Welcome to issue 24 of IBD Research Review.

A paper reporting that colonoscopic features are not reliable for predicting the development of colitis-associated neoplasia in patients with UC begins this issue. This is followed by a paper reporting that targeted and random biopsy strategies detect similar proportions of neoplasias in UC. An interesting review on the use of thalidomide for treating IBD is also included, which is followed by a paper reporting on switching from the infliximab originator to a biosimilar to conclude this issue.

I hope you have been finding your copies of IBD Research Review informative and helpful in your everyday practice. Your feedback and suggestions are very useful, so please keep them coming.

Kind Regards,
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Pattern of inflammation on surveillance colonoscopy does not predict development of colitis-associated neoplasia

Authors: Jegadeesan R et al.

Summary: This research investigated the correlation between colonoscopic features and risk of developing colitis-associated neoplasia in a retrospective group of 111 patients with UC and neoplasia who underwent surveillance colonoscopies during 1998–2011 and 356 matched controls without colon neoplasia. A univariate analysis revealed associations between colitis-associated neoplasia and male gender (odds ratio 2.58 [95% CI 1.71–3.89]) and smoking history (1.62 [1.1–2.39]) but not colonoscopic features such as tubular colon/shortened colon, scarring, segment of severe inflammation, inflammatory polyps, colonic stricture or macroscopically normal appearance colonoscopy. A multivariate analysis revealed that only male gender remained significantly associated with an increased risk of colitis-associated neoplasia (odds ratio 2.68 [95% CI 1.77–4.08]), and that the risk was decreased by 5-ASA (5-aminosalicylate) use (0.51 [0.31–0.84]).

Comment: It has been suggested that the level of inflammation and other findings seen at colonoscopy in UC patients can be used to determine a patient’s risk for the development of colitis-associated neoplasia. Such work has correlated the level of inflammation on the last colonoscopy and the average inflammation over all the surveillance colonoscopies with future risk of neoplasia. This retrospective study included UC patients over a 13-year period in the current era of aggressive medication therapy. A total of 111 UC patients had colitis-associated neoplasia and were compared with matched UC patients without neoplasia (1:3). As has been demonstrated previously, being male was a risk factor but the use of 5-ASAs decreased the risk. This suggests a role for reducing the level of mucosal inflammation. Surprisingly, features like colonic scarring severe inflammation, inflammatory polyps, colonic stricture and macroscopically normal mucosa were not predictive on white-light colonoscopy. These findings may suggest that the patient numbers included in this study were too small or that white-light endoscopy is not sufficient for surveillance of UC patients and chromoendoscopy should be performed, but it does support the use of chemoprevention with 5-ASAs.

Reference: Inflamm Bowel Dis 2016;22(9):2221–8

Abstract

Abbreviations used in this issue:

CD = Crohn's disease; C-reactive protein; CRP = FMT = faecal microbiota transplantation; IBD = inflammatory bowel disease; HCT = randomised controlled trial; TNF = tumour necrosis factor; UC = ulcerative colitis.

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Comparison of targeted vs random biopsies for surveillance of ulcerative colitis-associated colorectal cancer

Authors: Watanabe T et al.

Summary: Patients with UC for ≥7 years were randomised to four random biopsies collected every 10cm in addition to targeted biopsies (n=122) or biopsies collected from locations of suspected neoplasia (n=124). No significant difference was seen between the targeted versus random strategy for average number of biopsies containing neoplastic tissue per colonoscopy (0.211 vs. 0.168; ratio 1.251 [95% CI 0.679–2.306; criterion for noninferiority met]) or proportion of participants with neoplasias detected (11.4% vs. 9.3% [p=0.617]), but the random strategy was associated with more biopsy samples per colonoscopy (34.8 vs. 3.1 [p<0.001]) and a longer total examination time (41.7 vs. 26.6 min [p<0.001]). All neoplastic tissues identified in random biopsies with the random strategy were collected from mucosal areas with past or present inflammation.

Comment: Surveillance colonoscopies in both UC and CD patients are undertaken in an attempt to detect dysplasia or colitis-associated neoplasm at an earlier stage. This is not preventative against the development of cancer, but is associated with a better outcome due to the earlier cancers identified. Random colonic biopsies are taken to assess the level of inflammation, but surveillance of dysplasia has shifted from four random colonic biopsies every 10cm to target biopsies taken from locations of suspected neoplasia. This randomised study assigned 246 patients to four random biopsies collected every 10cm in addition to targeted biopsies (n=122) or targeted biopsies only (n=124). Dysplasia in the target group was detected in 0.211 (24/114) and 0.168 (19/107) in the random group (p value nonsignificant). In the target group, 11.4% of patients and 9.3% of patients in the random group had neoplasia (p value nonsignificant). This suggests that there was no difference between detection rates, but the time taken was longer with random biopsies. Appropriate use of chromoendoscopy, however, might modify these findings.

Reference: Gastroenterology; Published online Aug 11, 2016

Abstract

Systematic review: outcomes and post-operative complications following colectomy for ulcerative colitis

Authors: Peyrin-Biroulet L et al.

Summary: This was a systematic review of 28 studies reporting outcomes of total and subtotal colectomies and IPAA with J-, S-, W-pouch procedures performed in 20,801 adults with UC during 2002–2015. Ten studies reported complications occurring within 30 days of the procedure at rates of 9–65%, and rates for complications occurring after 30 days were 17–50%. The most frequent short-term complications were infections and ileus, with respective mean incidences of 20% and 18%, and the most frequent long-term complications were pouchitis, faecal incontinence and small bowel obstruction, with respective mean incidences of 29%, 21% and 17%. Between the periods 2002–2009 and 2010–2015, early infection rates decreased from 22% to 11% and late pouch failure rates decreased from 13% to 2%. Data from eleven studies revealed a mean postoperative mortality incidence of 1.0%.

Comment: Colectomy is often regarded as a last resort in the management of UC, but it has also been touted as a cure because it removes the inflamed colon. The most common indication for surgery is medical-refractory disease, but surgery is also a strategy for modifying a patient’s risk of neoplastic transformation. As surgery has changed, however, the risks of both long-term and short-term complications have changed. With mucosectomy and hand-sewn anastomoses for pouch surgery, there was an increased risk of incontinence that has been modified by the double-stapled anastomosis technique. This, however, may leave a cuff of rectal mucosa with potential continuing inflammation. This review examined 28 studies that included 28,081 patients and their outcomes of surgery since the introduction of biological therapies. As in all IBD surgery there are short-term complications, but it is overall the long-term complications that impact most on a patient’s wellbeing; most importantly, pouchitis ranges from 8–41%, fistula formation 6%, faecal incontinence in 21–22% and a late small-bowel obstruction in 17%. Fortunately, pouch failure has decreased from 8% to 2% in recent years, but reporting of the other late complications was not undertaken in the more recent studies, so it is unknown if these have altered with the use of biological medications. Proctocolectomy for UC is surgery that is required for a significant number of UC patients; however, it has numerous potential complications and these should not be underplayed to the patient prior to surgery. The alternative of an end ileostomy should also be discussed, as this may potentially lead to a greater quality of life.

Reference: Aliment Pharmacol Ther; Published online Aug 17, 2016

Abstract
Fecal microbiota transplantation for inflammatory bowel disease

Authors: Lopez J & Grinspan A
Summary: This was a review of the role of the gut bacterial microbiome in IBD. The authors discussed numerous case reports and cohort studies reporting on FMT (fecal microbiota transplantation) for treating IBD over the last two decades, the development of new sequencing techniques and findings from two recent RCTs that have improved our understanding of the relationship between the microbiome and the human host. However, they note that due to still limited knowledge, the place of FMT in IBD management remains uncertain, and further research is necessary before it can be considered as part of the armamentarium of treatment options in clinical practice.

Comment: A role for the gut bacterial microbiome in the development of disease and intestinal inflammation is centre stage since the success of FMT in the management of resistant C. difficile infection. In addition to the IBDs, disturbance of the microbial flora is associated with colorectal cancer, obesity, metabolic syndrome and IBS with the faecal flora being different to healthy controls. This article summarises the current position of FMT in IBD. Over 18 studies, case reports, cohort studies and randomised controlled studies have used FMT as the primary therapeutic agent in 122 patients, and these have demonstrated that 45% of IBD patients went into remission. Publication bias, however, could inflate this figure, but CD patients did appear to have a higher response rate of 61% compared with UC patients at 22%. There are, however, many things yet to be determined. The route and administration with enemas or colonic administration appears to be more effective than administration via a nasoduodenal tube. The donor of the FMT, as demonstrated by a Canadian study where donor B induced remission in seven of 18 patients (39%) when the overall findings were 25%, appears to be important, and the number of administrations may also impact the response rate. What is certain, however, is that there are more studies to come and be published, with one Australian study identifying efficacy of pooled-donor FMT in UC. Thus whether it is a single bacterial species, community of bacteria resulting in an anti-inflammatory microenvironment, the bacterial metabolites or nonbacterial components, further work is still required. Investigation of the role of viruses and fungi in IBD is also unknown, as is if there is a particular patient subgroup who might benefit most from FMT. Finally, we do not know if FMT is purely an induction therapy or should be used for maintenance as well.


Multi-center experience of vedolizumab effectiveness in pediatric inflammatory bowel disease

Authors: Singh N et al.
Summary: Experiences with vedolizumab were described for a retrospective group of 52 patients aged <18 years with IBD (56% with CD and 42% with UC). Failure of ≥1 anti-TNF agent was documented for 90% of the patients. The 14-week remission rate was significantly higher for patients with UC than for those with CD (76% vs. 42% p=0.005). Among anti-TNF-naïve patients, 80% had experienced remission by week 14. Compared with patients who had previously received anti-TNF agents, those who were anti-TNF-naïve had a higher remission rate at week 22 (100% vs. 45% p=0.04). No infusion reactions or serious adverse events/infections were reported.

Comment: The new α4β7 anti-integrin, vedolizumab, has been on the PBS in Australia for the use in adult UC and CD patients since August 2015. It is a medication targeting the homing of a subset of mature lymphocytes back to the intestinal mucosa, and is thus very specific in its action and appears to be safe with limited side effects and immunosuppression. Real-life prospective data are currently being collected in this country, but as it is not approved for the paediatric population, experience is limited. This paper presents off-label use of vedolizumab in children at three specialist IBD centres. A total of 52 patients, both CD and UC, were treated, with almost 60% of UC and 40% of CD patients achieving remission by 14 weeks. As expected, patients naïve to previous biological therapy did better. Of great importance was that there were no infusion reactions or serious adverse events/infections. Further work into the paediatric population will be required before registration for its use in this patient group, but initial findings are very encouraging.

Reference: Inflamm Bowel Dis 2016;22(9):2121–6

A randomized controlled trial on the effect of vitamin D3 on inflammatory and cathelicidin gene expression in ulcerative colitis patients

Authors: Sharifi A et al.
Summary: These researchers randomised 90 patients with UC in remission to receive intramuscular vitamin D 300,000IU or saline placebo. Baseline vitamin D levels increased significantly in the vitamin D arm after treatment (p<0.001). At 90 days, vitamin D versus placebo administration was associated with a significantly lower high-sensitivity CRP level (2.31 vs. 9.90 mg/L [p=0.023]), a significantly decreased erythrocyte sedimentation rate (6.7 vs. 11.4 mm/h [p<0.001]) and a significantly greater mean fold change in hCAP18 (cathelicidin) gene expression (p=0.001).

Comment: Patients with active CD are frequently low in vitamin D, as this is a negative acute phase reactant that drops in active inflammation. Vitamin D also has an immunomodulating effect, inhibiting innate immune cell production of proinflammatory cytokines and suppressing inflammation. Replacement of vitamin D in deficient patients could thus potentially positively impact on the disease course. This study randomised 90 UC patients to receive a single high dose of vitamin D intramuscularly (n=46) to determine if there was a benefit over placebo (n=40). Both groups were in the vitamin D deficient range with an average of 32–33 ng/mL, where sufficient levels are considered to be >50 or >75 ng/mL in other studies. Following the administration, the vitamin D levels rose to an average of 40.6±2.5 mg/mL. Despite this being significantly higher than the placebo group, it still did not place the majority of patients into the vitamin D sufficient range. CRP, however, decreased in the treated group (p=0.036) and calcium levels rose (p<0.001). Thus, although these findings are interesting, further studies must be undertaken to assess the efficacy of promoting sufficient levels of vitamin D on the inflammatory milieu.


Thalidomide for inflammatory bowel disease

Authors: Bramuzzo M et al.
Summary: This was a systematic review of two RCTs and 29 uncontrolled studies (n=489) reporting outcomes associated with thalidomide in the treatment of refractory UC or CD. The overall clinical response and clinical remission rates with thalidomide were 69.3% and 51.5%, respectively, and the respective 6-month (n=160) and 12-month (n=133) remission maintenance rates were 80.0% and 72.2%. Steroid dosages were reduced in 71.7% of the thalidomide recipients, and 60.5% and 34.6% experienced improvements and closure of fistulae, respectively. The endoscopic improvement rate was 69.7% and the complete mucosal healing rate was 53.0%. The respective cumulative incidences of total adverse events and of those leading to drug interruptions were 75.6 and 19.7 per 1000 patient-months. The most frequent adverse events leading to drug withdrawal were neurological disturbances, which accounted for 64.3% of all adverse events.

Comment: The mere mention of the word thalidomide provokes all sorts of emotions due to its disastrous effects in pregnancy. This oral immunomodulatory agent, however, is currently approved for the treatment of erythema nodosum lipozom and multiple myeloma. This review revisits the data for its use in CD or UC in both adult and paediatric populations. A total of 31 papers were included. There were only two prospective placebo-controlled randomised trials, with the rest being case series. These included 435 CD and 50 UC patients; 247 were male and 135 were children. Thalidomide was used at dosages ranging from 50 to 400 mg/day in adults and from 1.5 to 2.5 mg/kg/day in children. Out of 427 patients, 296 (69.3%) had a clinical response (27 studies) and 220 (51.5%) achieved remission (25 studies). Long-term clinical remission (15 studies) was 128/160 (80.0%) at 6 months (15 studies), 96/1153 patients (72.2%) at 12 months (13 studies), and 61/112 patients (54.5%) at 24 months (11 studies). Complete suspension of steroids occurred in 109/152 (71.7%) patients. Endoscopic mucosal improvement occurred in 46/66 (69.7%), and 35/66 (53.0%) had mucosal healing. Perianal fistulae were present in 50 patients, 18 had enteric fistulae and five had both. A clinical improvement was noted in 49/81 (60.5%) and complete fistula healing was reported in 26/81 (34.6%).

In a pilot RCT in children with UC, 18/23 (78.3%) achieved clinical remission, compared with 2/11 (18.2%) on placebo. In four other studies including 16 patients with UC, nine (56.2%) responded and seven (43.7%) achieved remission. Twelve papers identified drug discontinuation and 58/68 patients (85.3%) ceased thalidomide because of an adverse event. Neurological disturbances accounted for 64.3% of the adverse events. Peripheral neuropathy was the most common adverse event (109 cases; incidence 15.6 per 1000 patient-months) and drug was withdrawn in 56.8% of patients. Sedation or somnolence occurred in 25%, usually at commencement of therapy. This review identifies that thalidomide can be effective even following failure of biological therapies. This medication thus needs further consideration and study, as it may still yet have a role to play in IBD management.

Reference: Medicine (Baltimore) 2016;95(30):e4239
Clinical outcomes following a switch from Remicade® to the biosimilar CT-P13 in inflammatory bowel disease patients

Authors: Smits LJ et al.

Summary: In this prospective observational study, 57 adults with CD, 24 with UC and two with IBD unclassified treated with Remicade® were switched to the infliximab biosimilar CT-P13. The median infliximab trough concentration increased from 3.5 to 4.2 µg/mL by week 16 (p=0.010), but there were no changes in IBD disease activity scores after the switch and no significant changes in CRP and faecal calprotectin levels. New detectable antidrug antibody responses were seen in two patients during follow-up, and five discontinued CT-P13. There were no serious adverse events.

Comment: With the advent of the biosimilar infliximab, Inflectra™, the spectre of switching between the originator (Remicade®) and the biosimilar is ever present. In Australia the PBC has listed infliximab as a-flagged, which means that if the script is not written to prevent drug substitution, then the dispensing pharmacy and patient can determine which infliximab shall be dispensed. This could potentially lead to loss of response if increased immunogenicity is provoked by switching between biosimilars. This paper assessed 83 patients (57 with CD, 24 with UC and two with IBD unclassified). The CRP and faecal calprotectin levels did not change significantly. Two patients developed detectable antibodies during follow-up and five patients discontinued the biosimilar, which is consistent with expectations. No serious adverse events occurred. This study thus showed, in a small cohort, that switching from the infliximab originator to a biosimilar in IBD patients did not significantly impact on short-term clinical outcomes, suggesting that switching is feasible. At this stage the effects of multiple switching from one to the other is unknown, and thus further studies will be required.

Reference: J Crohns Colitis; Published online Apr 19, 2016

Abstract

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This program is prepared and reviewed by:
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