IBD Research Review™

Making Education Easy

Issue 40 – 2018

In this issue:

Abbreviations used in this issue

aHR = adjusted hazard ratio
BMI = body mass index
CD = Crohn's disease
CDAI = Crohn's Disease Activity Index
CDEIS = Crohn's Disease Endoscopic Index of Severity
CRP = C-reactive protein
HR = hazard ratio
IBD = inflammatory bowel disease
IR = incidence rate
TNF = tumour necrosis factor
UC = ulcerative colitis

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Welcome to Issue 40 of IBD Research Review.

Type 2 diabetic individuals receiving dipeptidyl peptidase-4 (DDP-4) inhibitors may be at an increased risk of developing IBD according to UK researchers. Following on, we discover that IBD patients taking a combination of thiopurines and an anti-TNF agent are at an increased risk of lymphoma. Also in this issue we investigate the topics of the interaction of thiopurine metabolites, adalimumab and adalimumab antibodies, adjunctive allopurinol in azathioprine/mercaptopurine nonresponders, UK trends in endoscopic, medical and surgical IBD admissions, combination immunosuppression in IBD, and tight control management of CD. Clinical nurse specialist Christine Ho, has selected two informative studies for review, one investigating the topic of sports participation in youth with IBD and the other, sexual dysfunction in men with IBD. Our Science Blog for this issue by Dr Srikantaiah Manjunatha explores intestinal ischaemia and hydroxylase inhibitors.

We hope you enjoy the latest issue of IBD Research Review and welcome your comments and feedback.

Kind regards,

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Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study

Authors: Abrahami D et al.

Summary: This population-based cohort study used data from the UK Clinical Practice Research Datalink (>700 general practices) to examine the use of dipeptidyl peptidase-4 (DPP-4) inhibitors and the incidence of IBD in type 2 diabetes mellitus patients. Over 552,413 person-years of follow-up, 208 incident IBD cases were identified (37.7 per 100,000 person years; 95% CI 32.7-43.1). DDP-4 inhibitors were associated with an increased IBD risk (53.4 vs 34.5 per 100,000 person-years; HR 1.75; 95% CI 1.22-2.49). HR gradually increased with longer use, peaking after 3 to 4 years (HR 2.90; 95% CI 1.31-6.41) and decreasing after >4 years (HR 1.45; 95% CI 0.44-4.76).

Comment (SM): The use of DPP-4 inhibitors (available as vidagliptin, sitagliptin and saxagliptin in New Zealand) in the management of type 2 diabetes has increased considerably in the last decade. Their better therapeutic profile includes lower risk of hypoglycaemia and neutral effects on both weight and cardiovascular outcomes. The inhibition of DPP-4 enzymes leads to a rise in glucagon like peptide (GLP-1) concentrations leading to better control of diabetes. There are various other effects of this enzyme as it is expressed on a variety of cells including those involved in immune response. Low concentrations of DPP-4 have been associated with increased IBD activity, although the association is unclear. This is the first observational study involving a large population-based cohort, which indicates that the use of DPP-4 inhibitors is associated with an overall 75% increase in the risk of IBD in patients with type 2 diabetes. Although the absolute risk is low, this study calls for awareness amongst physicians about the possible association and caution while prescribing these drugs especially for people at high risk (family history of IBD, other concomitant autoimmune conditions). IBD should be considered in the differential diagnosis in diabetic patients on DPP-4 inhibitors presenting with persistent gastrointestinal symptoms like diarrhoea and abdominal pain.

Reference: BMJ. 2018;360:k872
Abstract

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Interactions between thiopurine metabolites, adalimumab, and antibodies against adalimumab in previously infliximab-treated patients with inflammatory bowel disease

Authors: Holmstrøm RB et al.

Summary: This retrospective analysis examined whether principal cytotoxic thiopurine metabolites influenced adalimumab and anti-adalimumab antibodies in 98 IBD patients previously receiving infliximab (96%). Adalimumab-thiopurine combination therapy did not reduce anti-adalimumab antibody positivity versus adalimumab monotherapy (8 of 31 [26%] vs 19 of 67 [28%]). Thiopurine metabolite concentrations did not differ between anti-adalimumab antibody-positive and -negative patients. Adalimumab trough levels did not differ between anti-adalimumab-negative patients receiving adalimumab-thiopurine combination therapy versus adalimumab monotherapy (9.5 vs 7.6 µg/mL), nor between adalimumab monotherapy and combination therapy after stratification for 6-thioguanine nucleotides (6-TGN) and methylated mercaptopurine (6-MMP) metabolite quartiles. There were no correlations between 6-TGN and adalimumab levels, nor 6-MMP and adalimumab levels. Anti-adalimumab antibody positivity was associated with adalimumab treatment failure (OR 6; $p<0.01$), and higher trough adalimumab (9.6 vs 7.3 µg/mL; $p<0.05$) was associated with clinical remission.

Comment (SM): Infliximab and thiopurine combination therapy has proven to be more effective than monotherapy with either drug, and this is attributed to higher infliximab levels along with low immunogenicity with low infliximab antibody levels. It has been suggested that even sub-therapeutic 6-TGN (therapeutic metabolite of thiopurine) levels, and thus lower thiopurine doses, can be used in combination therapy with equal efficacy. However, these findings cannot be extrapolated to other anti-TNF agents and circulating adalimumab trough levels do not seem to differ in patients on adalimumab monotherapy or in combination with thiopurine. In this study, neither concomitant thiopurine treatment by itself nor the levels of thiopurine metabolites were associated with higher adalimumab trough levels or reduced detection of adalimumab antibodies. The treatment outcomes did not appear to be influenced either. The thiopurine treatment did not influence directly the pharmacokinetics of adalimumab or adalimumab antibodies. The efficacy of adalimumab treatment seems to be dependent primarily on adalimumab concentration and adalimumab antibody status, which does not seem to be influenced by concomitant thiopurine treatment or thiopurine metabolites. There are some earlier studies to this effect and the sum of available data along with this study supports that adalimumab can be used as monotherapy during the maintenance phase of IBD treatment avoiding the unnecessary side effects of thiopurine, in stark contrast to treatment with infliximab. This is of practical importance as patients are switched over to adalimumab if the infliximab failure is due to intolerance or development of antibodies to infliximab with low drug availability. However, to muddy the waters, there is some literature claiming the benefits of adding thiopurine after loss of response to anti-TNF monotherapy, including adalimumab and golimumab!

Reference: Dig Dis Sci. 2018;Mar 21 [Epub ahead or print]
Abstract

Independent commentary by Dr Srikantaiah Manjunatha (Manju) FRACP, Consultant Gastroenterologist at Southern DHB, Dunedin and Honorary Senior Clinical Lecturer at the University of Otago.
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Randomised clinical trial: efficacy, safety and dosage of adjunctive allopurinol in azathioprine/mercaptopurine nonresponders (AAA Study)

Authors: Friedman AB et al.

Summary: This multicentre, double-blind trial examined the effect of allopurinol 50 or 100 mg/day and thiopurine dose reduction on reversal of thiopurine shunting (hypermethylation to 6-MMP vs 6-TGN) in 73 patients with clinically active or steroid-dependent IBD. At 24-weeks, 39 (53%) patients had achieved steroid-free remission (primary endpoint), 54% with allopurinol 50 mg/day and 53% with allopurinol 100 mg/day, and 81% discontinued steroids. Therapeutic 6-TGN levels were achieved in both groups. Final thiopurine dosages were lower for allopurinol 100 mg/day recipients ($p < 0.005$). 6-MMP/6-TGN ratios decreased from a mean of 64 to a mean of 4 ($p < 0.001$), with a greater smaller reduction in allopurinol 50 mg/day (ratio of 6) than allopurinol 100 mg/day (ratio of 1; $p = 0.003$) recipients. Three patients receiving allopurinol 50 mg/day developed transient leukopaenia. Alanine aminotransferase concentrations decreased ($p < 0.001$) in both arms. Faecal calprotectin levels were reduced in patients who achieved steroid-free clinical remission (median 171 vs 821 ug/g; $p = 0.03$).

Comment (SM): Thiopurines are inactive pro drugs and of the two major metabolites, 6-TGNs are responsible for therapeutic efficacy and myelotoxicity. The other metabolites, 6-MMPs, have no correlation with efficacy, but are associated with hepatotoxicity. Up to 20% of patients preferentially metabolise thiopurines to produce high levels of 6-MMP and low levels of 6-TGN. These thiopurines "hypermethylators" or "shunters" are usually refractory to standard doses of thiopurines and are also prone to toxicity. Addition of the xanthine oxidase inhibitor allopurinol with reduction of thiopurines dose favours production of 6-TGN over 6-MMP, leading to optimisation of 6-TGN levels and 6-MMP/6-TGN ratios with improved efficacy in these hypermethylators. However, the data available so far has been retrospective, with a variety of allopurinol doses and thiopurines dose-reduction strategies. This is the largest prospective randomised trial of combination of thiopurines and allopurinol in thiopurine-refractory IBD patients with shunting. Therapeutic drug monitoring with metabolites is superior to weight-based thiopurine dosing and clinical response rates improved as early as 2 weeks after addition of allopurinol due to rapid rise in 6-TGN levels. This study refutes the previously published research that 50 mg of allopurinol can achieve the desired effect, because the metabolite profile was less stable and break-through shunting was seen at this dose. Allopurinol on its own, or in combination with thiopurines, has potential risks and side effects, but in this study both the doses of allopurinol were well tolerated. This study does not address the use of allopurinol in overcoming the non-specific thiopurine side effects by dose reduction, as all the patients in this study tolerated thiopurines well and were shunters. Greater stability of thiopurines metabolites without any additional toxicity with allopurinol 100mg/day and some of the limitations of 50 mg/day dose, may be of practical importance favouring regular usage of 100 mg/day of allopurinol in thiopurine hypermethylators.

Reference: Aliment Pharmacol Ther. 2018;47(8):1092-1102
Abstract

Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease

Authors: Lemaitre M et al.

Summary: This national cohort study used French National Health Insurance databases (2009-13; 189,289 patients, followed up until December 31, 2015) to determine the risk of lymphoma associated with thiopurines and anti-TNF agents for the management of IBD. Over a median 6.7 years of follow-up, 123,069 were never exposed, 50,405 received thiopurine monotherapy, 30,294 received anti-TNF monotherapy and 14,229 received combination therapy. Lymphoma occurred in 220 unexposed patients (IR 0.26 per 1000 person-years; 95% CI 0.23-0.29), 70 thiopurine monotherapy recipients (IR 0.54; 95% CI 0.41-0.67), 32 anti-TNF monotherapy recipients (IR 0.41; 95% CI 0.27-0.55) and 14 combination therapy recipients (IR 0.95; 95% CI 0.45-1.45). Multivariate Cox models versus unexposed patients suggested that the risk of lymphoma was higher in those receiving thiopurine monotherapy (aHR 2.60; 95% CI 1.96-3.44; p < 0.001), anti-TNF monotherapy (aHR 2.41; 95% CI 1.60-3.64; p<0.001), or combination therapy (aHR 6.11; 95% CI 3.46-10.80; p<0.001). Combination therapy recipients had a higher risk than thiopurine monotherapy recipients (aHR 2.35; 95% CI 1.31-4.22; p<0.001) or anti-TNF monotherapy recipients (aHR 2.53; 95% CI 1.35-4.77; p<0.001).

Comment (SM): Thiopurines and anti-TNF agents are widely used either as monotherapy or in combination in the management of IBD. Thiopurines are associated with an increased risk of lymphoma. It is unclear whether anti-TNF agents are associated with increased risk of lymphoma on their own or whether the reported increased risk is due to past or concomitant exposure to thiopurines. The risk of lymphoma with combination therapy is also largely unknown. This large French observational cohort study aims to address these issues. The risk of lymphoma was small, but higher with statistical significance in patients exposed to thiopurine monotherapy, anti-TNF monotherapy or combination therapy compared with those who were unexposed to either drug. The risk was even higher in patients exposed to combination therapy compared to either monotherapy. This is a large study involving a very comprehensive national database which outweighs limitations like possible selection bias, severity of inflammation, some deficiencies in data collection and duration of follow up etc., as admitted by the authors. These findings may also impact on informed decisions regarding benefits and risks of treatment. However, although the differences in the risk of lymphoma were significant in relative terms, their absolute magnitude of less than 1/1000 person years should be weighed against the potential benefits of effective treatment of IBD with these agents.

Comment (MS): Combination treatment of IBD, usually with an anti-TNF-alpha inhibitor combined with a thiopurine has been shown to be more effective and leads to a decrease in immunogenicity causing infusion reactions. On the other hand there is an increase in complications such as serious opportunistic infections and potentially also malignancies. Thiopurine monotherapy has been associated with an increased risk of lymphoma and non-melanomatous skin cancer. The authors evaluate the question of risk of lymphoma in combination therapy. Analysis of data on 189,289 patients showed that each therapeutic agent on its own increased the risk of lymphoma but the risk was highest in patients receiving combination therapy. While still small, this increase was statistically significant and needs to be discussed with the patient. Therapeutic drug monitoring including the measurement of anti-drug antibodies should be used to optimise treatment. Limited time exposure to combination therapy might also limit the risk of serious complications such as lymphoma.

Reference: JAMA. 2017;318(17):1679-86
Abstract

Independent commentary by Associate Professor Michael Schultz, Consultant Gastroenterologist for the Southern DHB and Associate Professor in Medicine (Gastroenterology) at the University of Otago, Dunedin School of Medicine.

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Changing nationwide trends in endoscopic, medical and surgical admissions for inflammatory bowel disease: 2003-2013

Authors: Ahmad A et al.

Summary: Utilising Hospital Episode Statistics and population data from the UK Office for National Statistics, these authors examined nationwide trends in IBD surgical/medical elective and emergency admissions, including endoscopy and cytokine inhibitor infusions, between 2003 and 2013. Between 2003-2004 and 2012-2013, age-sex standardised admission rates increased from 76.5 to 202.9/100,000 ($p < 0.001$) for CD and from 69.5 to 149.5/100,000 ($p < 0.001$) for UC. During this time period, elective admission rates fell from 2.6 to 0.7 for CD and from 2.0 to 0.7 for UC and emergency admission rates fell from 9.2 to 6.8 for CD and from 10.8 to 7.6 for UC. Meanwhile, mean length of stay (days) fell significantly for elective (from 2.6 to 0.7 for CD and from 2.0 to 0.7 for UC) and emergency admissions (from 9.2 to 6.8 for CD and from 10.8 to 7.6 for UC). With regard to abdominal surgery, elective lower GI endoscopy rates decreased from 6.3% to 3.7% for CD ($p < 0.001$) and from 18.4% to 17.6% for UC ($p = 0.002$), while elective major abdominal surgery rates decreased from 2.8% to 1.0% for CD ($p < 0.001$) and from 4.9 to 2.4 for UC ($p = 0.010$). Elective admission rates for cytokine inhibitor infusions showed an increase between 2006-2007 and 2012-2013, increasing from 11.1 to 57.2/100,000 for CD and from 1.4 to 12.1/100,000 for UC.

Comment (MS): Recent years have shown a dramatic change in the treatment of IBD with the introduction of highly effective biological agents. At the same time, however, the incidence of IBD is rising worldwide. There have been conflicting data on whether these trends are reflected in higher or lower hospital admission rates, surgical interventions or other medical care in relationship to IBD. The authors analysed national UK data concerning hospital admission rates and length of stay, endoscopic procedures and surgical interventions. While more people are admitted to hospital, the average length of stay is shorter. Fewer endoscopic procedures and surgical interventions are being recorded. The authors argue that the increase in hospital admission is a result of increasing incidence and prevalence of the disease while more effective drugs have led to a decrease in interventions. This data is highly useful especially with a view to planning future workforce initiatives. The recent publication of the Burden of Disease Report by Crohn's and Colitis New Zealand (CCNZ) highlighted an increase in incidence and prevalence in New Zealand comparable to other countries. Data comparable to the presented study is not available for New Zealand but with restricted access to modern biological therapy, the effect on the utilisation of health resources might not be as pronounced as in the presented study from the UK. Furthermore, IBD standards have been introduced in countries like the UK and Australia and while this has not been formerly studied in New Zealand, it is assumed that these standards are currently not being fulfilled.

Reference: BMJ Open Gastroenterol. 2018;5(1):e000191
Abstract

Combination immunosuppression in IBD

Authors: Bots S et al.

Summary/Comment (MS): Whether combination immunosuppressive therapy (in New Zealand usually a TNF-alpha inhibitor combined with an immunomodulator such as a thiopurine) is more effective in the treatment of IBD is debatable but, undoubtedly, the side-effect profile (predominantly infections but also malignancies) is increasing. However, combination therapy lowers the immunogenicity of the biological and leads to a lower rate of infusion reactions. While the early registration trials have not shown better efficacy of combination regimes, later trials, especially SONIC and UC-SUCCESS, have shown a clear superiority of infliximab combined with azathioprine in the treatment of CD and UC. The authors of the present review analyse available literature on the topic and recommend for patients naïve to biologicals to combine infliximab with azathioprine (or methotrexate in case of intolerance) for at least 1 year. It is being argued that most immunogenicity develops early in the treatment. Future studies need to clarify if lower immunomodulatory dosage is sufficient to suppress immunogenicity. Planning is also recommended with a view to stopping a biological. The authors also highlight that continuation of immunomodulators if biologicals are to be stopped is recommended, as this is associated with lower relapse rates. In view of limited access to biologicals in New Zealand, all effort must be taken to optimise available treatment options.

Reference: Inflamm Bowel Dis. 2018;24(3):539-45
Abstract

Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial

Authors: Colombel JF et al.

Summary: Clinical outcomes in adult patients (aged 18-75 years) with moderate-to-severe CD managed with a tight control algorithm (n = 122; mean disease duration 1 year), using clinical symptoms and biomarkers, were compared with those of patients (n = 122; 0.9 years) managed with a clinical management algorithm in CALM, an open-label, randomised, controlled phase III study, in 22 countries involving 74 hospitals and outpatient centres. Patients all had active endoscopic CD (CDEIS >6; sum of CDEIS subscores of >6 in one or more segments with ulcers), a CDAI of 150-450 depending on dose of prednisone at baseline, and all were immunomodulator or biologic naïve. Escalation of treatment was based on meeting the following treatment failure criteria: tight control group before and after random assignment (faecal calprotectin ≥250 µg/g, CRP ≥5 mg/L, CDAI ≥150, or prednisone use in the previous week); clinical management group before random assignment (CDAI decrease of <70 points compared with baseline or CDAI >200); clinical management group after random assignment (CDAI decrease of <100 points compared with baseline or CDAI ≥200, or prednisone use in the previous week). Both groups underwent treatment escalation in a stepwise manner, from no treatment, to adalimumab induction followed by adalimumab every other week, adalimumab every week, and then both weekly adalimumab and daily azathioprine. A significantly higher proportion of patients in the tight control group achieved the primary endpoint of mucosal healing (CDEIS <4) with absence of deep ulcers 48 weeks after randomisation (56 [46%] patients) than in the clinical management group (37 [30%] patients), with a Cochran-Mantel-Haenszel test-adjusted risk difference of 16.1% (95% CI 3.9-28.3; $p = 0.010$). A total of 105 (86%) patients in the tight control group and 100 (82%) patients in the clinical management group reported treatment-emergent adverse events; there were no treatment-related deaths. The most common adverse events were nausea (21 [17%] patients), nasopharyngitis (18 [15%]), and headache (18 [15%]) in the tight control group, and worsening CD (35 [29%] patients), arthralgia (19 [16%]), and nasopharyngitis (18 [15%]) in the clinical management group. Thirty-two (26%) patients in the tight control group and 29 (24%) patients in the clinical management group discontinued the study, mostly due to adverse events.

Comment (MS): Although biological drugs are highly effective in the treatment of IBD, they come at high costs and an increased side-effect profile. Intuitively, optimisation of available treatment regimes is advised but effect on outcome has not been studied extensively. Tools to optimise treatment in IBD comprise the use of Therapeutic Drug Monitoring but also the routine use of outcome measures such as faecal inflammatory markers and endoscopic evaluations. The difficulty of such an approach lies in the poor correlation of symptoms with endoscopic and biochemical evidence of inflammation. This study included 244 patients randomised into two arms. The patients had active CD and were naïve to immunomodulators and biologics. After 8 weeks of corticosteroids, treatment was stepwise escalated including adalimumab and azathioprine. The decision to escalate was either based on CDAI and symptoms or CDAI, faecal calprotectin and C-reactive protein at weeks 0, 11/12, 23/24 and 35/36. The primary endpoint was mucosal healing evaluated after 48 weeks. Biomarker-controlled escalation was superior to symptom-driven treatment with 46% versus 30% achieving the primary endpoint.

Reference: Lancet 2018;390(10114):2779-89
Abstract

Christine Ho Inflammatory Bowel Disease Clinical Nurse Specialist, Dunedin Hospital, Southern District Health Board

Sports participation in youth with inflammatory bowel diseases: The role of disease activity and subjective physical health symptoms

Authors: Greenley RN et al.

Summary: A cross-sectional analysis of data from the internet-based Crohn's and Colitis Foundation of America Partners (CCFA Partners) Kids and Teens Registry was conducted to study the influence of disease complications, BMI, subjective physical health and psychosocial functioning on sports participation in 450 youth (12-17 years) with IBD. Two-thirds (66.2%) of the cohort indicated that IBD impaired sports participation in some way, with a subset (18.3%) reporting that IBD "often" or "almost always" interfered with sports participation, and IBD disease activity was associated with the perceived impairment. In an analysis controlling for disease activity, the most salient correlates of impairment were fatigue, pain and past IBD-related surgery.

Comment: This study found that 66% of the participants had perceived impairment of physical activity due to their IBD related symptoms. Not surprising that pain, fatigue, disease activity and IBD-related surgery were the main reasons that this cohort did not engage in physical activity. But on the flipside we know that pain and fatigue can be improved with being active, along with improvement of depression and anxiety, which are also associated with living with a chronic illness. Physical activity has been shown to improve life satisfaction and can encourage youth to adopt healthy behaviours. This is important for teenagers diagnosed with IBD as they have the risk of becoming socially isolated during an important social development stage. So the question remains how we get youth diagnosed with IBD to engage in physical activity to improve these related symptoms such as fatigue and pain, to improve their quality of life, mental wellbeing and reduce the risk of complications related to inactivity, such as obesity.

Reference: Inflamm Bowel Dis. 2018;24(2):247-53
Abstract

Sexual dysfunction in men with inflammatory bowel disease: A new IBD-specific scale

Authors: O'Toole A et al.

Summary: This cross-sectional survey engaged male patients (n = 175) over 18 years of age attending IBD clinics at Boston hospitals to develop a new IBD-specific Male Sexual Dysfunction Scale (IBD-MSDS). Exploratory factor analyses suggested 10-items from the assessment battery (15-item scale on sexual functioning) had strong internal consistency reliability (α = 0.90). Criterion validity indicated that the IBD-MSDS correlated with all the subscales of the International Index of Erectile Dysfunction (IIEF; criterion validity), the Patient Health Questionnaire (PHQ-9; construct validity; $p < 0.001$) and the composite score for active IBD cases ($p < 0.05$). Male sexual dysfunction was associated with ileoanal pouch anastomosis ($p = 0.047$), depression ($p < 0.001$), and increased disease activity ($p = 0.021$).

Comment: Sexual dysfunction in men with IBD is often neglected, whether this is due to the fact that it is often overlooked or due to the intimate nature of the discussion. But it is something that our patients may benefit from if it were addressed. The development of the IBD-MSDS is a useful tool for initiating these difficult discussions. The fact that sexual dysfunction is different in the IBD cohort is important. That is not just related to the patient's function, but can be due to the symptoms that are often experienced by someone diagnosed with IBD such as fatigue, pain and increased bowel motions. Or due to body image related to having a stoma, surgery or fistulising disease. If we are able to identify the factors that contribute to male sexual dysfunction it then provides an opportunity to discuss, treat or manage these factors to improve the patients overall sexual function and quality of life.

Reference: Inflamm Bowel Dis. 2018;24(2):310-16
Abstract

Christine Ho is the IBD Clinical Nurse Specialist (CNS) at Dunedin Hospital, Southern District Health Board. She started as an IBD Nurse in 2012 and has continued with the development of the role to a CNS position for the DHB. Christine completed a Postgraduate Diploma in Health Science at Otago University in 2016. She has a varied nursing background including experience in surgical nursing, stomal therapy, bowel cancer screening in the UK and endoscopy.

SCIENCE BLOG

Dr S Manjunatha BSc, MD, FRCP, FRACP, Consultant Gastroenterologist

Intestinal ischaemia and hydroxylase inhibitors in IBD: A new therapeutic approach

Mucosal hypoxia is an integral part of IBD. Hypoxia triggers an adaptive transcriptional response mediated by oxygen sensitive Hypoxia Inducible Factor (HIF-1-3). HIF is comprised of an oxygen sensitive α subunit (HIF-1α, HIF-2α and HIF-3α) and a constitutive coactivator HIF-β. Under normoxic conditions HIF-α mRNA is constitutively expressed, but HIF protein is rapidly degraded by 2-oxyglutarate dependent deoxygenases, the prolyl hydroxylases (PHDs). This activity is hampered in hypoxia with stabilisation of HIF-α protein, which can translocate to the nucleus and activate gene expression with HIF-β. HIF is responsible for upregulation and expression of over 200 genes involved in erythropoiesis, angiogenesis, iron homeostasis, intestinal barrier integrity etc. This is the principle behind the development of pharmacological 'hypoxia mimetics' to exploit the stabilisation and activation of HIF pathways for therapeutic benefit. Most of these drugs are non-specific hydroxylase inhibitors structurally related to PHDs.

The increased presence of HIF was a key observation in the colons from both murine colitis and IBD patients that led to the investigation of pharmacological and genetic manipulation of the HIF pathway. Multiple studies have now shown that hydroxylase inhibition is protective in murine colitis. This may be mediated via the protection and maintenance of integrity of the intestinal barrier, which in turn is due to HIF-dependent reduction of intestinal cell apoptosis. HIF has been linked to the production of trefoil factors, mucin, β-defensin and the regulation of mucosal immune response, which are all important in barrier protection and integrity. Hydroxylase inhibition may also be implicated in barrier protection through the regulation of tight junctions by claudin-1 expression and occludin stabilisation. HIF hydroxylases have an important role in regulation of other processes. There is a close relation between HIF, HIF hydroxylases and the nuclear factor kappa beta (NFkB) pathway and there is significant evidence supporting the involvement of PHDs in the regulation of NFkB-dependent inflammatory pathways.

Anaemia is common in IBD and the cause is multifactorial. As a regulator of hypoxic responses, HIF strongly induces the expression of erythropoietin, stimulating erythrocyte proliferation. This could be an additional beneficial effect of hydroxylase inhibition in IBD patients with anaemia. Intestinal fibrosis is another common complication in IBD, more so in CD, and hydroxylase inhibition can be a negative regulator of transforming growth factor beta 1 (TGF-β1) -induced intestinal fibrosis.

Hydroxylase inhibition is not without undesirable side effects, like upregulation of erythropoietin in patients without anaemia, activation of HIF contributing to tumour growth and survival, promotion of angiogenesis and other cancer-related processes like metastases and cancer stem cell differentiation. A potential solution to these undesired side effects would be formulation of specific hydroxylase inhibitors in targeted release form. Recently, use of a colonic release form has been described to avoid undesirable side effects without compromising efficacy.

Epithelial disruption is one of the key drivers of IBD and restoring the integrity of epithelium and the barrier function is of prime importance in the development of new therapies. Pharmacologic targeting of oxygen-sensing hydroxylases results in both HIF-dependent and HIF-independent mechanisms contributing to restoration of, and maintenance of, barrier function. Development of specific inhibitors and their targeted delivery is a real challenge, promising exciting and potential therapy for IBD, when finally overcome!

Further reading:

Eltzschig HK et al. Nat Rev Drug Discov. 2014;13(11):852-69
Cummins EP and Crean D. Microbes Infect. 2017;19(3):210-21
Van Welden S et al. Nat Rev Gastroenterol Hepatol. 2017;14(10):596-611
Manresa MC and Taylor CT. Cell Mol Gastroenterol Hepatol. 2017:3(3):303-15

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