Welcome to issue 22 of IBD Research Review.

For this issue I have chosen several research papers focussing on paediatric patients with IBD, including predictors of loss of response to infliximab therapy for CD. There is also research reporting that children with IBD have increased hospitalisation rates for varicella and herpes zoster, and long-term outcomes were reported for proctocolectomy with ileal pouch anal anastomosis procedures performed during childhood, adolescence or young adulthood for UC. The issue concludes with the use of FC (faecal calprotectin) level as a surrogate marker for recurrence in paediatric patients who have undergone surgery for CD. We begin, however, with a look at current safety data for the α4β7 integrin receptor antagonist vedolizumab, which was recently PBS-listed for treating both CD and UC in adults.

I hope you find these and the other research papers selected for this issue informative and helpful. Please feel free to send me your feedback and suggestions.

Kind Regards,
Professor Ian Lawrance
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The safety of vedolizumab for ulcerative colitis and Crohn’s disease

Authors: Colombel J-F et al.

Summary: These authors analysed safety data from trial participants with UC or CD who had received ≥1 dose of vedolizumab or placebo; 2830 participants had 4811 person-years of exposure to the agent. Vedolizumab was not associated with increased risk of any infection or serious infection; serious Clostridial infections, sepsis and tuberculosis were reported in ≤0.6% of participants. There were no cases of progressive multifocal leucoencephalopathy. Independent risk factors for serious infection were failure of prior TNF antagonists and narcotic analgesic use in UC, and younger age, corticosteroid use and narcotic analgesic use in CD. Infusion-related reaction rates were ≤5% in each study, and malignancies were reported in <1% of vedolizumab-exposed participants.

Comment: Vedolizumab, an α4β7 anti-integrin, has been approved for use in Australia under the PBS for both UC and CD in adult patients since November 2015. As this medication is still very new, the identification of any side effects is in its early days, particularly for any rare adverse outcomes. This analysis included 2830 patients from six clinical trials between 2009 to 2013 for patients who had received at least one vedolizumab infusion. The findings are encouraging with no increase in serious infections or tuberculosis. No cases of progressive multifocal leucoencephalopathy were identified. Helpfully, identified risks factors associated with serious infections were similar to previous investigations and included narcotic and corticosteroid use. Infusion reactions were also noted to be very low (<5%). Thus, although it is still very early days, the safety profile of vedolizumab is encouraging. However, data must still be collected in order to identify any rare complications.

Reference: Gut; Published online Feb 18, 2016

Abstract

Abbreviations used in this issue:
- CD = Crohn’s disease; FC = faecal calprotectin; IBD = inflammatory bowel disease; OR = odds ratio; TNF = tumour necrosis factor; UC = ulcerative colitis.
Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease

Authors: Kennedy NA et al.

Summary: These researchers conducted an observational study of outcomes following anti-TNF agent withdrawal following sustained remission in 146 patients with CD and 20 with UC or unclassified IBD. The respective 1-year and 2-year relapse rates were 36% and 56% in patients with CD, and 42% and 47% in those with UC or unclassified IBD. Factors associated with increased risk of CD relapse were age <22 years at diagnosis (hazard ratio 2.78) and white cell count >5.25 x 10^9/L (3.22) and faecal calprotectin level >50 µg/g (2.95) at drug withdrawal; immunomodulators and endoscopic remission were not predictive. In a systematic review and meta-analysis >50 µg/g (2.95) at drug withdrawal; immunomodulators and endoscopic remission were not predictive. In a systematic review and meta-analysis performed by the authors of 11 additional cohorts of patients with CD (n=624) and UC (n=122), the respective estimated 1-year relapse rates for these patient groups were 39% and 35%. Restarting anti-TNF agents was successful in 88% of patients with CD and 76% of those with UC or unclassified IBD.

Comment: De-escalation of medical therapy is something that is not infrequently broached by patients within the consulting room, as many patients would like to cease medications. The anti-TNF medications, however, are frequently more effective than the immunosuppressing medications in both CD and UC and generally have a better side-effect profile. This study retrospectively assessed the rate of flares in IBD patients withdrawn from anti-TNF therapy and then performed a meta-analysis of a further 11 studies. It identified that flares were common, occurring in over one-third of patients by 1 year and around half by 2 years. Immunosuppressant usage did not predict relapse but a raised FC level at time of withdrawal did. Recapture of remission was good, with 80–90% responding to a second course of induction therapy. Thus although health costs must always be considered, withdrawal of all patients may appear to be a false economy. Individual patient assessment is thus suggested and according to other studies should include endoscopic evaluation and FC and C-reactive protein levles, and only when all these identify complete or 'deep' remission should de-escalation of therapy be considered.

Reference: Aliment Pharmacol Ther; Published online Feb 19, 2016

Abstract

Patients and gastroenterologists’ perceptions of treatments for inflammatory bowel diseases: do their perspectives match?

Authors: Vaucher C et al.

Summary: Using four vignette clinical cases, these researchers explored and compared gastroenterologists’ and patients’ perceptions of the risks and benefits associated with IBD treatments and prioritisation of expected outcomes. Conversations on these issues by three independent focus groups of seven gastroenterologists, eight patients with UC and six patients with CD were analysed. The patients with UC were more often in agreement with gastroenterologists about treatment choices than those with CD. The patients with CD often considered mesalazine (5-ASA) as a placebo and those with UC viewed topical mesalazine as a temporary solution that was neither comfortable nor practical when professionally active. The treatment for which the risks were believed to most outweigh the benefits was azathioprine. The potential for loss of response was the main patient-perceived risk for anti-TNF agents. Treatment cessation was one area on which the groups’ perceptions diverged. Patients with UC did not easily concur with stopping a treatment, which differed from gastroenterologists’ expectations of patients’ perceptions. The patients with CD were more likely to consider stopping treatment than gastroenterologists. Another point of difference among groups was perception of outcomes. The physicians focussed on long-term objective goals, whereas patients’ expectations were shorter term and mainly concerned with stress management, nutritional advice and information on treatment effects.

Comment: Patient compliance to medication use depends on the patients’ perception of risk and benefit. A medication perceived as having a high benefit and low risk is more likely to be taken than one with a low benefit and high risk. For patients with a life-long incurable disease that has very significant potential disease complications, managing a patient’s understanding of their medications is vital. This study examined the perspectives of gastroenterologists and UC and CD patients with regard to various medications. The thiopurines were perceived as having the highest risk-to-benefit ratio, while the concern for the anti-TNF medications was loss of response for both the patient and physician. Unfortunately, despite the physicians having a long-term perspective of disease control, this was not shared by the patients who had a more short-term focus. Discussion with and education of patients is vital in order to manage expectations and promote good patient compliance. Methods to address this can include the use of a specialist pharmacist, an IBD nurse or dedicated consultation time to address patient perspectives and their disease and medication concerns. Without such measures patient compliance will not be optimised and patient outcomes may not be as desired.

Reference: Scand J Gastroenterol; Published online Feb 19, 2016

Abstract

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Resting energy expenditure was evaluated in patients with clinically stable CD receiving immunosuppressive therapy (n=24) or not (n=12) and age- and sex-matched control subjects. While the two CD groups were similar for age, height and body mass index, significant differences were seen between immunosuppressant recipients versus nonrecipients for both men and women. The effect of immunosuppressant therapy, immunosuppressant usage decreased to 26% at 6 months and 18% at 12 months. Seventy patients (36%) discontinued immunosuppressant therapy during follow-up and 25 (13%) for an anaesthetic reaction, but 79% were still on immunosuppressant therapy at 1 year. Receiving immunosuppressant therapy was associated with induction or durability of the remission response, but isolated colonic disease had a lower response. This is in contrast to other studies and the cessation of immunosuppressant therapy in the first year of immunosuppressant therapy is something that still needs to be determined on an individual basis.

Comment: Paediatric IBD patients often present with more severe disease than their adult counterparts. The use of biological medications is thus frequently required, but as IBD is an incurable lifelong disease, the loss of response to these medications can greatly compromise the management of the patients throughout their adult years. The use of multiple medications in such a young population, however, is something that is often avoided due to complications like hepatotoxicity. This retrospective study followed paediatric CD patients until their transition to adult care or until loss of follow-up to determine factors that were associated with loss of response to immunosuppressant therapy. Almost 16% had loss of response at 1.6 years. About 60% of patients were receiving immunosuppressant therapy at commencement of immunosuppressant therapy, 21% were considered as primary nonresponders, and during maintenance immunosuppressant therapy, immunosuppressant usage decreased to 26% at 6 months and 18% at 12 months. Seventy patients (36%) discontinued immunosuppressant therapy during follow-up and 25 (13%) for an anaphylactic reaction, but 79% were still on immunosuppressant therapy at 1 year. Receiving immunosuppressant therapy was associated with induction or durability of the remission response, but isolated colonic disease had a lower response. This is in contrast to many other studies and may be due to lack of statistical power due to the low number of patients on immunosuppressant therapy during maintenance therapy. Isolated colonic disease has also previously been associated with response and not loss of response, which is confusing. This paper, although detailed, is in contrast to other studies, and the cessation of immunosuppressant therapy in the first year of immunosuppressant therapy is something that still needs to be determined on an individual basis.

Reference: J Crohns Colitis; Published online Jan 28, 2016

Hospitalization for varicella and zoster in children with inflammatory bowel disease

Authors: Adams DJ & Nylund CM

Summary: This cross-sectional analysis of paediatric inpatient data explored the relationship between secondary diagnosis of IBD and a primary diagnosis of varicella or herpes zoster. Among 8,828,712 weighted admissions meeting the study criteria, 4434 and 4488 were for varicella and herpes zoster, respectively. Associations were seen for IBD and immunocompromising conditions with hospitalisation for varicella and herpes zoster, with stronger associations with varicella and herpes zoster in children with CD (OR 12.75 [95% CI 8.30–19.59] and 7.91 [9.60–11.18]) than in those with UC (4.25 [1.98–9.12] and 3.90 [1.98–7.67]).

Comment: The most common opportunistic infections in immunocompromised IBD patients are viral, and of these the herpes viruses are the most frequent. In line with the European CD and colitis recommendations, all IBD adult patients not immune against herpes varicella zoster should be vaccinated, as this is a particularly unpleasant primary infection in adults and many patients do receive immunomodulating medications. This study investigated the paediatric IBD population and the association with hospitalisation and varicella zoster infection. There were strong associations between CD and hospitalisation for both varicella (OR 12.75) and herpes zoster (OR 7.91) and also in UC for varicella (OR 4.25) and herpes zoster (OR 3.90). Children receiving immunomodulation had the greatest association with hospitalisation for herpes zoster. Of note is that hospitalisations for varicella or herpes zoster in IBD children reduced with the commencement of the varicella vaccine. This highlights the importance of determining if a child is immune against herpes varicella zoster at the diagnosis of IBD and the vaccination of those who are not, if at all possible.

Reference: J Pediatr; Published online Jan 27, 2016

Independent commentary by Professor Ian Lawrance

MB, BS (Hons), PhD, FRACP

Ian Lawrance is a Consultant Gastroenterologist and a Professor in the School of Medicine and Pharmacology, Faculty of Medicine and Dentistry at the Harry Perkins Institute of Medical Research University of Western Australia, Murdoch.

He was the Head of the department of Gastroenterology and Hepatology at Fremantle Hospital (2004–2007) and the Director of Endoscopic services at Kaleeya Hospital (2004–2007). In 2000 he developed the Centre for Inflammatory Bowel Diseases at Fremantle hospital and was its director since its formal opening in 2008. In 2015, he created a Centre for IBD at Saint John of God Hospital, Subiaco, and is currently its head. He was a founding committee member of a physician-initiated interest group IBD Australia in 2002 and was its secretary (2005–2006). He is currently a committee member of the Australian and New Zealand IBD Consortium (ANZIBD), a board member of the Australian IBD Association (AIBDA), a board member of Crohn’s Colitis Cure (CCC), a member of the Western Australian Drug Evaluation Panel (WADEP) and the co-chair of the International IBD Genetics Consortium (IBDGC). Prof Lawrence currently sits on numerous pharmaceutical IBD drug advisory committees. He reviews papers, abstracts and research grants for numerous scientific organisations, is a member of nine editorial boards and is the Genetics Section Editor for Inflammatory Bowel Diseases.
Abstract

The association between FC level and postoperative paediatric CD recurrence was explored in 22 patients. Fifteen patients had undergone ileoceleal resection, six had undergone small bowel resection and one had undergone left hemicolectomy; median age at surgery was 15.1 years. FC level decreased significantly post-surgery from 659 to 103 μg/g (p=0.001). During median 5.7 years follow-up, the endoscopic/histological recurrence rate was 77%. Endoscopic recurrence was suggested by FC level >139 μg/g at time of endoscopy or FC level increase of 79 μg/g from first postoperative value, whereas histological recurrence was indicated by FC level >101 μg/g or an increase of 21 μg/g. Combining the FC level at endoscopy and its postoperative increase was most accurate for predicting recurrence – the respective areas under receiver operating characteristics were 0.74 and 0.81 for endoscopic and histological recurrence.

Comment: FC in adult patients has been associated with clinical relapse in UC and CD and also the presence of recurrent CD postoperatively. FC level can also predict relapse in adult IBD patients at the time of anti-TNF medication withdrawal. This study examined its utility in paediatric patients post-CD surgery. Regardless of the bowel surgery type, FC level decreased in all patients postsurgery. A rise of 79 μg/g of FC level compared with the first postoperative FC level suggested an endoscopic recurrence as did an FC level >139 μg/g. This is similar to the POCER findings, which showed an FC level >100 μg/g indicated endoscopic recurrence with 89% sensitivity, 58% specificity and a negative predictive value of 91%. These findings suggest that FC level is also of use postoperatively in the paediatric population.

Reference: J Pediatr Surg; Published online Feb 15, 2016

Fecal calprotectin in the prediction of postoperative recurrence of Crohn's disease in children and adolescents

Authors: Hukkinen M et al.

Summary: The median ages at UC diagnosis and surgery were 15 years and 18 years, respectively, and median follow-up was 20 years. Complications during follow-up included pouchitis in 45%, strictures in 16%, fistulae in 30%, obstruction in 20% and diagnosis revision to CD in 28%; no complications were reported by 23% of the patients. Pouch failure was reported by 14% of patients, among whom the most frequent complications were CD and fistulae. At 20 years follow-up, 79% of the patients reported being very satisfied with their outcome.

Comment: It is known that at least a third of all UC patients and almost half of UC patients who have had an episode of acute severe colitis will undergo colectomy for their disease. Proctocolectomy and ileal pouch anal anastomosis is the operation of choice for many, but this is not without long-term consequences. As with adult patients, the paediatric population suffer complications like pouchitis, surgical complications and infertility in a quarter of women, and almost a third of patients had their diagnosis changed to CD over a 20-year period in this study. Unfortunately, only a quarter of patients did not suffer a pouch complication. About 1 in 7 patients had pouch failure, or an 11% failure rate at 20 years, which was primarily associated with a change in diagnosis to CD. Despite these problems, however, three-quarters of patients were very happy with their pouch function, indicating that although surgery does not induce normality, it is often a much better situation for the patient with uncontrolled active inflammation.

Reference: J Pediatr Surg; Published online Feb 11, 2016

Authors: Shannon A et al.

Summary: Long-term outcomes were reported for a cohort of 74 patients aged <21 years who underwent proctocolectomy with ileal pouch anal anastomosis for UC. The median ages at UC diagnosis and surgery were 15 years and 18 years, respectively, and median follow-up was 20 years. Complications during follow-up included pouchitis in 45%, strictures in 16%, fistulae in 30%, obstruction in 20% and diagnosis revision to CD in 28%; no complications were reported by 23% of the patients. Pouch failure was reported by 14% of patients, among whom the most frequent complications were CD and fistulae. At 20 years follow-up, 79% of the patients reported being very satisfied with their outcome.

Meet Vicky...

Vicky is a 37-year old working mother of two school-aged children who was diagnosed with left-sided UC ten years ago. She had a recent bone densitometry scan which showed osteopenia. Vicky presents to your clinic for the second time in 11 months complaining of diarrhoea and abdominal cramping.

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