Welcome to the eighteenth issue of IBD Research Review.

The first issue for 2015 begins with findings from an Australian/New Zealand study investigating the optimal strategy for preventing CD recurrence after intestinal resection. Researchers from Spain have reported that the efficacy of a second anti-TNF agent for CD after initial anti-TNF failure is largely dependent on the reason for switching. Data from the three ULTRA trials suggest maintenance adalimumab for ≤4 years is safe and effective in patients with moderately to severely active UC. This issue concludes with research reporting significant reductions in radiation exposure out to 3 years with anti-TNF versus corticosteroid therapy.

I hope you find this month’s selection useful in your clinical practice, and I look forward to your questions and feedback.

Kind Regards,

Dr Steven Brown
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Crohn’s disease management after intestinal resection

Authors: De Cruz P et al.

Summary: Consecutive patients undergoing intestinal resection of all macroscopic CD received metronidazole for 3 months, with those at high risk of recurrence also receiving a thiopurine or adalimumab, and were then randomised to undergo colonoscopy at 6 months (n=122) or no colonoscopy (n=52). Participants with endoscopic recurrence stepped up to thiopurine, fortnightly adalimumab with thiopurine or weekly adalimumab. Compared with the no colonoscopy group, the colonoscopy group had a significantly lower rate of endoscopic recurrence at 18 months (49% vs. 67% [p=0.03]) and a higher rate of maintained complete mucosal normality (22% vs. 8% [p=0.03]). Among colonoscopy recipients who needed stepped-up treatment (n=47), 38% were in remission 12 months later, while 41% of those who did not receive stepped-up therapy had experienced recurrence by 12 months. The risk of endoscopic recurrence was significantly increased in smokers (odds ratio 2.4 [95% CI 1.2–4.8; p=0.02]) and in those with ≥2 clinical risk factors (including smoking; 2.8 [1.01–7.7; p=0.05]). No between-group differences were seen for the incidences and types of adverse and severe adverse events.

Comment: This multidimensional Australian/New Zealand study examined early colonoscopy (6 months) and escalation of drug therapy if needed, in postoperative CD. The primary endpoint was endoscopic recurrence at 18 months, and patients in the ‘standard care’ cohort, who did not receive 6-month endoscopy, fared significantly worse. This study really establishes the importance of early postoperative endoscopic assessment, and most critically demonstrates that escalation of therapy can ‘salvage’ active patients. Other intriguing aspects of postoperative CD revealed by this study include the finding that even ‘low-risk’ patients experience significant rates of clinical and endoscopic recurrence, indicating they too should be carefully monitored. Furthermore, smoking clearly worsens outcomes, with twice the rate of endoscopic recurrence, highlighting the importance of smoking cessation programmes. Also, thiopurine therapy appeared only modestly effective, with almost half of thiopurine-treated patients who had 6-month endoscopy requiring therapy escalation.

Reference: De Cruz P et al. Lancet; Published online Dec 23, 2014

Abstract

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Abstract
Does fecal calprotectin predict short-term relapse after stopping TNF-α-blocking agents in inflammatory bowel disease patients in deep remission?

Authors: Molander P et al.

Summary: This research involved 16 evaluable patients with CD and 33 with UC/IBD reclassified in clinical, endoscopic and FC-based (<100 μg/g) remission after receiving ≥11 months of anti-TNF-α therapy who were followed for relapse over 12 months after discontinuing such treatment. The 12-month relapse rate was 31%. Participants who relapsed had consistent FC level elevations for a median of 94 days prerelapse, with significant increases seen 2, 4 and 6 months before endoscopic relapse. Consistently normal FC levels predicted clinical and endoscopic remission, and normal levels in participants in remission were associated with histological remission.

Comment: Emerging studies indicate it is possible to de-escalate medical therapy in some IBD patients in deep remission. This study examined the role of FC level in monitoring such patients, and demonstrates that persistently normal FC levels are strongly predictive of sustained clinical and endoscopic remission over 12 months. Patients had FC levels measured 4-weekly for the first 6 months, then 8-weekly. They also routinely underwent colonoscopy at 4 and 12 months, and again at the time of clinical relapse. Interestingly, FC levels were found to be elevated well prior to clinical or endoscopic relapse, often up to 6 months. Furthermore, once the FC level was elevated, it remained so on subsequent measures until relapse declared itself clinically or endoscopically. This suggests that not only is FC cheaper and easier than colonoscopy, it may be better at earlier identifying of patients in need of reintroduction of therapy. Noteworthy was the finding that 13% of patients with endoscopic relapse had normal FC levels, confirming no test is perfect.


Abstract

Systematic review with meta-analysis: the efficacy of a second anti-TNF treatment has failed

Authors: Gisbert JP et al.

Summary: This was a systematic review and meta-analysis of studies investigating the efficacy of switching to a second anti-TNF agent. Studies in patients with CD, including 32 switching from infliximab to adalimumab, four from infliximab to certolizumab-pegol and one from adalimumab to infliximab, showed that the respective overall remission and response rates after switching from failed infliximab were 43% and 63%. First anti-TNF intolerance was associated with higher remission rates after switching than secondary and primary failure (61% vs. 45% and 30%, respectively); the respective response rates were 72%, 62% and 53%. Six of eight studies in patients with UC, all of which involved switching from infliximab to adalimumab, reported remission rates of 0–50%.

Comment: Loss of response to anti-TNF therapy is an emerging problem, and strategies for managing this remain poorly defined. This paper reported on 46 IBD studies that examined switching anti-TNF therapy for various reasons. It confirmed the efficacy of switching in CD is modest in cases of primary nonresponse, reasonable in cases of secondary nonresponse and good in patients with intolerance to the initial agent. The efficacy of switching in UC was less well defined. It was not clear whether switching between agents in one particular direction (e.g. infliximab to adalimumab) was more efficacious than the other (e.g. adalimumab to infliximab), since only one small study has reported on the latter scenario. Furthermore, this review did not examine the role of drug concentrations or antidrug antibodies in determining switching strategies. Nonetheless in the current climate in Australia, where dose escalation is not readily obtained, this review reassures us that switching is a good strategy in some patients.

Reference: Aliment Pharmaco Ther; Published online Feb 4, 2015

Abstract

Independent commentary by Dr Steven Brown: MBBS, PhD, FRACP

Dr Brown is a Physician Gastroenterologist at St Vincent’s Hospital, Melbourne. He undertook specialist training at Box Hill and The Canberra Hospitals before completing a PhD at the University of Melbourne, examining a novel mouse model of colitis with a focus on T-cells in IBD. After this, he spent a year in New York at the Mount Sinai Hospital as the Present-Levinson Clinical IBD Fellow and the de Rothschild Research Fellow. He returned to Melbourne to take a position at St Vincent’s, where he now works within the IBD Unit and acts as Director of IBD Clinical Trials. He also works in private practice, with a focus on younger patients with IBD and luminal gastroenterology.

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Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis

**Authors:** Adedokun OJ et al.

**Summary:** The relationship between serum infliximab concentration and outcomes was explored in 728 participants with moderate-to-severe UC from ACT (Active Ulcerative Colitis Trials)-1 and -2. Compared with nonresponder, participants with a clinical response, mucosal healing and clinical remission had significantly higher median serum infliximab concentrations at weeks 8, 30 and 54, with significant relationships between infliximab serum concentration quartile and efficacy at these timepoints (p<0.01). Compared with higher quartiles, the lowest infliximab concentration quartile was associated with less infliximab efficacy, a lower serum albumin level and a higher incidence of antibodies to infliximab. Despite variation among participants in the relationship between infliximab exposure and response, optimal outcomes were seen in participants with a serum infliximab concentration of ~41 μg/mL at week 8 of induction therapy and ~3.7 μg/mL at steady-state during maintenance therapy.

**Comment:** Serum concentrations of infliximab depend on factors such as bodyweight, albumin level and antibodies to infliximab. GI tract losses also occur, and may be significant in UC. This paper analysed patients from the ACT-1 and -2 studies, and confirmed that clinical efficacy and mucosal healing positively correlate with trough serum concentrations. This effect was present at completion of induction (week 8), but became particularly evident at weeks 30 and 54, and was seen for both 5 and 10 mg/kg dosing. It was not evident at week 2, which may represent a drug loading timepoint, rather than a drug clearance one. Receiver operating characteristic curves identified optimal threshold concentrations for induction (week 8) of 41 μg/mL, and maintenance (week 30) of 3.7 μg/mL, similar to optimal concentrations in CD. Infliximab antibodies and lack of concomitant immunomodulator use were both more common in the lowest infliximab concentration quartile. Overall, these data suggest that infliximab concentration-guided dose escalation may have a role in UC.

**Reference:** Gastroenterology 2014;147(6):1296–307

Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases

**Authors:** Langhorst J et al.

**Summary:** These authors systematically reviewed RCTs and controlled trials reporting on the use of CAMs (complementary and alternative medicines) for treating IBD, including 29 on herbal medicines, one on Trichuris suis ova, seven on mind/body interventions and two on acupuncture; the risk of bias was quite heterogeneous. For UC, the best evidence was seen for the herbal medicines Plantago ovata and curcumin for maintenance therapy, mind/body therapy, self-intervention and acupuncture, while for CD the best evidence was seen for wormwood and acupuncture.

**Comment:** Patients with IBD frequently use CAM. Increasingly, CAMs are subjected to scientific investigation, and this review identified 26 RCTs and three controlled trials using CAMs in IBD. Study quality was diverse with short observation periods, high bias and dropout rates, and poor blinding common. Nonetheless, some evidence supports the use of wormwood in CD (two short RCTs), curcumin in UC (a 6-month RCT), hypnotherapy in UC and acupuncture in IBD. Probiotics were not examined in this review. Trichuris suis ova were examined in one RCT in UC, with differences in response, but not remission, observed. Similar findings were reported for cannabinoids in one double-blind RCT in 22 patients with CD. It behoves IBD clinicians to be aware of CAMs, and acknowledge that benefit might be seen in some patients. However, clear scientific evidence, as a rule, is lacking.

**Reference:** J Crohn Colitis 2015;9(1):86–106

Thiopurine withdrawal during sustained clinical remission in inflammatory bowel disease: relapse and recapture rates, with predictive factors in 237 patients

**Authors:** Kennedy NA et al.

**Summary:** These researchers sought to determine rates and predictors of relapse over >12 months following thiopurine withdrawal, comparing 129 patients with CD and 108 with UC in sustained clinical remission. The respective 12- and 24-month moderate-to-severe relapse rates were 23% and 39% in patients with CD and 12% and 26% in those with UC; the 12-month relapse rate was significantly greater in patients with CD than those with UC (p=0.035). Significant predictors of relapse at 12 months were elevated CRP (C-reactive protein) level in CD (p=0.005) and elevated white cell count in UC (p=0.007).

**Comment:** This multicentre retrospective study from the UK provides further evidence that a subset of patients on long-term thiopurines may cease therapy, but it was hampered by the lack of a clear definition of disease recurrence. Clinical relapse was defined by the surrogate measure of any change in drug therapy (including reintroduction of thiopurines), rather than disease activity indices, biomarkers or endoscopic findings. Nonetheless, the findings are similar to other reports, with around 40% of CD patients and 25% of UC patients relapsing after 24 months. As expected, markers of disease activity such as CRP level and white cell count predicted relapse, but only poorly, and haemoglobin level and smoking status did not. Interestingly, a tapered withdrawal of thiopurine seemed to predict relapse in CD, but this may represent a lead time bias. Posing aspects of this study were the suggestion that relapse is often not severe and the observation that reintroduction of thiopurine therapy was generally successful.

**Reference:** Aliment Pharmacol Ther 2014;40(11–12):1313–23

Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis

**Authors:** Colombel J-F et al.

**Summary:** Data from 600 adalimumab recipients from the ULTRA (Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab)-1 and -2 placebo-controlled trials out to 4 years, and from their open-label extension (ULTRA-3), were presented; 199 participants were still receiving the agent at ≥3 years’ treatment, in 129 patients with CD and 108 with UC in sustained clinical remission. The respective remission rates according to partial Mayo score, remission (ULTRA-3), were presented; 199 participants were still receiving the agent at ≥3 years’ treatment, in 129 patients with CD and 108 with UC in sustained clinical remission. The respective 12- and 24-month moderate-to-severe relapse rates were 23% and 39% in patients with CD and 12% and 26% in those with UC; the 12-month relapse rate was significantly greater in patients with CD than those with UC (p=0.035). Significant predictors of relapse at 12 months were elevated CRP (C-reactive protein) level in CD (p=0.005) and elevated white cell count in UC (p=0.007).

**Comment:** The long-term efficacy of adalimumab in UC is reported in this paper that combines the 52-week ULTRA-1 and -2 induction/maintenance trials with the 3-year open-label extension study (ULTRA-3). Over half of the patients who entered remission during ULTRA-1 or -2 fared even better, with clinical and endoscopic remission sustained in 64% and 60%, respectively, after a further 3 years of therapy. Hospitalisation and colectomy rates were also lower in the ULTRA-3 extension study than the randomised studies, and quality of life and productivity improved. Together, these data confirm that early responders are likely to enjoy prolonged disease control with adalimumab, although 20% of patients entering ULTRA-3 eventually required dose escalation. Like CD, the 15% of patients who were anti-TNF ‘experienced’ responded less well. No new safety signals emerged, but two fatal adverse events occurred during ULTRA-3 along with three B-cell lymphomas (all thiopurine exposed).


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**Reference:** J Crohn Colitis 2015;9(1):86–106
Risk of melanoma and non-melanoma skin cancer in ulcerative colitis patients treated with thiopurines

Authors: Abbas AM et al.

Summary: The impact of thiopurine therapy for UC on the risk of developing melanoma and NMSC (nonmelanoma skin cancer) was investigated using 10 years of retrospective data on 14,527 patients with UC from the US Veterans Affairs healthcare system; 3346 had received thiopurine therapy for a median of 1.6 years, and 421 cases of NMSC and 45 of melanoma were recorded during median follow-up of 8.1 years. Compared with thiopurine nonrecipients, the risk of developing NMSC was increased while receiving thiopurines (adjusted hazard ratio 2.1 [p<0.0001], but not after stopping them [0.7 [p=0.07]]. NMSC incidence rates increased as duration of thiopurine therapy increased from 5.8 per 1000 person-years during the first year of thiopurine use to 13.3 per 1000 person-years during the fifth year of use; the incidence rate with no thiopurine use was 3.7 per 1000 person-years. Thiopurine use did not increase the risk of melanoma (odds ratio 0.8 [p=0.6]).

Comment: While it is generally accepted that thiopurines increase the risk of NMSC, the magnitude and mechanisms remain ill defined. This huge retrospective study examined Veterans Affairs UC patients, predominantly white males with a median age of 59 years. Over 100,000 person-years of follow-up were included, and approximately one-quarter of all patients were exposed to thiopurines. There was a 2.1-fold increase in NMSC risk in thiopurine users, and this increase was more notable with longer durations of therapy. Reassuringly, excess risk resolved after stopping therapy, with a hazard ratio of 0.7, and this was seen even in patients who had been on drug for >5 years. This observation differs from the CESAME cohort where risk was evident in ex-users, but supports other recent studies. These findings suggest patients with prolonged disease control may benefit from ceasing thiopurine therapy. No dose effect was observed with this study, and no excess risk was observed in patients aged <40 years. Pleasingly no excess risk of melanoma was reported. Ongoing ‘sun-smart’ approaches and surveillance are advised.


Abstract

Anti-TNF therapy is associated with a reduction in radiation exposure in patients with Crohn’s disease

Authors: Aggarwal D & Lindi JK

Summary: This retrospective review of patients who received infliximab or adalimumab (n=114) or corticosteroids (n=56) for CD found that compared with the corticosteroid recipients, the anti-TNF recipients underwent significantly fewer radiology studies between the year preceding and the year following therapy (mean –2.0 vs. –0.2 [p=0.001]) and a significantly lower cumulative radiation dose (–3.1 vs. +0.3 mSv [p=0.001]). The mean number of radiology studies between the year preceding therapy and 3 years following therapy was significantly higher among corticosteroid recipients than anti-TNF recipients (+2.3 vs. +0.3 [p=0.003]) as was the cumulative radiation dose (+6.8 vs. +1.3 mSv [p=0.003]). Anti-TNF therapy was associated with a significant 2-fold reduction in the number of imaging studies within a year of therapy after adjusting for predictors of high diagnostic radiation exposure (p<0.001).

Comment: In addition to conventional measures of disease control, anti-TNF therapy has been linked to many other desirable outcomes including quality of life improvements, reduced hospitalisation and need for surgery, improved health economics and increased growth in children. This retrospective study identified reduced exposure to ionising radiation as another benefit of anti-TNF therapy, and this was seen both 1 and 3 years after initiating therapy, compared with a steroid-treated cohort. This outcome is clearly desirable, especially in younger patients, and importantly was seen even though the anti-TNF cohort had significantly higher rates of penetrating disease, a subset traditionally exposed to more imaging studies. The groups were otherwise matched. Both the number of radiological studies and the cumulative radiation exposure were impacted. A reduced need for magnetic resonance image scanning was also observed. These data highlight the indirect benefits of anti-TNF therapy, presumably due to improved disease control.


Abstract