European Crohn's & Colitis Organisation Congress

Conference Review

Making Education Easy

ECCO 2010, Prague, Czech Republic

In this issue:

Welcome to our review of the 5th Congress of the European Crohn's and Colitis Organisation (ECCO).

The ECCO Annual Scientific Meeting is fast becoming one of the premiere forums for the dissemination of inflammatory bowel disease (IBD) knowledge worldwide. Held over 2-3 days in February each year, abstracts presented at this meeting are not precluded from being presented at either Digestive Disease Week (DDW) or United European Gastroenterology Week (UEGW), leading to many key studies being presented multiple times. The ECCO is taking a worldwide lead in the promotion of IBD science and clinical excellence through this meeting, and others, including task forces that examine specific issues and produce comprehensive guidelines, the latest of which were published in the most recent edition of the ECCO journal, *Journal of Crohn's and Colitis*. Next year, the congress will be held in Dublin and is to be recommended for those who wish to attend a comprehensive IBD conference. Below are summaries of, and commentaries on, selected abstracts that were presented at the ECCO 2010 congress held in Prague, in the Czech Republic, in late February.

Kind regards,

Associate Professor Richard Gearry
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Genetic variants that predispose to early complications in Crohn's disease identified by re-analysing genome-wide association study data from 3 consortia

Authors: Lee JC et al

Summary: These researchers set out to identify a panel of genetic variants that associate with early complications in Crohn's disease (CD), in particular, the need for surgery for penetrating or stenosing disease within a year of diagnosis. Patients with mild or aggressive disease were identified from a combined sample set from three genome-wide association (GWA) studies. From a total of 2653 patients, 396 individuals with aggressive CD (requiring abdominal surgery for stenosing or penetrating disease within the first year of diagnosis) and 466 with mild CD (inflammatory disease without perianal involvement and no requirement for surgery during a minimum of 5 years' follow-up) were identified. A panel of single nucleotide polymorphisms (SNPs) was identified that surpassed the accepted threshold of significance for replication ($p < 1x10^{-5}$). The findings suggest the existence of polymorphisms that specifically predispose to an aggressive disease course in CD.

Comment: GWA studies have provided us with over 30 susceptibility genes for CD. However, they assume that CD is a homogenous group when in reality CD comprises a heterogeneous group of patients. Revisiting data from GWA studies published thus far, and drilling down to look at severe compared with mild phenotype, has been richly rewarded with 26 significant SNPs being discovered. What is more remarkable is that none of these SNPs have previously been associated with CD! Not surprisingly, many are associated with cell signalling molecules and also one pro-apoptotic tumour suppressor gene. These data need replication but may, at last, provide some clinically useful genetic biomarkers that may determine prognosis.

Abstract Oral 5

http://tinyurl.com/yk5vrp6

Independent commentary by Associate Professor Richard Gearry, Senior Lecturer, Department of Medicine, University of Otago (Christchurch). He has clinical and research interests in luminal Gastroenterology, particularly IBD epidemiology, aetiology, biomarkers, therapeutics and clinical outcomes. He is a member of the Asia Pacific and World Congress of Gastroenterology Consensus Groups for inflammatory bowel disease.

Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis

Authors: Reinisch W et al

Summary: The efficacy and safety of adalimumab (ADA) for the induction of clinical remission in ulcerative colitis (UC) was investigated in this multicentre, randomized, double-blind, placebo-controlled study involving anti-tumor necrosis factor (TNF) naive patients with moderately to severely active UC. Adult patients (n = 186) with a Mayo score of ≥6 points and an endoscopic subscore of ≥2 points in spite of treatment with corticosteroids and/or immunosuppressants were randomized to subcutaneous treatment with ADA 160/80 (160 mg at week 0, 80 mg at week 2 and 40 mg at weeks 4 and 6) or placebo in a 1:1 ratio. After trial initiation, ADA was approved in Europe for the treatment of Crohn's disease at an induction dose of 80/40 mg or 160/80 mg. The protocol was amended and an additional 390 patients were randomized in a 1:1:1 ratio to ADA 160/80, ADA 80/40 (80 mg at week 0, 40 mg at weeks 2, 4 and 6) or placebo. Significantly more patients in the ADA 160/80 group achieved clinical remission (primary efficacy endpoint; Mayo score ≤2 with no individual subscore >1 at week 8) compared with the placebo group (19.2% vs 9.2%; p = 0.021); there was no significant difference between ADA 80/40 and placebo recipients (10% vs 9.2%). Serious adverse events in the ADA 160/80, ADA 80/40 and placebo groups occurred in 4.0%, 3.8% and 7.6% of patients, respectively.

Comment: We are all becoming increasingly comfortable with prescribing Adalimumab for CD but it appears that we may soon have a second indication for this drug, with this study showing that adalimumab is twice as likely as placebo to induce remission in patients with moderate to severe UC. While the absolute remission rate at week 8 seems low (19.2%), the remission rate appears to be trending upward at this point and it is likely that longer term data may show a greater effect over time and that the placebo rate will reduce. Funding adalimumab for UC once it is indicated in NZ is likely to be at DHB level in the short-to-medium term.

Abstract Oral 7

http://tinyurl.com/yktqoey

Predictors of intestinal failure in inflammatory bowel disease

Authors: Gearry RB et al

Summary: The study investigated clinical and surgical factors that predispose to intestinal failure in inflammatory bowel disease (IBD). A prospective database from a UK tertiary-referral specialist-hospital was used to identify consecutive IBD patients with intestinal failure. A total of 87 patients were identified, 82 with Crohn's disease (CD) and 5 with ulcerative colitis; all patients were confirmed as having a requirement for IV nutrition or fluid. All cases were matched and compared with population-based controls. Factors found to be significantly associated with the development of intestinal failure were diagnosis at <17 years of age (p = 0.01) and a family history of IBD (p = 0.02). Perioperative complications contributing to intestinal failure were evident in 53% of the CD patients. Intestinal failure due to perioperative complications was associated with the absence of extra-intestinal manifestations (p = 0.03) or stricturing behaviour (p = 0.01), but with a greater number of abdominal surgeries (p = 0.05). Intestinal failure due to primary active CD was associated with early age at first surgery (p = 0.004) and stricturing behaviour (p = 0.02).

Comment: This work (supported by the Olympus-NZSG Travelling Fellowship) from St Mark's Hospital in London was also presented at the NZSG ASM in Wellington in November 2009. While there are few IBD patients in NZ receiving long-term intravenous nutrition, many of the risk factors identified in this study are (predictably) similar to those that are associated with poor prognosis in CD (early age of diagnosis, complicated disease behaviour and family history of IBD). Such patients should be identified early and be treated aggressively in an attempt to prevent such outcomes.

Abstract Oral 22

http://tinyurl.com/yzlrzwu

Long-term outcome of treatment with infliximab in paediatric Crohn's disease: A population-based study

Authors: Crombe V et al

Summary: The long-term clinical benefit and safety of infliximab (IFX) was assessed in an inception population-based cohort (<17 years of age) who had newly-diagnosed Crohn's disease (CD). From the cohort (n = 537), 120 (69 female, 51 male) were identified who had received IFX. Those who had discontinued IFX while in remission and those who were still receiving IFX at last follow-up were considered as `IFX efficacy', while those who stopped IFX due to adverse effects and those who were primary or secondary non-responders to IFX were considered as `IFX failure'. The median time to follow-up was 111 months. In 80% of subjects, IFX was started with concomitant azathioprine (AZA) and AZA was continued in 60%. Scheduled IFX was administered in 58% of patients, while 42% received episodic IFX. Sixty-six (55%) patients were in the IFX efficacy group (39 still receiving IFX at last visit, 27 stopped IFX while in remission) and 54 (45%) were in the IFX failure group (15 due to side effects, 39 were non-responders). The likelihood of receiving continuous maintenance IFX therapy at 1 year was 77% and at 3 years was 50%. The cumulative risk of surgery at 1 and 3 years was significantly reduced in the IFX efficacy group compared with the IFX failure group (6% vs 22% and 13% vs 36%; p = 0.009), and within the IFX efficacy group, the risk was significantly smaller in patients with scheduled rather than episodic treatment (2.5% vs 14% and 8% vs 23%; p < 0.03). Furthermore, individuals in the IFX efficacy group exhibited a significant catch-up of nutritional status (p = 0.01), while those in the IFX failure group did not.

Comment: These real life data from a population-based study of paediatric CD from northern France show that responders to infliximab not only have less surgery, but also catch up on nutritional status compared to non-responders. These end points are likely to reflect a dramatically improved quality of life that is particularly important during adolescence and early adulthood.

Abstract Oral 19

http://tinyurl.com/yj7q2o4

Severe auto-immune driven arthralgia as a new side effect in anti-TNF-α treated IBD patients?

Authors: Van Moerkercke W et al

Summary: In this Belgian study, 21 patients (17 with Crohn's disease and 4 with ulcerative colitis) with invalidating polyarthralgia were identified from a series of almost 1300 patients in remission receiving either infliximab (IFX) or adalimumab (ADM). Eight of the 21 patients were receiving IFX, while 13 were receiving ADM (all but one of whom had previously received IFX). Two of the patients had known spondylarthropathy with axial localisation, but had developed peripheral polyarthralgia during treatment with the agents. All of the 21 patients displayed very high antinuclear antibody (ANA) titres, with 15 having a titre of 1/640, 1/1280 or >1/1280). Seventeen were anti-double stranded (ds) DNA positive. The very high ANA and anti-dsDNA levels observed in all of the patients suggest an autoimmune lupus-like phenomenon.

Comment: With the increasing use of biological agents in clinical practice new adverse events are emerging. Skin reactions including psoriaform and pustular lesions, eczematous eruptions and bacterial and fungal skin infections are now well described and appear to be class effects of these agents. While the cause of these adverse effects remain elusive, we should remain vigilant for new adverse effects in our biologically-treated IBD patients.

Abstract Oral 18

http://tinyurl.com/ykhb9af

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Deep remission for adalimumab-treated patients with moderate to severe ileocolonic Crohn's disease: Results from EXTEND

Authors: Colombel J et al

Summary: The multinational, randomized, placebo-controlled EXTEND (EXTend the Safety and Efficacy of Adalimumab Through ENDoscopic Healing) study investigated the efficacy of adalimumab for achieving 'deep' remission, defined as clinical remission (Crohn's Disease [CD] Activity Index [CDAI] <150) and mucosal healing (absence of mucosal ulceration). A total of 135 patients with moderate-to-severe ileocolonic CD (CDAI 220-450) and baseline mucosal ulceration received open-label adalimumab 160/80mg induction therapy at weeks 0/2. At week 4, 129 patients were randomized to maintenance therapy with adalimumab 40 mg every other week or placebo. From week 8, patients with nonresponse or flares were able to receive open-label adalimumab. The analysis included 123 patients with ulceration at screening, with a post-hoc sensitivity analysis performed for the entire intention-to-treat population (n = 129). At week 52, significantly ($p < 0.001$) more patients in the adalimumab group (12/62) *vs* the induction-only placebo group (0/61) had achieved both clinical remission and mucosal healing (determined by colonoscopy); at week 12 the difference between groups in the number of patients in deep remission (10 vs 6) was nonsignificant. In the *post-hoc* sensitivity analysis, at week 12, patients randomized to adalimumab were 3.4-fold more likely than placebo to achieve deep remission ($p < 0.05$). In these patients, adalimumab therapy improved the likelihood of achieving deep remission compared with placebo. The true impact of adalimumab therapy at week 12 may be underestimated partly due to residual effects of induction therapy.

Comment: The latest therapeutic target for CD is deep remission, defined as a CDAI of <150 and mucosal healing. EXTEND demonstrates that this is possible in 1/5 CD patients at one year. While this study missed its primary endpoint of deep remission at 12 weeks, the one year data is of more clinical use to patients and gastroenterologists. While the therapeutic targets continue to evolve, we should remember that patients can gain tremendous benefit from these agents without reaching such difficult endpoints. Many patients will be happy to have a 100 point drop in CDAI without achieving deep remission as it will provide a clinically meaningful improvement. While we should always aim for the best possible response for all therapies, patients will often be satisfied with a lesser result if it leads to an improved quality of life.

Abstract Oral 16

http://tinyurl.com/ygfmryy

Liver histology of IBD patients who are treated with 6-thioguanine due to failure of conventional thiopurines reveals very few cases of nodular regenerative hyperplasia

Authors: van Asseldonk DP et al

Summary: This prospective cross-sectional multicentre cohort study, by researchers from The Netherlands, assessed the short-term hepatotoxicity of 6-thioguanine (6-TG) in 99 inflammatory bowel disease (IBD) patients (61 with Crohn's disease, 38 with ulcerative colitis) who had previously failed therapy with conventional thiopurines. The patients (mean age 43.8 years; 36 male) received 6-TG at an intended dose of 0.3 mg/kg (mean actual dose 0.28 mg/kg) for at least 6 months and underwent a liver biopsy for safety assessment according to European consensus guidelines. The median duration of IBD prior to initiation of 6-TG was 9 years (range 1-54) and the median duration of 6-TG treatment, from initiation to first liver biopsy, was 25 months (range 6-65). Results showed no abnormalities in 51 specimens, mild steatosis in 14, severe steatosis in 2, mild fibrosis in 3, sinus dilatation in 8, steatohepatitis in 2, cholangitis/PSC in 4, aspecific regeneration in 11 and nodular regenerative hyperplasia (NRH) in 4.

Comment: 6-TG received very bad press a few years ago when it was thought to be linked to NRH of the liver. However, this and other studies by the Amsterdam group have shown prospectively that NRH is present in IBD patients who have not been treated with thiopurines and, more importantly, that 6-TG is unlikely to be a risk factor for NRH if dosed according to the IBD therapeutic range for thiopurine metabolites.

Abstract Oral 17

http://tinyurl.com/yzfm7um

Long-term maintenance of clinical remission with reduced dosing frequency of adalimumab in patients with moderate to severe Crohn's disease

Authors: Panaccione R et al

Summary: This study assessed maintenance of clinical remission, defined as a Crohn's Disease Activity Index (CDAI) score <150, in patients with moderate-to-severe CD who had their adalimumab administration frequency reduced from weekly to every other week (eow). The analysis involved 75 patients who were in remission after completing the 56-week CHARM (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance) study and who had enrolled in the open-label ADHERE (Additional long-term Dosing with Humira (adalimumab) to Evaluate sustained Remission and Efficacy in Crohn's disease) trial. During their participation in CHARM, they had received open-label induction with adalimumab 80 mg at week 0 and 40 mg at week 2, followed by blinded adalimumab 40 mg weekly. At the start of ADHERE, these patients received open-label adalimumab 40 mg eow; patients experiencing a disease flare or non-response were able to move to weekly administration. Sixty four patients (85%) maintained a reduced frequency of adalimumab 40 mg eow during ADHERE. Clinical remission was maintained in 54 patients (84%) at 92 weeks' follow-up and in 50 patients (78%) at 116 weeks' follow-up. These findings indicate that a high percentage of patients are able to maintain clinical remission after a reduction in adalimumab administration frequency from 40 mg weekly to 40 mg eow.

Comment: Long-term studies from referral centres have told us that at least 1/6 CD patients treated with infliximab or adalimumab are likely to require dose escalation, usually in the form of a reduction in dose interval. While this is not specifically prohibited under the Pharmac guidelines for the use of adalimumab in New Zealand, Pharmac may argue that it is not in the spirit of the agreement to fund adalimumab for CD. The study by Panaccione et al demonstrates that almost all patients who require dose escalation can be re-established on fortnightly administration eventually. Other options for secondary non-responders may be re-induction with 160/80 mg, but there are no data supporting this approach.

Abstract P102

http://tinyurl.com/yhqkk3s

Immunomodulatory treatment reduces the need for ileocecal resection in Crohn's disease

Authors: D'Haens G et al

Summary: This study investigated patients at a single centre who were diagnosed with Crohn's disease (CD) of the terminal ileum between 1995 and 2005. Patient characteristics, results from endoscopic and radiological studies and all medical treatment received from diagnosis until August 2008 were reviewed. Patients that had required an ileocolonic resection were identified, and the impact of the type and duration of medical treatments on the incidence of these resections was analyzed. Seventy-four patients (mean age at diagnosis 38 years; 35 male) with ileitis/ileocolitis and complete follow-up were identified. However, 8 of these patients had initially presented with intestinal complications and immediate need for surgery, and were excluded from further analysis. During follow-up (median time to follow-up 73 months; range 8-142), 23 additional patients (31%) required surgery. Multivariate analysis including smoking and use of different medications, revealed that treatment with azathioprine or methotrexate significantly ($p = 0.037$) protected against surgery (OR 0.214; 95% CI 0.050, 0.914), while treatment with steroids had a significant ($p = 0.0290$) negative impact on the need for surgery (OR 3.667; 95% CI 1.141, 11.787). Patients who had ever been treated with antiTNF and/or immunomodulators had the lowest risk for surgery ($p = 0.024$, OR 0.218; 95% CI 0.058, 0.819).

Comment: These data from the Leuven group add more fuel to the fire regarding the association of steroid use with poor outcome; requirement for bowel resection in this case. While longitudinal cohort studies have not clearly shown a benefit of immunomodulators in preventing surgery, this study confirms our clinical experience that these agents significantly benefit a proportion of patients. While steroids appear as a villain once again, it is unclear whether factors such as disease severity at diagnosis may have confounded this association and there is presently no hard evidence to cease using steroids in short courses for induction of remission in IBD.

Abstract P151

http://tinyurl.com/yhxp4t7

Predictors of suboptimal medication adherence in IBD patients: A single Australian tertiary centre experience

Authors: van Langenberg D et al

Summary: A large prospective Australian inflammatory bowel disease (IBD) cohort was investigated in order to determine patient factors associated with suboptimal medication adherence. A total of 256 IBD patients with any encounter(s) at a tertiary care hospital over a 6 month period were prospectively identified and verified. A survey including medication adherence, patient IBD knowledge, quality of life (QoL), satisfaction with medical care, mental health and other clinical/demographic data was sent to each patient. Adherence was assessed using the Medication Adherence Report Scale (MARS-5), with a total score of <20 indicating suboptimal adherence. Predictors of suboptimal adherence were then analyzed using bivariate then subsequent multivariate logistic regression. A total of 162 individuals (53% female) responded to the survey; 95 had Crohn's disease and 65 had ulcerative colitis (UC). Overall, 36% exhibited suboptimal adherence. Medication adherence score was significantly ($p = 0.04$), though weakly, negatively associated with anxiety ($r = 0.17$) and significantly ($p < 0.03$) positively correlated with patient age, satisfaction with medical care and QoL ($r = 0.42, 0.37, 0.19$, respectively). Multivariate analysis revealed predictors of suboptimal adherence including a diagnosis of UC (OR 2.861; 95% CI 21, 6.76), younger age (OR 1.06; 1.03, 1.09) and poor satisfaction (OR 4.63; 2.11, 10.16).

Comment: It's all very well prescribing drugs for our patients, but if our patients do not adhere to our treatment plans we are wasting our time. This group from Adelaide assessed adherence in 162 IBD patients from a single centre and showed that younger patients with UC are most likely to be poorly adherent. This is concerning as these patients are likely to be receiving 5-ASA, which will not only reduce the risk of disease flare but is also associated with a reduced long term risk of developing colorectal dysplasia or neoplasia. Adherence may be improved with once daily dosing of 5-ASAs which is at least as effective at maintaining remission as split dosing.

Abstract P152

http://tinyurl.com/ylk795k

A multidisciplinary virtual biologic clinic: Is it worthwhile?

Authors: Duncan J et al

Summary: Patients receiving biologic drugs require regular review but, due to service limitations, this may be difficult. A recently introduced Virtual Biologics Clinic (VBC) in London was assessed to determine whether it was an effective tool in managing such patients. The clinic is a multidisciplinary weekly one hour meeting comprising three consultant gastroenterologists, a clinical nurse specialist and a specialist pharmacist. The clinic reviews cases of all patients who have received infliximab that week and 1/8th of the patients taking adalimumab in rotation. The results of the VBC were reviewed and assessed for the period May to October 2009 in order to determine whether the clinic had resulted in management-changing decisions. At the start of the 6 month period, 40 patients were receiving infliximab and 17 adalimumab, with a median treatment duration of 12 months. During the assessment period, 13 patients started infliximab and 2 started adalimumab. Concomitant immunomodulation (IM) was used in 48 patients; 25 received azathioprine, 11 received 6-mercaptopurine, 8 received methotrexate and 4 received thioguanine. Within the clinic, the case records of 72 patients (35 male; median age 32 years) with inflammatory bowel disease (IBD) including 65 with Crohn's disease (CD), 1 with IBD unclassified type and 6 with orofacial granulomatosis, were reviewed 178 times (median 2; range 0-5). A total of 159 management decisions were made in 53 patients and included the following; 20 dose alteration decisions, 3 withdrawals from treatment, 3 biologic changes (adalimumab to infliximab in 1 patient, infliximab to adalimumab in 2), request for endoscopy in 9 cases, MRI in 5, an urgent clinic appointment in 19, 5 specialist referrals and 94 other management decisions, including the need for, or optimisation of, IM. These findings show that the VBC is an effective forum in which to make management decisions and that it has the advantage over clinic of ensuring that complex management decisions are reviewed by a multidisciplinary team.

Comment: This study from Guy's and St Thomas' in London shows that once CD patients have been placed on biological drugs, there is still plenty to be achieved through regular review of patients and close attention to optimising biologic, immunomodular and nutritional therapy. While it is unlikely that any single clinic in NZ will have this number of patients on anti-TNF drugs, the importance of ongoing review at a conventional clinic is underlined in this abstract.

Abstract P143n

http://tinyurl.com/yhybor2

Audit of prevention of opportunistic infections in immunosuppressed patients with IBD: how close are we to ECCO guidelines?

Authors: Elliott T et al

Summary: A consensus statement on screening for, and prevention of, opportunistic infections associated with immunomodulatory (IM) therapy in inflammatory bowel disease (IBD) has recently been published by the European Crohn's and Colitis Organisation (ECCO). IBD patients at risk of opportunistic infections are defined by the ECCO statement as those who are treated with thiopurines, methotrexate, infliximab, adalimumab or prednisolone >20 mg daily for >2 weeks. This investigation compared current practice of screening for, and prevention of, opportunistic infections at a UK IBD tertiary referral centre with the ECCO recommendations, and examined the implications of following the guidelines. Ninety consecutive IBD patients (46 male) at risk of opportunistic infections according to the ECCO consensus statement, were selected from attendance at an IBD clinic and infliximab infusion service from July to November 2009. Seventy one patients had Crohn's disease, 19 had ulcerative colitis and 1 had IBD-unclassified. All of the patients had started IM between 2001 and 2009; 41% thiopurine monotherapy, 34% concomitant thiopurine and antiTNF therapy, 14% antiTNF monotherapy, 6% prednisolone >20 mg daily for >2 weeks and 5% methotrexate. The proportion of patients who underwent recommended screening tests prior to IM therapy were as follows; HbsAg 28%, antiHBs 8%, antiHBc 9%, HCVAb 28%, HIVAb 11%, VZVAb 15%, CXR 46%, cervical smear 57%. The following percentages of patients received the recommended vaccinations prior to initiation of IM; hepatitis B 10%, VZV 0%, HPV 0%, influenza 16%, *S. pneumoniae* 2%. The study showed that patients on antiTNF therapy were significantly ($p < 0.05$) more likely to have undergone CXR, hepatitis B and C screening. The cost of undertaking the recommended ECCO screening tests and vaccination strategy (excluding HPV) was calculated at €279 EUR per patient; equipment and manpower costs not included. These findings clearly indicate that the current practice at this centre is not in line with recent ECCO recommendations.

Comment: One of the big stories in IBD over the last two years has been the expert recommendations and guidelines concerning testing for and vaccinating against infections prior to commencing not just antiTNF drugs but also immunomodulators such as azathioprine, 6-mercaptopurine and methotrexate. While TB testing prior to the initiation of antiTNF drugs has been universally adopted by most, local experience (and that in the UK) suggests that more widespread testing is not occurring prior to the commencement of other immunomodulators. As noted in this abstract, more data will be needed to convince most that such testing and vaccination is both worthwhile and cost-effective.

Abstract P126

http://tinyurl.com/yf75qr2

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