Digestive Disease Week

Conference Review

Making Education Easy

DDW 2011, Chicago, USA, May 7-10, 2011

In this review:

Independent commentary by Drs John Wyeth and Michael Schultz.

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Welcome to our review of Digestive Disease Week (DDW) 2011, held recently in Chicago, USA.

The review is a summary of some of the latest and most exciting developments in digestive disease research presented at the meeting. Every year, DDW attracts close to 16,000 physicians, researchers and academics from around the world who aim to keep up-to-date with current research in their fields. Drs John Wyeth and Michael Schultz attended the meeting, and have selected and reviewed the presentations that they felt were most significant and relevant to local practice. Information about DDW is available from http://www.ddw.org.

Kind regards,

Dr Chris Tofield
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Induction and maintenance adalimumab therapy for the treatment of moderate to severe Crohn's disease in children

Authors: Hyams JS et al

Summary: The efficacy and safety of two adalimumab dosage regimens for the induction and maintenance of clinical remission in 192 paediatric patients with moderate-to-severe Crohn's disease (CD) were compared in this multicentre, randomised, double-blind study. Subjects received induction therapy with open-label adalimumab and were stratified at week 4 according to clinical response and prior infliximab (IFX) exposure, and randomised to maintenance therapy with either high- (n = 93) or low-dose (n = 95) adalimumab for 48 weeks. At week 26, clinical remission (PCDAI ≤10), the primary endpoint, was achieved by a higher proportion of high-dose recipients than low-dose recipients (39% vs 28%), but this comparison only reached significance in the group of patients who were IFX-naive (57% vs 35%; p = 0.026). With regard to safety, no new safety signals were detected.

Comment: (John) CD commonly presents in younger age groups, particularly in the teenage years. However, most clinical trials only include patients over 18 years. As a consequence, there is a lack of evidence in this younger group of patients. In this trial, weight-based dosing for adalimumab is being assessed for induction of remission in moderate-to-severe CD disease and then two dosage regimens were assessed for maintenance therapy, with stratification for prior use of infliximab. Safety data was also gathered. Excellent response rates during the induction phase were noted. Maintenance of remission was observed in both the high- and low-dose groups with no statistically significant difference. Previous exposure to infliximab was associated with a lower rate of remission. Most importantly, the adverse event profiles were judged similar to an adult population. This study gives evidence to support safe and efficacious use of adalimumab in patients under the age of 18 years. There is also evidence that weight-based dosing in children does not affect rates of induction and maintenance.

Oral presentation: #450

Prednisolone and budesonide for short-and long-term treatment of microscopic colitis: a systematic review and meta-analysis

Authors: Stewart M et al

Summary: This systematic review and meta-analysis included eight randomised controlled trials (RCTs; n = 248) investigating the short- and long-term efficacy of corticosteroids for the treatment of microscopic colitis (collagenous and lymphocytic). Budesonide was significantly more effective than placebo for both the induction of remission and long-term maintenance; RR 3.07 (95% CI 2.06-4.57) and RR 3.22 (95% CI 1.05-9.89), respectively. Prednisolone was not found to be superior to placebo for short-term clinical response. Both types of microscopic colitis exhibited similar clinical responses to short-term budesonide (28/32 vs 38/50; p = 0.2594). Significant histological improvement was evident with both short- and long-term budesonide therapy; pooled RR 3.76 (95% CI 2.00-7.06) and RR 2.50 (95% CI 1.25-4.98). Within 1-6 months of discontinuing budesonide, relapse occurred in 46-80% of patients.

Comment: (John) Microscopic colitis is generally considered a rare disorder. Evidence was presented of an increasing incidence of microscopic colitis and to levels approaching that of other forms of inflammatory bowel disease (IBD). Treatment options are limited for microscopic colitis. Budesonide is a glucocorticoid that resists absorption in the gastrointestinal (GI) tract leading to greater luminal concentrations in the distal GI tract. The study presented a review of published data on the use of glucocorticoids in the management of microscopic colitis. Budesonide was found to be significantly better in induction and maintenance of remission than prednisolone. This effect was the same for collagenous and lymphocytic colitis. Most importantly, high rates of relapse were found with cessation of therapy. This paper is of particular relevance to NZ as funding for budesonide in these conditions is not approved, and it gives more evidence in support of a review of this policy.

Oral presentation: #125

About Research Review

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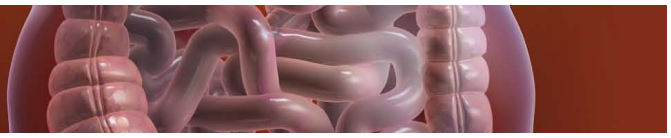


Factors which impact readmission in those with inflammatory bowel disease (IBD); a retrospective case series

Author: Hazratjee N

Summary: Factors associated with readmissions for IBD were assessed in this retrospective case series. Readmission was defined as admission to any service within 30 days from the discharge date of the index admission. Out of 106 patients admitted, 78 were readmitted (28 more than once). Just over two-thirds of those patients were readmitted within 2 weeks of their initial discharge; these patients were more likely to have not received a plan for pain control (34% vs 14%; p = 0.034) and prescription of oral non-narcotic medications was significantly less common in this group (44% vs 69%; p = 0.016). Patients readmitted due to surgery were more likely to have only one readmission. Patients admitted with dehydration, obstruction or pseudo-obstruction were at high-risk for readmission.

Comment: (John) Digestive diseases are the second most common cause of readmission to US hospitals. Readmission rates are important for a number of reasons, including increased costs, restrictions on available beds and as a measure of quality of medical care. Modifiable factors were identified from this study that theoretically would reduce rates of readmission. A large majority of patients readmitted did so prior to having any outpatient follow-up occurring or being arranged. Not surprisingly, patients with sub-obstructive symptoms not having had surgery were very likely to be readmitted. The message for NZ, where hospital beds are at a premium, is in pre-discharge planning. It also raises the importance of the role of the IBD nurse who could either see the patient pre-discharge or be available on a `hot line' to assess patients not responding to treatment.

Oral presentation: #290

Should screen-detected and asymptomatic celiac disease patients be treated? a prospective and randomized trial

Authors: Kurppa K et al

Summary: This study aimed to determine if asymptomatic individuals with coeliac disease diagnosed by screening would benefit from a gluten-free diet. A total of 3031 healthy family members of patients with coeliac disease were screened and 40 endomysial antibody positive asymptomatic subjects aged ≥18 years were randomised to either continue with their normal gluten-containing diet or to start a gluten-free diet. All of the subjects on the gluten-free diet exhibited small-bowel mucosal structural improvements and a decrease in coeliac antibodies at 1-year follow-up (no significant change was seen in the gluten group). Despite being asymptomatic, the gluten-free group exhibited significant improvements in the total Gastrointestinal Symptom Rating Scale and Psychological General Well-Being scores (these scores did not significantly change in the gluten group). Vitamin B12 and folic acid levels also significantly increased in the gluten-free group. At completion of the trial, 85% of the gluten-free group were willing to continue on the diet.

Comment: (John) There is much debate about whether screening for coeliac disease should be offered. One of the reasons against screening is whether an asymptomatic patient will benefit from being identified and started on a gluten-free diet. This methodology does have some drawbacks, as once identified as antibody positive, subjects in the control arm may voluntarily reduce gluten intake. Also, the use of the endomysial antibody is less specific for coeliac disease, but during questions the authors commented that anti-TTG levels were also obtained. This study clearly demonstrated that screening identified asymptomatic subjects who benefited from being diagnosed and starting treatment. There is expert consensus in Australia and NZ that coeliac disease is underdiagnosed and recent media attention has highlighted the need for screening. Whether this study on family members of coeliac sufferers can be applied to the general population is unknown.

Oral presentation: #620

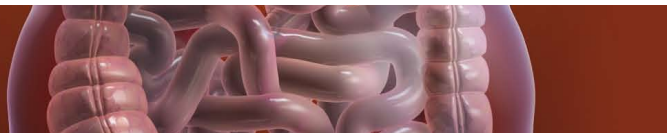
Upper esophageal sphincter compliance and 'somatization' are independently associated with symptom levels in globus patients

Authors: Rommel N et al

Summary: The association between sensitivity and compliance of the upper oesophageal sphincter (UOS) and oesophageal body (OB), psychiatric symptoms, 'somatisation' and globus symptoms was investigated in this study involving 28 patients with globus. UOS and OB compliance and sensitivity were assessed by oesophageal balloon distension. OB and UOS compliance and discomfort thresholds (volume and pressure) were measured, and globus symptoms were assessed using the validated Glasgow-Edinburgh Throat Scale. A validated self-report questionnaire was used to measure depression, 'somatisation' and different forms of anxiety (social anxiety, post-traumatic stress, anxiety sensitivity and gastrointestinal-specific anxiety). UOS compliance, depression and 'somatisation' correlated significantly with globus symptoms.

Comment: (John) With the advent of impedance studies of the oesophagus there has been considerable interest in motility disorders using the new technology and a large number of posters were present on oesophageal motility disorders. This study looked at a very common oesophageal symptom, globus, utilising a barostat to vary pressure and determine compliance within the UOS and the OB. For many years there has been an assumed relationship between globus symptoms and psychological events. Initially globus was referred to as globus hystericus, but this term is no longer used. Many studies have tried to associate oesophageal events, such as reflux, to globus with no strong association being found. In addition when reflux has been aggressively managed, little or no improvement in globus symptoms has been reported. The results of this study for the first time have shown the relationship of upper oesophageal sphincter compliance to globus symptoms. Furthermore, globus symptoms were found to be associated with depression and 'somatisation'. These positive findings will hopefully lead to a better understanding of globus and better ways to manage this common and distressing problem.

Poster presentation: #Sa1385



Intravenous glucagon reduces cecal intubation time during colonoscopy in patients with IBS

Authors: Kaswala DH et al

Summary: The benefits of IV glucagon during colonoscopy in patients (n = 34) with irritable bowel syndrome (IBS) were investigated in this double-blind RCT. Both groups received an initial dose sedation with ≤100 µg IV fentanyl and ≤5 mg of IV midazolam. One of the groups then received 1mg IV glucagon while the other group received 1 mL of saline (controls). Patients receiving IV glucagon exhibited a significant reduction in caecal intubation time compared with controls (7.53.2 minutes vs 10.94.8; p <0.019).

Comment: (John) The total number of colonoscopies being performed in NZ is increasing a rate of about 10% per annum and with the Colorectal Cancer Screening Program about to start there will be an even larger increase in volumes. It is always important to have a comfortable and safe procedure, but with screening procedures in healthy asymptomatic subjects it is even more so. Patients with IBS are generally considered to have more difficult intubations for colonoscopy. This study has demonstrated a simple addition of IV glucagon can decrease intubation times in patients with irritable bowel syndrome. Often these patients would have more discomfort due to a longer procedure, and as a result require sedation from an anaesthetist using propofol. Both time and costs may be reduced by using glucagon.

Oral presentation: #127

Surveillance for hepatocellular carcinoma

Author: El-Serag H

Summary/Comment: (Michael) The world-wide incidence of hepatocellular carcinoma (HCC) could be drastically decreased if hepatitis B virus (HBV) vaccination was available globally. However, this is not the case and over the last few years the incidence in the US has tripled. Five-year survival is estimated at approximately 12%, and about 90% of cases are related to liver cirrhosis as a consequence of chronic hepatitis B infection. Regular screening of HBV-positive patients with ultrasound and alpha-fetoprotein (AFP) measurement can reduce the mortality by 39%. The screening guidelines of the American Association of the Study of Liver Disease (AASLD) was reviewed last year (Bruix J & Sherman M, Hepatology 2011;53:1020-2) and it is obvious that screening should now only consist of 6-monthly abdominal ultrasound while the addition of the measurement of AFP is no longer required. The speaker pointed to a recent survey which showed that only about 9% of all patients in the US were offered regular, guideline-conforming screening with ultrasound and AFP while the rest were only offered either ultrasound (minority) or AFP (majority). However, the guideline developers' review of the literature comes to the conclusion that AFP is less sensitive than ultrasound as a screening test for HCC. The target of surveillance is identification of HCC at its earliest possible stage when treatment has the highest possible likelihood of cure, and data suggests that it is rare for the AFP to be elevated in lesions that are smaller than 2 cm in diameter. Nevertheless, the speaker made an urgent plea for the continuation of screening with AFP and ultrasound!

Oral presentation: #Sp88

Safety, immunogenicity and clinical phase I-II results of TNF-alpha kinoid immunotherapeutic in Crohn's disease patients

Authors: Vandepapeliere P et al

Summary/Comment: (Michael) An interesting study in which the investigators used a TNF-α kinoid to induce antibody formation against endogenous TNF-α in 21 patients with moderate-to-severe IBD. The authors aimed to achieve prolonged symptom control through TNF-α blockade. The medication was given IM in three different dosages on days 0, 7 and 28, with a fourth dose on day 168 for some patients. Antibodies against TNF-α were already measurable after two IM doses (day 7) in the higher dosage arms. The antibodies persisted for an average of 3-4 months and could be boosted with a further injection after 6 months. Although not sufficiently powered to detect clinical efficacy, a 70% response rate was seen at week 4, and this was sustained in 60% of patients through to week 12. Remission rates (CDAI ≤150) of 36% and 45% were seen at weeks 4 and 12. Remission was strongly associated with TNF–α antibodies and accompanied by decreased faecal calprotectin levels. No safety concerns were detected and a larger confirmatory trial is planned.

Oral presentation: #743

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Budesonide MMX 9mg for the induction of remission of mild-to-moderate ulcerative colitis (UC): data from a multi-centre, randomised, double-blind, placebo-controlled study in North America and India

Authors: Sandborn WJ et al

Summary/Comment: (Michael) Corticosteroids are effective in the treatment of UC and CD, but are associated with significant side effects. The MMX® technology for targeted gradual colonic release has been effectively used with mesalamine preparations and is now being tested with budesonide to deliver steroids to the colon of patients with moderate-to-severe UC without the unpleasant side effects. Once daily budesonide at 6 mg and 9 mg was compared to Asacol (800 mg TDS) and placebo over 8 weeks. A total of 489 patients were assessed clinically and endoscopically. Although a statistically significantly higher proportion of patients achieved remission at week 8 in the budesonide MMX® 9 mg group, a result of 18% is not extraordinary. Approximately 13% and 12% reached remission with budesonide MMX® 6 mg and Asacol, while in the placebo arm only 7% were in remission at week 8. There was no difference between the groups regarding adverse and serious adverse events. Budesonide is funded in NZ for ileal CD and only if glucocorticosteroids are not tolerated.

Oral presentation: #746

Top-down therapy in IBD in 2011: When, where, and for whom?

Author: Sandborn WJ

Summary/Comment: (Michael) The controversy between a top-down approach in which maximal therapy is given in early CD and a bottom-up approach with stepwise escalation of medication continues. The speaker, clearly a believer of the top-down approach justified aggressive therapy in early disease with several studies by Cosnes, Thia and Pariante who demonstrated convincingly that in CD only about 15-20% of patients will remain without complications, and more than a quarter of patients with UC will undergo colectomy. At least for CD, significant risk factors have been identified that are associated with an overall severe course of disease. If two out of three risk factors are present (disease onset < age 40, perianal disease, need for steroids with first presentation, deep ulcerations on colonoscopy) the chance of severe disease has been calculated as over 60%, or in other words, only 1:4 patients will be in steroid-free remission by the end of the first year. Prof. Sandborn suggested at least to introduce a steroid-sparing medication if the patient requires more than three months of steroid treatment and pointed again to the SONIC trial that demonstrated a remission rate by week 16 which was significantly higher if azathioprine is given together with IFX. However, it was acknowledged that this might be not achievable in some countries due to funding restrictions as in NZ, however, in patients with sufficient risk factors, early combination of steroids and azathioprine needs to be considered. Although smoking cessation is advocated strongly in patients with active CD, the additive beneficial effect is estimated at approximately 9%.

Oral presentation: #Sp336

The Role of Vitamin D in the Pathogenesis of Inflammatory Bowel Diseases

Oral administration of $1,25(OH)_2d_3$ protects against mucosal injury and epithelial barrier disruption in acute dextran sulfate sodium-induced colitis

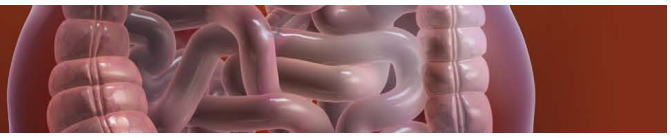
Authors: Zhang X et al

Summary: This animal study investigated the effect of $1,25(OH)_2d_3$, the hormonally active form of vitamin D, on acute dextran sulphate sodium (DSS)-induced colitis in mice. The mice were separated into three groups, a control group who received only regular water, the DSS model group who received 2% DSS water and the vitamin D3 group who received 2% DSS water and $1,25(OH)_2d_3$. Results revealed that the colons of the DSS model group showed more severe ulceration and inflammatory cell infiltrate than those of the control and $1,25(OH)_2d_3$ groups. Myeloperoxidase (MPO) activity was significantly increased in the DSS model group compared with the control group (0.92 vs 0.48; $p < 0.05$), and was significantly decreased in the $1,25(OH)_2d_3$ group compared with the DSS model group (0.61 vs 0.92). Fluorescein isothiocyanate dextran (FITC-D) was used to show change in intestinal permeability and the levels of FITC-D were found to be higher in the DSS model group compared with the control and $1,25(OH)_2d_3$ groups. Bacterial translocation was only present in the DSS model group (evident in 80%). The protein and mRNA levels of Zo-1, occludin and clandin-1 expression were decreased in the DSS group compared with controls, and the levels of these markers were found to be enhanced in the $1,25(OH)_2d_3$ group compared with the DSS group.

The authors concluded that $1,25(OH)_2d_3$ appears to protect against mucosal injury and epithelial barrier disruption in mice with acute DSS-induced colitis.

Comment: See page 4.

Oral presentation: #Su1947



High sun exposure is associated with a decreased risk of incident Crohn's disease in the E3N cohort study

Authors: Jantchou P et al

Summary: The relationship between level of sun exposure and incident CD and UC was investigated in this French study involving 91870 women. A total of 123 incident cases of IBD (71 UC; 45 CD; 7 indeterminate colitis) were identified. High sun exposure was found to be associated with a decreased risk of CD 0.46 [95% CI 0.22-0.98]), but not UC.

Comment: See below.

Oral presentation: #630

Vitamin D deficiency in inflammatory bowel disease

Authors: Gaidos J et al

Summary: The incidence of vitamin D deficiency was investigated in this retrospective chart review of all patients (n = 248) ≥18 years of age with IBD who presented to the IBD clinic at the University of Florida between January 2010 and June 2010. A total of 64 (25.8%) patients had had their vitamin D level measured in the past 2 years and 85.9% of those patients had CD; 30% were vitamin D deficient (serum 25-hydroxyvitamin D level ≤20 ng/mL) and 44% were vitamin D insufficient (serum 25-hydroxyvitamin D level 21-29 ng/mL). Eighteen patients were taking vitamin D supplements (daily doses 400-800 IU), but 26% remained deficient and 21% remained insufficient. Elevated CRP was found to correlate with vitamin D deficiency and this may reflect decreased outdoor activities or malabsorption.

Comment: See below.

Oral presentation: #Su1234

A prospective study of Vitamin D status and risk of incident Crohn's disease and ulcerative colitis

Authors: Ashwin N et al

Summary: This prospective study investigated the influence of predicted levels of pre-diagnostic plasma 25-hydroxyvitamin D and intake of dietary vitamin D in relation to the risk of incident UC or CD in 121,700 women taking part in the US Nurses' Health Study established in 1976. Through 2002, 105 incident cases of UC and 104 incident cases of CD were identified. Among 104,404 women followed up, the median predicted 25-hydroxyvitamin D level was 28 ng/mL (range 13-37 ng/mL). A higher 25-hydroxyvitamin D score was significantly associated with a decreased risk of incident UC and incident CD; multivariate HR for UC 0.45 (95% CI 0.24-0.85) and for CD 0.57 (95% CI 0.33-1.00) when women with 25-hydroxyvitamin D scores in the lowest quartile were compared with those with scores in the highest quartile. Women with a dietary vitamin D intake of >400 IU/day had a significantly lower risk of incident IBD than those who took <100 IU/day (HR 0.31; 95% CI 0.11-0.86).

Comment: See below.

Oral presentation: #629

Vitamin D status in inflammatory bowel disease: association with disease activity

Authors: O'Neill R and Mahadevan U

Summary: Data from 335 adult patients with IBD (208 CD and 127 UC) and a documented 25-hydroxyvitamin D level were analysed in order to determine whether there is an association between low vitamin D status and disease severity in IBD. Overall, 57.2% of patients had 25-hydroxyvitamin D levels that were deficient (<10 ng/mL) or insufficient (<30 ng/mL). Mean serum 25-hydroxyvitamin D levels were similar between CD and UC patients (28.2 ng/mL and 28.4 ng/mL), and were similar between patients with active disease and disease in remission. Prior surgery and current use of biologic agents were independently associated with low 25-hydroxyvitamin D levels in CD patients, while steroid use in the last 6 months was associated with lower 25-hydroxyvitamin D levels in patients with UC.

Comment: See below.

Oral presentation: #1207

High dose Vitamin D therapy in paediatric IBD

Authors: Day AS et al

Summary: The use of intermittent high-dose vitamin D (STOSS therapy) in children with IBD and vitamin D deficiency was evaluated in this retrospective study of 28 patients. Subjects received up to 800,000 units of vitamin D as a single dose. In total, 35 STOSS treatments had been performed; seven children had required repeat dosing after a mean of 12.6 months. The mean 25-hydroxyvitamin D level prior to treatment had been 37.9 (range <12-49), 1 week after STOSS therapy had been 216.6 (89-298) and 4 weeks after therapy had been 144.3 (62-253).

Comment: See below.

Oral presentation: #Su1925

Combined commentary on Vitamin D studies by Michael Schultz

It is well recognised that vitamin D plays an important role in the innate and adaptive immune response. The role of vitamin D in wound healing and barrier function has been demonstrated by Zhang et al. Animals without high levels of vitamin D developed significant mucosal injury as indicated by high MPO levels and furthermore, bacterial translocation was increased. Vitamin D induced increased Zo-1, occludin and claudin-mRNA levels indicating a direct impact on barrier integrity. Vitamin D can be consumed to a certain degree in foods, but is mainly manufactured in the skin in response to sunlight exposure. There are several reasons why patients with IBD might be Vitamin D deficient and while during phases of active inflammation or post-surgery, vitamin D cannot be absorbed in sufficient quantities, un-well patients might not get enough exposure to sunlight. Several studies examined the connection between disease activity and vitamin D status. Gaidos et al found 75% of patients with IBD to be vitamin D deficient or insufficient and almost half of all patients on vitamin D supplements were still deficient. Jantchou et al analysed a cohort of 91870 women living in France and found a lower incidence of CD in women with high sun exposure. A further study analysed the 121,700 women of the Nurses' Health Study and found that higher levels of Vitamin D usually correlated with a lower incidence of IBD. Only one study investigated the correlation between Vitamin D levels and disease activity. In that study, a low Vitamin D level was associated with surgery, use of biologics and need for steroid medication in the 6 months prior to the study. This indicates a more severe course of disease. Day et al successfully corrected the Vitamin D status in paediatric patients with IBD with a single dose of up to 800,000 units. However, interval and correct dosing is the subject of further investigations. Data does not exist whether the significant difference in sunshine exposure between the NZ North Island and South Island correlates with IBD incidence.

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