflammatory Bowel Diseases (AIBD) 2016

Conference Review™

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8-10 December 2016, Orlando, Florida, USA

In this review:

- Pro-inflammatory effects of dietary emulsifiers on the human gut microbiota
- Factors predicting loss of response to vedolizumab in IBD
- Is there an anti-infliximab antibody threshold to predict infliximab durability?
- 6-TGN levels correlate with anti-infliximab antibodies in IBD patients
- Thiopurine metabolites, adalimumab and anti-adalimumab antibodies
- HDWL endoscopy vs HDCE for detection of dysplasia in UC
- The impact of IBD nurse navigators on resource utilisation
- Adherence to biologic therapies in IBD
- Modifiable risk factors for hospital readmission among IBD patients
- Does pre-medication reduce the risk of acute infliximab infusion reactions?

Abbreviations used in this review:

6-TGN = 6-thioguanine nucleotide;
6-MeMP = methylated mercaptopurine metabolites;
AUCROC = area under the curve receiver operating curve;
CD = Crohn's disease; **HDCE** = high definition chromoendoscopy;
HDWL = high definition white light; **HR** = hazard ratio;
IBD = inflammatory bowel disease; **IQR** = interquartile range;
OR = odds ratio; **TNF** = tumour necrosis factor; **UC** = ulcerative colitis.

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Welcome to this review of the Advances in Inflammatory Bowel Diseases (AIBD) meeting which was held in Orlando, Florida on December 8-10, 2016.

This review has been created to allow those unable to attend, but with a keen professional interest, to access a summary of some of the presentations. Selection and review of the research has been carried out independently by Dr Jake Begun.

Highlights of this review include several investigations into the durability of biologics in IBD focusing on the role of anti-drug antibodies, the relationships between thiopurine metabolites and anti-drug antibody formation, and the role of dose escalation therapy in antibody-positive patients. We also present a fascinating study examining the pro-inflammatory effects of dietary emulsifiers on bowel microbiota, investigate adherence amongst IBD patients on biologic therapy, and examine the risk factors for hospital readmission in IBD.

We hope you enjoy these selections, and as always, look forward to hearing your comments and feedback.

Kind Regards,

Dr Janette Tenne

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Dietary emulsifiers directly impact the human gut microbiota increasing its pro-inflammatory potential and ability to induce intestinal inflammation

Speaker: Chassaing Benoit, Georgia State University, Atlanta, GA

Summary: These authors investigated the impact of the dietary emulsifiers polysorbate 80 (P80) and carboxymethylcellulose (CMC) on human gut microbiota *in vitro* using the M-SHINE (Mucosal Simulator of the Gastrointestinal Microbial Ecosystem) model. Following addition of P80 and CMC at concentrations ranging from 0.00% to 1.00%, microbial composition, meta-transcriptomic and pro-inflammatory potential were measured. The effect of the treated microbes on gut inflammation *in vivo* was determined following transplantation into germ-free murine models. *In vitro* both compounds had pro-inflammatory effects via increased levels of bioactive flagellin; resulting from altered gene expression (CMC) and altered species composition (P80). *In vivo*, pro-inflammatory effects, similar to those observed resulting from direct treatment with dietary emulsifiers, were observed following transplant of the treated microbiota.

Comment: Recent evidence from animal studies has implicated the commonly used emulsifiers CMC and P80 as decreasing gut barrier function and increasing intestinal inflammation. This study used a system of anaerobic incubators to stimulate the human gut microbiota *in vitro* and examined the effects of varying emulsifier concentrations simulating dietary intake. Increasing emulsifier concentrations resulted in changes in microbial gene expression resulting in the increased expression of pro-inflammatory mediators such as flagellin. This study supports the findings in animal models of emulsifier intake leading to a more inflammatory microbiome. However it remains to be demonstrated in clinical trials that decreasing emulsifier intake can improve inflammatory burden in IBD patients.

Reference: O-013 — 2016

Abstract

Assessing risk factors predicting loss of response to vedolizumab in ulcerative colitis and Crohn's disease

Speaker: Eugenia Shmidt, Icahn School of Medicine at Mount Sinai, New York, NY

Summary: This presentation detailed outcomes from the Vedolizumab for Health Outcomes in Inflammatory Bowel Disease (VICTORY) consortium cohort. Subjects were 504 patients with moderate-to-severe, active IBD (293 with CD, 214 with UC) who received vedolizumab therapy and ≥ 1 follow-up assessment. Median follow-up was 270 days (IQR 160, 408). Clinical responses and clinical remission were observed in 115 and 61 CD patients and 115 and 83 UC patients respectively. Loss of response (LOR) by 12 months occurred in 51% and 45% of CD and UC patients respectively; median onset 143 days (IQR 67, 270). Risk of LOR was increased by baseline albumin < 3g/dL (HR 2.18; 95% CI 1.08, 4.42) and incrementally by number of prior anti-TNFs (HR 1.26; 1.03, 1.54) under multivariate analysis.

Comment: In this study the investigators followed a cohort of patients started on vedolizumab for the treatment of Crohn's and UC. In this real world cohort the overall response rate was 39% (CD) and 54% (UC) and remission rates were 21% (CD) and 39% (UC). After 12 months a total of 47% of patients experienced LOR. The predictors of LOR included albumin < 30 g/L and prior anti-TNF failure. Response could be re-captured in 36% of patients with interval shortening to every 4 weeks. This study demonstrates the efficacy of vedolizumab in a real world setting and that there is a significant loss of response (similar to anti-TNFs) and that dose intensification is a potential strategy to overcome this in some patients.

Reference: P-040 — 2016
Abstract

Establishing an anti-infliximab antibody threshold to predict infliximab durability

Speaker: Ruby Greywoode, The Mount Sinai Hospital, New York, NY

Summary: This US study was a retrospective chart review investigating relationships between anti-infliximab antibody levels and other factors, and the clinical durability of infliximab. Participants were infliximab-treated IBD patients who were anti-infliximab antibody positive (n = 62). The primary outcome measure of infliximab durability (in steroid-free remission with infliximab at final follow-up) was achieved by 25% (16/62) participants. Factors associated with infliximab durability included: mean age, 26 vs 37 years (P = 0.03); mean anti-infliximab antibody concentration, 7.6 vs 31 U/mL (P = 0.005); proportion of detectable infliximab concentration, 44 vs 17% (P = 0.03); using a dose/interval adjustment strategy amongst anti-infliximab antibody positive patients, 50 vs 2% (P < 0.0001). Addition of an immunomodulator was associated with a trend towards significance (P = 0.07), however there was no impact of gender, disease duration or type of IBD.

Comment: This retrospective multi-centre study of infliximab levels and anti-infliximab antibody levels using a drug tolerant mobility shift assay correlated antibody levels with clinical loss of response. The authors identified 62 patients with positive anti-infliximab antibodies of whom 25% were in stable steroid-free remission on infliximab at the conclusion of the study period. An antibody cut-off level of 9 U/mL was found to have 81% sensitivity and 76% specificity for durability of treatment. There was also an association of durable response with detectable drug levels (p = 0.03). The majority of anti-drug antibodies detected were transient. These results indicate that low antibody titres may not affect durability of infliximab treatment, and that detectable infliximab concentrations remain a good predictor of durable response. Addition of an immunomodulator had a non-significant improvement in infliximab durability in this study.

Reference: P-051 — 2016 (Young Investigators)
Abstract

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Independent commentary by Dr Jake Begun

Dr. Jakob Begun completed his Biochemistry BSc at Cornell University and an MPhil in Biochemistry at Cambridge University. He then obtained his MD and PhD in genetics at Harvard Medical School. He completed his clinical training in internal medicine at Brigham and Women's hospital and went on to complete general gastroenterology training as well as advanced training in Inflammatory Bowel Disease (IBD) at Massachusetts General Hospital (MGH). He returned to Brisbane Australia in 2014 to pursue his interest in academic gastroenterology. He treats patients with IBD at the Mater Hospital Brisbane and the Queen Elizabeth II Hospital where he is the clinical lead for IBD. He was appointed Senior Research Fellow in the Immunity, Infection, and Inflammation Program at the Mater Research Institute – University of Queensland and is a Senior Lecturer at the University of Queensland School of Medicine and Faculty of Medicine and Biomedical Sciences. He is the recipient of the Reginald Ferguson Fellowship. He runs a basic and translational laboratory at the Translational Research Institute in Brisbane investigating the interaction between the innate immune functions of the gut and the microbial community with a focus on therapeutic interventions. He also performs clinical research examining the natural history of IBD and investigating barriers of care for adolescents and young adults with IBD.

Thiopurine metabolite, 6-thioguanine nucleotide, correlates with detection of antibodies against infliximab in patients with inflammatory bowel disease

Speaker: Casper Steenholdt, Copenhagen University Hospital, Herlev, Denmark

Summary: This retrospective cohort study examined associations between thiopurine metabolite (6-TGN and 6-MeMP) concentrations, infliximab concentrations and the development of anti-infliximab antibodies amongst IBD patients receiving infliximab maintenance. Cohort A comprised 40 patients receiving combination infliximab-thiopurine therapy and 49 infliximab-only patients. Cohort B comprised 8 patients who had experienced infliximab failure during combined infliximab-thiopurine therapy but subsequent clinical response to 12 weeks of infliximab dose intensification (with stable thiopurine). The proportion of Cohort A patients with detectable anti-infliximab antibodies was significantly lower amongst those receiving concomitant thiopurines; 20 vs 45%, OR 0.31 (0.12, 0.80), p = 0.01. Those with detectable antibody levels had lower 6-TGN concentrations (median 50 vs 105 pmol/8 x 108 RBC; P < 0.01) and all antibody positive patients had 6-TGN < 117 pmol/8 x 108 RBC (sensitivity 100%, specificity 47%, AUCROC 0.82, P < 0.01). Trough infliximab concentrations were similar in antibody negative patients regardless of whether they received thiopurine therapy. No associations were observed between concentrations of infliximab, 6-TGN or 6-MeMP. Amongst the Cohort B subjects, infliximab intensification resulted in increased trough levels of infliximab but had no impact on 6-TGN or 6-MeMP concentrations.

Comment: Previous studies have demonstrated that thiopurine use decreases the incidence of anti-infliximab antibody formation and increases infliximab concentrations. This study examined the relationship between infliximab and thiopurine metabolite levels as well as anti-infliximab antibody formation. Patients on combination therapy had significantly decreased incidence of anti-infliximab antibodies, but comparing patients without antibodies there was no effect of thiopurines on infliximab levels or an association between thiopurine metabolites and infliximab levels. In addition, in a small cohort of patients on combination therapy who underwent infliximab dose intensification, there was no effect on thiopurine metabolite levels. Therefore this study supports a role for combination therapy in decreasing antibody formation, but did not confirm studies showing a relationship between thiopurine use and infliximab levels.

Reference: P-116 — 2016
Abstract

Interactions between thiopurine metabolites and adalimumab and anti-adalimumab antibodies in inflammatory bowel disease

Speaker: Casper Steenholdt, Copenhagen University Hospital, Herlev, Denmark

Summary: This retrospective cohort study investigated associations between thiopurine metabolites, adalimumab concentrations and anti-adalimumab antibodies amongst 98 IBD patients (77 with CD) on adalimumab maintenance therapy (31 in combination with thiopurines). The proportion of patients in clinical remission at the time of sampling was 39% for those on dual therapy and 31% on monotherapy (P = 0.50). Median circulating trough adalimumab levels were higher amongst antibody-negative patients (8.4 µg/mL) than antibody-positive patients amongst whom levels were undetectable (P < 0.0001). There was a strong correlation between adalimumab treatment failure and the presence of anti-adalimumab antibodies (OR 5, P < 0.01), but no difference in the proportion of patients with antibodies was observed between those on combination therapy and those on monotherapy; 26 vs 28% respectively (P = 1.00).

Comment: Previous studies have demonstrated that combination therapy with thiopurines and infliximab leads to decreased incidence of anti-drug antibodies. This retrospective study examined whether thiopurine levels are associated with decreased formation of anti-adalimumab antibodies in a cohort of patients with adalimumab levels in which ~30% were on thiopurines. In this cohort the incidence of detectable anti-adalimumab antibody was ~30% and there was no difference in antibody formation with thiopurine use, and no association of adalimumab drug levels with thiopurine metabolite levels. These results mirror the recently published DIAMOND study, which did not show a clinical improvement with combination therapy compared to adalimumab monotherapy, although there was significantly better mucosal healing in the combination arm.

Reference: P-120 — 2016
Abstract

High-definition white-light endoscopy versus high-definition chromoendoscopy in detection of dysplasia in long-standing ulcerative colitis

Speaker: Jung Park Soo, Gastroenterology, Seoul, Seodaemun-gu

Summary: The aim of this Korean, multicentre, prospective, randomised, controlled clinical trial was to compare the diagnostic efficacy of high-definition white-light endoscopy (HDWL) with random biopsies and high-definition chromoendoscopy (HDCE) with water-jet pump with target biopsies for the detection of colitis-associated dysplasia in patients with long-term UC. HDCE was not significantly more effective than HDWL for detecting colitis-associated dysplasia (2.9 vs 4.6%; P = 0.722) or all dysplasia (20.6 vs 12.0%, P = 0.093). There was no increase in procedure time in the HDCE group vs those that received HDWL (17.8 vs 18.9 minutes, P = 0.288), however HDCE was associated with a significantly reduced number of total biopsies vs HDWL (9.2 vs 33.6, P < 0.001).

Comment: Multiple studies have confirmed the superiority of chromoendoscopy over standard white light endoscopy for the detection of colitis-associated dysplasia in patients with long standing colitis, leading to society guidelines recommending this modality. However, the introduction of high definition colonoscopes into routine practice has significantly improved mucosal visualisation, which may increase the sensitivity for dysplasia detection. In this randomised controlled trial of 210 patients with long standing colitis, HDWL with random biopsies was compared to HDCE with targeted biopsies for the detection of dysplasia. The overall dysplasia rate was low and there was no statistical difference between HDWL and HDCE. These results indicate that chromoendoscopy may not add significantly to dysplasia detection over high definition white-light endoscopy, although larger studies are still required before recommendations will be changed.

Reference: P-013 — 2016
Abstract

The impact of a nurse navigator program on telephone calls and emergency department utilization among IBD patients

Speaker: Sonia Divakaran, Cedars-Sinai Medical Center, Los Angeles, CA

Summary: This before and after study investigated the impact of using dedicated IBD 'nurse navigators' to manage telephone calls to an outpatient IBD centre, where previously calls were taken by general gastroenterology nurses. An automated call distribution system was used to monitor call data including the number of calls, length of calls and calls that were put on hold, transferred or lost. Emergency department (ED) utilisation was also tracked and linked for IBD-related illness by chart review. Data were collected for a 4 month period following the employment of one nurse navigator (N1) and for a further 4 months following the employment of a second nurse navigator (N2). Between N1 and N2 average call time was reduced from 151 to 132 seconds (P = 0.02). Hold-time was also reduced from 39 to 29 seconds (P = 0.01). Most (89%) IBD-related ED visits were not preceded by a phone call to the IBD centre. Hospital admission for IBD-related illness via the ED occurred amongst 80% of those who had phoned prior visiting the ED, and 75% of those who had not.

Comment: This study relied on prospectively collected data after the sequential introduction of two dedicated IBD nurses to answer telephone enquires to the IBD help line. Over an 8-month period 10,441 calls were received and the introduction of dedicated nurses reduced the length of each call, the hold time, and decreased the numbers of abandoned calls. While there was no effect on ED hospitalisation rates, the majority of presentations (85%) were not preceded by a phone call to the IBD help line. This study supports the presence of IBD nurses in high volume centres and suggests that greater utilisation of an IBD help line could reduce ED presentations.

Reference: O-008 — 2016 (Young Investigators)
Abstract

Adherence to biologic therapies in inflammatory bowel disease

Speaker: Brian Wentworth, University of Virginia School of Medicine, Charlottesville, VA

Summary: The aim of this single centre, retrospective chart review was to investigate adherence rates and risk factors for non-adherence amongst adult IBD patients receiving biologic therapy. Modified medication possession ratios were calculated as the number of self-administered medication deliveries received (verified by pharmacies), or number of infusions received, divided by the number of expected treatments. Amongst 175 subjects included in the analysis 21% missed ≥ 1 treatment and 20% received ≤ 20% of scheduled treatments. The overall rate of non-adherence was 21%. Adherence was greater with facility-administered vs self-administered therapy; 86% vs 71%, P = 0.021. Lack of commercial insurance was significantly associated with non-adherence (30 vs 20%, P < 0.001), whereas proximity to the medical centre was inversely associated (93.6 vs 69.3 miles, P = 0.048). No impact of age, gender, marital status or disease activity was observed.

Comment: Non-adherence is a significant cause of therapeutic failure in IBD patients. Although adherence to biologic therapy is often assumed to be high, several studies have described significant rates of non-adherence both to intravenous and sub-cutaneous biologic therapy. In this retrospective study the adherence of IBD patients on biologic therapy was assessed by auditing pharmacy dispensing and infusion centre records. Adherence to intravenous biologics (vedolizumab and infliximab) was higher than sub-cutaneous biologics (adalimumab, certolizumab) but 13-29% of patients on biologic therapy were non-adherent. A greater distance from a medical centre was associated with non-adherence. This reinforces the practice of exploring medication adherence with all IBD patients regardless of treatment modality.

Reference: P-139 — 2016
Abstract

Modifiable risk factors for hospital readmission among patients with inflammatory bowel disease in a nationwide database

Speaker: Edward Barnes, University of North Carolina School of Medicine, Chapel Hill, NC

Summary/Comment: This database study attempted to identify 'modifiable' risk factors that predict hospital readmissions among 129,103 patients admitted with IBD in the USA during 2013. Overall a quarter of IBD patients were readmitted within 90 days of their initial hospitalisation and multivariate analysis identified younger age, male gender, stricturing (obstructive) or fistulising disease, and longer index hospitalisations as being associated with a greater risk of readmission. Of the modifiable risk factors identified, chronic pain (OR 1.42) and depression (OR 1.18) represented the factors most likely to predict readmission. This study reinforces current practice of holistic care of IBD patients to address factors in addition to disease activity to prevent hospital readmission, and identifies pain and depression as being particular factors to focus on.

Reference: P-041 — 2016 (Young Investigators)
Abstract

Acute infliximab infusion reactions: do pre-medications actually reduce the risk?

Speaker: Stephanie Gold, Weill Cornell Medical College/New York Presbyterian, New York, NY

Summary: These authors conducted a retrospective chart review to determine the efficacy of prophylaxis for infliximab infusion reactions. All IBD patients treated with infliximab between 2008 and 2016 were included (n = 150). Acute infusion reactions occurred in 1.7% of infusions (28/1595) and in 21 individuals. In 71% of cases pre-infusion prophylaxis had been administered. No associations between infusion reactions and type of IBD, age, gender, drug allergies or comorbid conditions were observed. Acute infusion reactions were more common in those with previous infliximab exposure (OR 6.23, 95% CI 1.72, 23.08, P = 0.002). Prophylaxis with any agent (oral diphenhydramine, IV diphenhydramine, IV hydrocortisone, IV saline) was not associated with a reduction in acute infusion reactions (P = 0.29); prophylaxis with oral diphenhydramine (P = 0.048) or IV hydrocortisone (P = 0.019) was associated with an increased risk of acute infusion reaction.

Comment: Pre-medication before infliximab infusions is frequently performed both reactively and prophylactically to prevent infusion reactions. This retrospective chart review study examined the rates of infliximab infusion reactions and the effect of pre-medication. Overall the rate of infusion reactions was low (< 2%), and the majority of reactions occurred during induction (53%). The major risk factor for an infusion reaction was prior exposure to infliximab. The use of premedication (antihistamine, glucocorticoid or saline infusion) did not significantly reduce the risk of infusion reaction. This study does not support the routine use of premedication to prevent infliximab infusion reactions.

Reference: P-153 — 2016
Abstract

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