# European Crohn's & Colitis Organisation Congress

## Conference Review

Making Education Easy

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## In this review:



## About the Reviewer


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Richard's research focuses on luminal gastroenterology including the genetics of inflammatory bowel disease (Crohn's disease and ulcerative colitis) and the pharmacogenetics of thiopurine drugs. He collaborates widely with groups within the University of Otago, New Zealand and internationally.

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# Welcome to our review of the 7th Congress of the European Crohn's and Colitis Organisation (ECCO).

ECCO was once again an excellent forum for the presentation of high-quality inflammatory bowel disease (IBD) research ranging from basic science to clinical research. A strength of this year's meeting was a strong presence of patient groups in both satellite meetings and also the main scientific meeting. I would recommend this meeting to those of you who would like to attend an IBD-focused meeting.

Below are summaries of selected abstracts that were presented at the ECCO 2010 congress held in Barcelona, Spain in February.

Kind Regards,


**Dr Richard Gearry**

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## Mortality and cancer in paediatric inflammatory bowel disease: A population-based study

**Authors:** Gower-Rousseau C et al


**Summary:** In this retrospective French study, 698 patients under 17 years of age with IBD (538 with Crohn's disease [CD] and 160 with ulcerative colitis [UC]) were identified from the EPIMAD (Registre des Maladies Inflammatoires Chroniques du Tube Digestif) patient registry and the incidence of death and cancer compared to those of the general population. Median age at diagnosis was 14 years and overall mortality during a median follow-up period of 11.5 years was 0.84% and did not differ from the general population (standardised mortality ratio 1.4; 95% CI 0.5–3.0; $p = 0.27$). 1.3% of the study population (9 patients) had a diagnosis of cancer after a median follow-up period of 15 years and this represented a higher risk of cancer than in the general populace (standardised ratio of incidence 2.7; 95% CI 1.1–5.6; $p < 0.02$). Of the nine patients who developed cancer, six had received immunosuppressive and/or anti-TNF therapy. Just over half of the patients developing cancer had been exposed to combination therapy.


**Comment:** Northern France leads the way in IBD epidemiological research with excellent databases in the form of EPIMAD. This abstract was one of only 20 awarded oral presentations and reported no overall significant risk of mortality in this paediatric disease onset cohort. However, the increased risk of cancer was significant and reminds us that young age of colitis diagnosis is, in its own right, an important risk factor for colorectal cancer. Finally, the role of immunosuppression in the development of these cancers is difficult to tease out, but should remain in the back of our minds for those receiving immunosuppressive therapy, especially in combination.

***Oral presentation: #OP04***

Available from: http://tinyurl.com/798op72

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## Use of fecal calprotectin as marker of disease activity in patients under maintenance treatment with infliximab for ulcerative colitis [on behalf of BIRD]

**Authors:** De Vos M et al

**Summary:** In a Belgian/Norwegian study, 113 UC patients were followed-up for 1 year while in remission under treatment with infliximab 5mg/kg every 8 weeks in order to evaluate the evolution of faecal calprotectin levels under maintenance therapy. Faecal calprotectin levels measured at monthly intervals were less than 50 mg/kg at all time points in 30 (26.5%) patients in "deep remission" (normal endoscopy at the start of the study and at week 52 with clinical Mayo scores <3), whereas in 13 [11%] patients who experienced a flare (clinical Mayo score during the study or an endoscopic score of ≥2 at week 52) calprotectin levels were significantly elevated at the time of flare (median 477 mg/kg) and a significant increase in calprotectin levels was observed up to 3 months prior to the flare. Receiver operating characteristic (ROC) analysis suggested that deep remission is associated with calprotectin levels <50 mg/kg (sensitivity 83.3% and specificity 83.3%), while two consecutive calprotectin levels of >300 mg/kg are predictive of a flare (sensitivity 61.5% and specificity 100%).

**Comment:** Despite the wide availability of faecal calprotectin testing in New Zealand through Canterbury Health Laboratories for many years, most of the rest of the world is only now looking at faecal calprotectin testing more seriously. This is particularly the case in health systems such as our own, however, there is less of a demand for faecal calprotectin testing in insured populations where colonoscopy remains favoured. This study shows that faecal calprotectin not only reflects current degrees of inflammation, but also is predictive for both relapse and remission. Increasingly, faecal calprotectin and other non-invasive tests are likely to be included in algorithms to optimise treatments.

***Oral presentation: #OP07***

Available from: http://tinyurl.com/7gve5ds

## Anti TNF-α therapy is a major cost driver in inflammatory bowel disease: Results from the COIN study

**Authors:** Van der Valk M et al

**Summary:** In this large study conducted in The Netherlands, researchers attempted to define the cost of IBD in the era of biologic therapy using a web-based questionnaire. In total, 2554 patients with CD (1304 [51%]), UC (928 [36%]) or unspecified IBD (322 [13%]) were followed-up for 3 months, and costs were calculated according to Dutch pharmacoeconomic guidelines. Costs included those associated with outpatient clinics, diagnostic procedures, surgery, hospitalisation and medication use, as well as productivity costs (work days lost to sick leave). Mean total costs in 3 months in patients with CD were €1738, with €1468 (84%) attributed to healthcare costs and €270 (16%) to productivity costs. The mean total costs reported for patients with UC were significantly lower than in those with CD (€896 total costs, 60% healthcare costs, 40% productivity costs). Medication was the primary cost, mainly due to anti-TNF-α therapy which accounted for an average of €1044 (71%) in patients with CD versus €186 (33%) in those with UC.

**Comment:** This very large Dutch study has tried to assess total costs of IBD including direct (healthcare) and indirect (social) costs. Typically, indirect costs are thought to represent double direct costs in most clinical studies. Recently our group looked at similar data in a small group of CD patients and found similar findings to these investigators, that the major driver of cost was in fact biological drugs. While this study does not yet assess the cost savings of using biologics (to follow), it reminds us that drugs are most cost-effective when they are working and we must rigorously review our patients receiving these drugs to ensure that they remain cost-effective.

***Oral presentation: #OP09***

Available from: http://tinyurl.com/7turpvt

## Importance of trough levels and antibodies on the long-term efficacy of infliximab therapy in ulcerative colitis

**Authors:** Arias MT et al

**Summary:** In this retrospective European study, researchers aimed to define the influence of infliximab trough concentration and antibodies on the long-term outcome of treatment of UC with infliximab induction and maintenance therapy in 135 consecutive patients. A treatment response was observed in 81% of patients by week 10, while dose optimisation was required in 50% of patients as a result of loss of response during follow-up. A low trough concentration of infliximab early after induction was associated with a higher risk for loss of response and discontinuation ($p = 0.02$). ROC analysis at week 14 indicated a trough concentration cut-off value for sustained benefit of 7.19 µg/mL (specificity 80%, sensitivity 57%). In patients where a trough concentration was undetectable at least once during follow-up, significantly shorter times to dose optimisation (log-rank $p = 0.02$) and loss of response (log-rank $p = 0.01$) were observed. After dose optimisation, an increase in trough concentration was associated with restoration of response (median 8.7 vs 3.2 µg/mL; $p = 0.05$). Infliximab was stopped for complete loss of response in 29 (26%) patients and in 12 (11%) patients undetectable trough concentrations and antibodies were measured at least once. While concomitant immunomodulator therapy did not affect discontinuation rates, median trough concentrations during the study were higher while patients were receiving immunomodulators (median 10.5 vs 7.9 µg/mL; $p = 0.02$) and antibodies were less frequently observed (OR 0.6; $p < 0.0001$).

**Comment:** Personalised medicine is becoming more relevant as we develop the tools to help us to optimise therapies for individual patients. It has become clear in recent years that both trough infliximab concentrations and antibody to infliximab titres may help determine loss of response to infliximab and help us to optimise or stop this drug appropriately for patients with CD. These investigators present similar data for UC showing that patients can be optimally managed using such a strategy. The data appear less clear for adalimumab trough concentrations and antibodies, but hopefully these data will emerge soon and testing may become appropriate in those losing response.

***Oral presentation: #OP10***

Available from: http://tinyurl.com/87upgws

## Adenomas in patients with inflammatory bowel disease: Increased risk of advanced neoplasia

**Authors:** van Schaik F et al

**Summary:** To determine whether patients with IBD and colonic adenomas are at increased risk of progression to colorectal cancer than non-IBD patients with sporadic adenomas, Dutch researchers reviewed data from a national pathology database from 1995-2005. Over a mean duration of 88 months, the cumulative risks of advanced neoplasia (high-grade dysplasia or colorectal cancer) were significantly higher in 110 patients with IBD and adenoma compared with 123 nonadenoma IBD patients and 179 adenoma patients without IBD (16%, 7% and 4% respectively; $p < 0.01$). In IBD plus adenoma patients, those who had typical (solitary sessile or pedunculated) adenomas had a lower cumulative risk of advanced neoplasia than patients with atypical (all other descriptions) adenomas (12% vs 29%; $p = 0.03$).

**Comment:** We all recognise the importance of colorectal cancer in the setting of IBD, but these cancers could occur through an inflammatory or adenoma pathway. This database linkage study probes this question further looking at clinical outcomes amongst a large group of patients with and without IBD and with and without adenomas. The bottom line is that IBD patients with adenomas were more likely to develop subsequent advanced neoplasia. Most, but not all, of this increased risk was due to the presence of atypical adenomas.

***Oral presentation: #OP14***

Available from: http://tinyurl.com/7nfppyz

## Immunosuppressive co-treatment with adalimumab (ADA) may be more effective than ADA monotherapy for maintaining remission in Crohn's disease (CD)

**Authors:** Reenaers C et al

**Summary:** This retrospective UK/Belgian study sought to evaluate whether immunosuppressive combination therapy (thiopurines or methotrexate) with adalimumab was more effective than adalimumab monotherapy for CD patients. A total of 181 patients were included and they received 569 6-month treatment semesters, including 147 semesters in 45 patients who received combination therapy during their first semester. In those receiving combination therapy during the first semester, treatment failures (dose modification during therapy, drug modification, perineal complications or surgery for active CD) were less frequent in semesters with (20%) than in those without (80%) immunosuppressive drugs (OR 0.30; p = 0.02) and this protective effect was maintained over time (p = 0.01). When all patients were considered, combination therapy in the first semester was associated with a lower frequency of treatment failure (34% vs 66%; OR 0.69; p = 0.046) in univariate analysis (this was not seen with multivariate analysis). Risk factors for treatment failure in multivariate analysis were female gender (OR 1.68; p = 0.01), previous surgery (OR 1.89; p = 0.001) and active perianal disease (OR 1.57; p = 0.02). Failures were less common in Oxford than in Liege (OR 0.52; p = 0.001), but more failures in Oxford had perianal complications (OR 3.33; p = 0.01) or surgery (OR 8.85; p = 0.001) and fewer were receiving weekly adalimumab (OR 0.24; p = 0.0003). Thiopurines appeared to have greater efficacy in preventing failure when compared to methotrexate (OR 0.35; p = 0.03).

**Comment:** The debate surrounding combination immunosuppression with infliximab appears to be over with combination clearly preferred. However, the data are less clear for adalimumab where the clinical trial data do not support combination therapy, while anecdotally there appears to be some benefit in selected patients. While retrospective and with some limitations, this abstract suggests some benefit for those with concomitant immunosuppression with regards to need for dose escalation. Obviously clinical trials often do not mimic real life. New Zealand Crohn's disease patients starting adalimumab are sicker than many (CDAI >300) and therefore may benefit from additional immunosuppression, but the data are not clear for our population. I tend to err on the side of co-prescription.

***Oral presentation: #OP15***

Available from: http://tinyurl.com/6p85kvj

## Adding ciprofloxacin to adalimumab results in a higher fistula closure rate in perianal fistulizing Crohn's disease [on behalf of ICC (Initiative on Crohn's and Colitis)]

**Authors:** Dewint P et al

**Summary:** The efficacy of adalimumab (induction therapy with subcutaneous adalimumab 160 mg on week 0, 80 mg on week 2, maintenance therapy 40 mg every other week) in combination with ciprofloxacin (500 mg twice daily for 12 weeks) or placebo in the treatment of active fistulising, perianal disease was examined in a multicentre, double-blind, placebo controlled trial conducted with the support of Abbott. In 74 patient's with CD and perianal fistulas, the primary endpoint (clinical response defined as a reduction of at least 50% of the number of draining fistulas from baseline to week 12) was met in 50% of placebo treated (n = 37) and in 74% of ciprofloxacin treated (n = 37) patients (p = 0.048), but this difference was not maintained at week 24 after discontinuation of antibiotic therapy (55% vs 64%).

**Comment:** The IBD literature is littered with single agent studies which are important, but do not reflect the real world where drugs are usually used in combination. Anti-TNF drugs have been a revelation in the management of perianal CD, leading to improvement of perianal fistula in many and healing in some. However, frequently these drugs are combined with antibiotics due to concerns about concurrent infection. This study shows that where ciprofloxacin is prescribed there is an advantage over placebo, but that this advantage is not maintained. Therefore, concomitant ciprofloxacin with adalimumab leads to a more rapid healing of fistulae, but not a sustained benefit.

***Oral presentation: #OP16***

Available from: http://tinyurl.com/7klmkbd

## Cyclosporin A as rescue therapy for steroid-refractory acute severe ulcerative colitis: Oral administration is as effective as intravenous

**Authors:** Kumar P and Rowbotham D

**Summary:** This retrospective New Zealand study sought to evaluate whether 3 months of oral cyclosporin A (CSA) 7 mg/kg (adjusted according to blood levels) is as effective as published data on IV CSA in the prevention of acute colectomy. In a retrospective case note review of 41 patients with UC refractory to IV corticosteroids admitted to hospital and treated with oral CSA from September 1999 through to June 2010, 76.1% of patients treated with oral CSA avoided colectomy during admission or within 7 days of discharge, while 11 (23.9%) patients failed to respond and progressed to surgery. Success rates reported for IV CSA in the literature average 79% of patients avoiding colectomy in the short term. A further 6 (13%) patients receiving oral CSA underwent colectomy within 6 months of discharge. Median follow-up in 29 patients who did not require colectomy within the first 6 months was 71 months and 10 of these have since undergone planned colectomy; median time to surgery was 29.5 months after commencement of oral CSA. Oral CSA was well tolerated with only 1 patient stopping treatment due to abdominal discomfort.

**Comment:** This retrospective study from Auckland was one of three accepted abstracts involving New Zealand investigators. For many years Auckland city hospital has used oral cyclosporin as rescue therapy for patients with severe UC not responding to IV steroids. While such an approach seems sensible in theory, this is one of the first reports of oral cyclosporin use for this indication. The short-term efficacy rates are comparable to published data for IV cyclosporin yet avoid the risk of many of the potential adverse effects including seizures.

***Poster presentation: #P330***

Available from: http://tinyurl.com/84abdhj

## Adalimumab in the treatment of perianal Crohn's disease: Long-term results in a single tertiary center

**Authors:** Tambasco R et al

**Summary:** The efficacy of adalimumab in the treatment of active perianal CD was examined in a prospective, single-centre study of 100 consecutive patients with complex (trans or suprasphinteric, horse-shoes, multiple with or without rectal involvement) perianal fistulising disease who were intolerant or resistant to immunosuppressive therapy or had experienced secondary failure to infliximab. After 52 weeks of adalimumab (160/80 mg induction, 40 mg every other week if responders), 60% (59/98) of patients were in remission and 69 (70%) had achieved a clinical response. After 2 and 3 years of treatment 75% (54/72) and 77% (47/61) of patients, respectively, were in remission, and 85% and 87% had a clinical response. Five patients lost response and required a temporary loop-ileostomy; 24% switched to weekly treatment. No serious adverse events were reported.

**Comment:** At present New Zealand gastroenterologists are limited in the way in which they can prescribe anti-TNF drugs. Pharmac have provided excellent access to adalimumab for luminal CD. However, despite adalimumab being effective for the treatment of perianal CD, at present Pharmac do not provide access to this drug for such an indication. Perianal disease is amongst the most disabling types of CD experienced by out-patients and the anti-TNF drugs are effective at inducing and maintaining remission in a significant proportion of patients. Hopefully Pharmac can reassess its criteria for access to adalimumab and consider perianal CD as an indication for anti-TNF therapy.

***Poster presentation: #P361***

Available from: http://tinyurl.com/8xe29op

## Long-term outcome after infliximab treatment for distal refractory ulcerative colitis. A single tertiary center experience

**Authors:** Gionchetti P et al

**Summary:** The efficacy of infliximab 5 mg/kg (induction at week 0, 2, 6 and maintenance every 8 weeks) in the treatment of moderate-to-severe UC was examined in a prospective, single-centre Italian study of 109 consecutive patients with distal active refractory UC (mean Mayo score 6, range 4–9). During a median follow-up of 40 months, 31 (28.5%) patients underwent colectomy; mean time to colectomy was 24 months after first infliximab infusion. An absence of short-term endoscopic response and steroid-dependency were independent predictors of colectomy. A short-term clinical response (a decrease in the partial Mayo score of ≥3 points at week 12) was observed in 73 (67%) patients and 62 (57%) patients experienced short-term mucosal healing (endoscopic portion of Mayo score ≤1); sustained clinical response occurred in 78 (71.5%) patients. No serious adverse events were observed.

**Comment:** Severe refractory distal colitis is one of the most frustrating forms of IBD to treat. A very small burden of inflammatory disease causes significant symptomatology, morbidity and risks the loss of the entire colon if effective therapy cannot be found. Infliximab has demonstrated efficacy in the management of UC and now this tertiary referral centre from Italy shows in a prospective study that infliximab is effective in maintaining clinical response in over two-thirds of patients with this difficult to manage phenotype of UC. Access to infliximab for induction of remission let alone maintenance of UC remains a challenge in New Zealand.

***Poster presentation: #377***

Available from: http://tinyurl.com/75tkzy2



## Effectiveness of smoking cessation in Crohn's disease patients

**Authors:** Nunes T et al

**Summary:** This prospective multicentre Spanish study examined the effectiveness of a smoking cessation program designed for CD patients who were active smokers (>7 cigarettes weekly). Different strategies were followed in each centre based on available resources and included intensive medical counseling, follow-up by pulmonologist, otolaryngologist or psychologist and pharmacological treatments. After a median follow-up period of 18 months, of 408 enrolled patients 62% had tried quitting, 31% quit smoking and 23% remained smoking-free until the end of their current follow up; 8% relapsed. Those who failed to quit smoking had a higher median tobacco load (15 vs 10 pack year), a longer median disease duration (96 vs 61 months) and had more surgery (42% vs 29%) than quitters. Most patients (88%) tried to quit smoking with no pharmacological therapy.

**Comment:** While drug therapies are often at the front of our thoughts, there are few treatments as effective for maintaining remission for patients with CD as cigarette smoking cessation. Unfortunately, our ability to achieve smoking cessation for our patients is often limited. This Spanish study used a variety of methods to encourage smoking cessation and was tailored for patients with CD. While the results are promising, the variety of interventions used makes it difficult to generalise too much. Ideally, a programme that is standardised and easy to initiate in any health care environment would be preferable. The long-term results of this study are awaited with interest.

***Poster presentation: #P384***

Available from: http://tinyurl.com/7um84vc

## High restarting rate among patients with Crohn's disease after cessation of one-year treatment period with biologicals: Result of national RASH study

**Authors:** Molnár T et al

**Summary:** This prospective, multicentre Hungarian study aimed to assess the frequency and the time to restart anti-TNF therapy after discontinuation and involved 152 CD and 35 UC patients (mean age at diagnosis 27.6 years) who were receiving infliximab (68.4% of CD patients) or adalimumab (31.6% of CD patients). Remission was achieved in 78.5% of patients after a one-year treatment period. Biological therapy was restarted due to clinical flare in 45.9% of CD patients and in 28.6% of UC patients after a median of 8 months; 41.1% of those who restarted biologics were in remission at the end of the second year. Logistic regression analysis indicated that corticosteroid use at induction (OR 1.58, 95% CI 1.04–2.41, $p=0.034$), previous anti-TNF-alpha therapy (OR 2.84, 95% CI 1.11–7.30, $p=0.03$) and dose intensification (OR 6.25, 95% CI 1.62–24.2, $p=0.008$) were associated with the need to restart therapy.

**Comment:** Patients who are prescribed biologics in New Zealand have severe CD. This is similar to the situation in Hungary where these investigators showed that almost one half of those who stopped biologics needed to restart them. Those most likely to need to restart are those with stigmata of severe disease. Specifically, steroid use at biologic initiation, biologic intensification and previous biologic therapy were associated with the recommencement of biologics. Of interest, the median duration of biological use in patients enrolled in this study was 8 months, less than one might imagine in New Zealand. Nevertheless, biologic cessation studies should be performed to determine those who do not need long-term maintenance.

***Poster presentation: #P378***

Available from: http://tinyurl.com/74b4rch

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