ECCO 16th Congress 2021 Conference Review™

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Abbreviations used in this review:

CD = Crohn's disease; **CI** = confidence interval;
COVID-19 = coronavirus disease 2019;
IBD = inflammatory bowel disease; **HR** = hazard ratio;
NS = not significant; **PCR** = polymerase chain reaction;
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2;
SCCAI = Simple Clinical Colitis Activity Index;
TNF = tumour necrosis factor; **UC** = ulcerative colitis.

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Welcome to our review of the 16th Congress of the European Crohn's and Colitis Organisation (ECCO) virtual meeting.

The ECCO Congress has become the leading world congress for Inflammatory Bowel Diseases (IBDs). The year's programme had a major focus on precision medicine for IBD. Highlights included direct comparison and combinations of drugs. Top specialists provided new insights on the real burden of IBD, the optimal management of disease complications, the best way to monitor patients and the ultimate therapeutic goals. I have selected some standout presentations for commentary in this review.

We hope you enjoy these selections and look forward to your comments and feedback.

Kind Regards,

Associate Professor Britt Christensen
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OP01 Comparison of fecal transplantation, fecal transplantation with the novel UC diet or the UC diet alone for refractory mild to moderate active ulcerative colitis: The CRAFT UC randomized controlled trial

Authors: Levine A et al.

Summary: This blinded randomised controlled pilot trial tested the use of a special diet (for the dysbiosis of UC and to decrease factors that impair goblet cells or mucous production) in donors and recipients (n = 51) of faecal microbial transplantation (FMT). Recipients had UC refractory to medication and 28 patients had failed a biologic. The trial was stopped early for futility. Steroid-free remission (SCCAI <3 at week 8) in free diet and standard FMT recipients was achieved by 2 of 17 (11.8%) patients, in patients receiving the UC diet and dietary pre-conditioning of the FMT donor, remission occurred in 4 of 19 (21.1%), in patients receiving the UC diet alone, remission was achieved by 6 of 15 (40%). Endoscopic remission occurred in 2 of 17(12%), 3 of 19 (16%) and 4 of 15 (27%), respectively. Mucosal healing (Mayo score 0) was achieved in 3 of 15 (20%) of UC diet recipients versus 0 of 36 FMT recipients (p = 0.022). Disease exacerbation did not differ between groups; 3 of 17 (17.6%), 4 of 19 (21.1%), and 1 of 15 (6.7%), respectively.

Comment: FMT is effective at inducing remission in active UC with one-third of patients with moderate-to-severe UC achieving steroid-free clinical remission in clinical trials. Success of FMT appears to depend on the donor microbiota composition but donors are selected randomly. This is overcome by multi-donor transplants which appears to improve overall response rates. Microbial analysis of successful FMT donors has demonstrated an increase in bacteria that are involved in butyrate production. Diet can modulate the microbiota and a diet rich in plant fibre may provide substrates for commensals thought to be pivotal in restoring gut health and which provide butyrate. This study by Levine et al., hypothesised that firstly, a novel donor diet for 2 weeks prior to stool donation would result in a superior donor microbiome and subsequently improved donor recipients' clinical outcomes and secondly, that FMT combined with a novel UC exclusion diet in the recipient could also result in superior clinical outcomes. Both these treatment groups were compared to a UC exclusion diet alone. This study failed to demonstrate improved efficacy in either FMT arm and points to a lack of utility in moderating diet in the donor before transplant or recipient following transplant. The study was stopped prematurely due to futility although it is important to note the FMT algorithm used in this study was with a lower than standard FMT dose. However, of note, no patient with severe disease responded to any of the three therapies and therefore these therapies may need to be reserved for mild-to-moderate disease. Secondly, of all three arms, the UC exclusion diet alone was most effective for induction of clinical and endoscopic remission in patients with a milder spectrum of disease. This points to a possible role of utilising a simple exclusion diet in UC to induce remission and is currently being explored further.

Reference: J Crohns Colitis 2021;15(Suppl 1):S001
Abstract

OP02 Ustekinumab versus adalimumab for induction and maintenance therapy in moderate-to-severe Crohn's disease: The SEAVUE study

Authors: Irving PM et al.

Summary: The 52-week, multicentre, randomised, blinded, parallel-group, active-controlled SEAVUE study compared ustekinumab versus adalimumab in 386 biologic-naive patients with moderate-to-severe CD. Overall, there was no difference in the proportion of ustekinumab (65%) and adalimumab (61%) recipients achieving clinical remission (difference 4.0%; 95% CI -5.5 to 13.5%). Among ustekinumab and adalimumab recipients, 34.0% and 40.5% experienced infections, 2.6% and 7.2% had serious adverse events of worsening CD, and 6.3% and 11.3% had adverse events that led to discontinuation of drug. Injection-site reactions associated with active treatment occurred in 1.0% of ustekinumab versus 10.3% of adalimumab recipients. Discontinuations occurred in 15.2% of ustekinumab and 23.6% of adalimumab recipients, primarily for lack of efficacy (2.1% vs 5.1%), adverse events (5.7% vs 10.7%), and withdrawal of consent (5.8% vs 5.1%). Post hoc analysis suggested that time to treatment discontinuation was longer with ustekinumab than adalimumab.

Comment: There are multiple biologic therapies available with different mechanisms of action to treat CD. Head-to-head trials are needed to inform patient and physician treatment decisions. This superiority study comparing ustekinumab with adalimumab in biologic-naive patients with moderate-to-severe CD failed to demonstrate superiority of ustekinumab over adalimumab. Clinical remission rates between both groups were not statistically significant at about 60% and both treatment arms demonstrated rapid onset of action and robust endoscopic results with 30% achieving healing. Discontinuation of drug was numerically lower for ustekinumab at 15% versus 25% by 1 year. There were also more injection site reactions in the adalimumab arm at 10% compared to 2% in the ustekinumab arm despite using citrate-free adalimumab. Overall, this study demonstrates that both ustekinumab and adalimumab are effective medications for CD. It is important to note the study design did not allow dose-optimisation of the biologic or the addition of an immunomodulator, and both these factors are likely to handicap response rates in the adalimumab arm over ustekinumab.

Reference: J Crohns Colitis 2021;15(Suppl 1):S001-S002
Abstract

OP03 Anti-SARS-CoV2 antibody responses are attenuated in patients with inflammatory bowel disease treated with infliximab

Authors: Kennedy NA et al.

Summary: The multicentre, prospective, observational, CLARITY IBD cohort study examined whether 4685 patients with IBD receiving infliximab have attenuated serological responses following SARS-CoV-2 infection compared to 2250 patients receiving vedolizumab, a gut-selective anti-integrin α4β7 monoclonal antibody not associated with impaired vaccine responses or increased systemic infections. Multivariate analyses suggested that infliximab versus vedolizumab (OR 0.66; 95% CI 0.51-0.87; p = 0.0027) and immunomodulator use (OR 0.70; 95% CI 0.53-0.92; p = 0.012) were independently associated with reduced seropositivity. In those with confirmed SARS-CoV-2 infection, seroconversion occurred in fewer infliximab than vedolizumab recipients (48% vs 83%; p = 0.00044) and anti-SARS-CoV2 reactivity was lower. An initial increase in anti-SARS-Cov2 antibody reactivity occurred 4 weeks after a positive PCR test in vedolizumab but not infliximab recipients. Antibody responses after initial positive tests were less durable in infliximab recipients (HR 5.15; 95% CI 2.95-9.00).

Comment: It is known that anti-TNF biologic therapies are associated with a higher risk of certain infections and lower response to vaccination. The effect of these biologic therapies on immune response to infection and vaccination in the setting of the COVID-19 pandemic is important to understand. These studies aimed to determine the seroprevalence of anti-SARS-CoV-2 antibodies, the magnitude of this reactivity and the durability of these antibodies as well as response to vaccination. Almost 7000 patients on vedolizumab or infliximab were recruited and followed every 8 weeks for 20 weeks. Positive PCR for SARS-CoV-2 infection was evident in 5.3% of the infliximab treated group versus 4.4% of those on vedolizumab. Both groups had approximately 0.2% hospitalised for severe COVID-19. Baseline seroprevalence was 3.4% in the infliximab arm versus 6% ($p < 0.0001$) in the vedolizumab arm. On multivariate analysis, infliximab and immunomodulators were significantly associated with reduced seroconversion with an approximately 35% reduction with anti-TNF and 30% with immunomodulators. In those that did get antibody responses, vedolizumab responses were significantly higher than those in infliximab. This was both early on in infection and late after infection. In terms of durability, vedolizumab also had much higher durability of seropositivity with a 50% drop over time much more quickly in the infliximab group. Those with infliximab had a hazard ratio of 3.41 (95% CI 2.71-4.28) of losing antibodies with time. Overall, infliximab results in lower seroprevalence and lower seroconversion in PCR confirmed cases with lower magnitude and durability of anti-SARS-CoV-2 antibodies. The study also looked at vaccination response. It was found that two vaccine doses but not one elicited a good immune response in patients regardless of vaccine (Pfizer or AstraZeneca) or biologic (anti-TNF or vedolizumab). After only one dose there was sub-optimal or lack of seroconversion in those on infliximab. Vedolizumab did not appear to be affected. Infection rates following vaccination were examined and it was found that there was no protection after one dose of vaccine no matter what medical therapy the patient was on, but once two doses were given, they had 80% effectiveness. Although the antibody drop and lack of seroconversion in patients infected with COVID-19 is slightly concerning, the vaccination data is reassuring. However, we do not have long-term data so studies looking at durability and need for booster vaccination are urgently required. In addition, these studies only look at humoral immunity and do not take into account cellular immunity, which may be more important. Future studies will need to examine this.

Reference: J Crohns Colitis 2021;15(Suppl 1):S002-S004
Abstract

DOP10 Persistent sonographic inflammation as a predictor of clinical complications in patients with Crohn's disease

Authors: Vaughan R et al.

Summary: This retrospective study examined persistent intestinal ultrasound changes and their relationship with clinical complications in 212 CD patients in clinical remission. At baseline, 61% of patients had inflammation (bowel wall thickness >3mm and/or hyperaemia on colour doppler imaging) detected by intestinal ultrasound. During a median follow-up of 19 months, medical escalation was required in 51%, corticosteroid use in 23%, hospitalisation in 20% and IBD-related surgery in 13% of patients. Baseline sonographic inflammation was associated with increased risk of medical escalation, corticosteroid use, hospitalisation and surgery. Multivariate analysis suggested that only maximal bowel wall thickness predicted medical escalation (HR 1.22; 95% CI 1.02-1.46; p = 0.0268), while hyperaemia at baseline was associated with corticosteroid use (HR 2.20; 95% CI 1.13-4.28; p = 0.02). Sonographic parameters did not predict IBD-related hospitalisation or surgery, but surgery was predicted by baseline immunomodulator use (HR 3.59; 95% CI 1.22-10.54; p = 0.02) and stricturing phenotype (HR 4.01; 95% CI 1.14–14.03; p= 0.03).

Comment: Persistent inflammation has been associated with worse CD outcomes including increased rates of surgery, corticosteroid use and clinical relapse. This study investigated whether persistent sonographic inflammation in CD patients in clinical remission was associated with clinical complications. Sonographic inflammation was defined as any of bowel wall thickness >3mm, hyperaemia on colour doppler imaging, loss of bowel wall stratification and presence of mesenteric fat hypertrophy. Clinical complication-free survival was compared between those with and without sonographic inflammation in 202 patients. Sonographic inflammation significantly predicted medication and corticosteroid use and there was also a trend toward increased hospitalisations and surgery in those with persistent sonographic inflammation. This study demonstrates that patients in clinical remission with persistent sonographic inflammation have worse clinical outcomes in CD and that intestinal ultrasound may be used as a non-invasive biomarker to predict need for medication escalation and corticosteroid use. The study provides further evidence of the strength of intestinal ultrasound as a non-invasive assessment tool with the findings demonstrating that those patients who achieve sonographic healing do better long term and may even require less frequent monitoring. Future studies should examine if patients who achieve sonographic healing can be considered for treatment de-escalation and there is a need to analyse whether sonographic remission can be considered a feasible treatment target.

Reference: J Crohns Colitis 2021;15(Suppl 1):S048-S049
Abstract

OP18 Treatment of perianal fistulas in Crohn's Disease: Surgical closure after anti-TNF induction treatment versus anti-TNF without surgery (PISA II) - A patient preference RCT

Authors: Meima-van Praag E et al

Summary: This multinational, patient preference (or randomised if there was no preference) controlled trial compared MRI healing in 93 CD patients with a high perianal fistula and a single internal opening receiving surgical closure following anti-TNF induction for 4 months (n = 37) or anti-TNF therapy without surgery (n = 56). At 18 months, MRI healing rates were higher in surgical closure patients (41% vs 11%; p = 0.002). Clinical healing rates (65% vs 45%) and surgical reintervention rates (19% vs 34%) did not significantly differ between groups. After a median of 38 months, 12 anti-TNF recipients crossed over to surgical closure; long-term MRI healing (46% vs 11%; p = 0.002) and clinical closure rate (65% vs 29%; p = 0.006) remained higher in surgical patients. More patients with a Magnetic Resonance Novel Index for Fistula Imaging in CD (MAGNIFI-CD) score >5 developed a recurrent fistula after 46 months compared to those with a MAGNIFI-CD score ≤5 (4% vs 37%; p = 0.004).

Comment: CD fistulae are associated with a significantly reduced quality of life. Even with gold-standard therapy which often includes a combination of seton insertion and anti-TNF therapy, fistula healing rates only approach 50%. Therefore, novel approaches are required. This study examined whether a surgical arm consisting of anti-TNF induction combined with surgical closure (ligation of the intersphincteric fistula tract [LIFT] procedure or advancement flap) could improve fistula healing compared to an anti-TNF therapy arm which consisted of at least 52 weeks of anti-TNF therapy with seton placement. This was a patient preference study where patients without a preference were randomised. In an intention-to-treat analysis, radiologic healing by MR pelvis occurred in more surgical closure patients compared to anti-TNF patients. Similar results were found in a per-protocol analysis. Clinical closure, in contrast, was similar between groups. In a per-protocol examination the difference reached significance with 71% having clinical closure in the surgical arm compared to 50% in the anti-TNF arm (p = 0.02). Quality of life was similar across both groups early in the study, but by 18 months was significantly worse in the anti-TNF arm compared to the surgical arm. Recurrence-free survival was similar between both groups at 15% and 17%, as was re-intervention-free survival. No recurrence occurred in those who achieved MRI healing. Overall, anti-TNF induction with surgical closure using either a LIFT procedure or advancement flap induced MRI healing significantly more frequently than anti-TNF therapy alone. This is associated with improved quality of life. Therefore, consideration of surgical closure should be considered early on when managing perianal CD. It is just important to note that patients with proctitis were excluded and would not be appropriate for such procedures.

Reference: J Crohns Colitis 2021;15(Suppl 1):S017
Abstract

DOP87 Disease clearance as a new therapeutic target in patients with ulcerative colitis: A multicenter retrospective cohort study

Authors: D'Amico F et al.

Summary: This multinational retrospective cohort study examined the impact of disease clearance (clinical [partial Mayo score ≤2 with no subscore >1], endoscopic [endoscopic Mayo score 0], and histological [Nancy index 0]) remission of disease) on long-term outcomes in 302 UC patients; 42 patients (13.9%) had disease clearance at baseline. Over a median follow-up of 32.2 months, there was no difference in surgery rate between disease clearance and non-disease clearance patients (0.0% vs 8.5%). Hospitalisation rate was lower in disease clearance versus control patients (7.1% vs 25.4%; p = 0.01). Among 51 (16.9%) patients who achieved both endoscopic and histologic remission there was a lower rate of surgery (0.0% vs 8.8%; p = 0.05) and hospitalisation (7.8% vs 25.9%; p = 0.008) than among patients with endoscopic and/or histologic disease activity. Kaplan Meier curves confirmed that patients with disease clearance at baseline had a lower risk for surgery (p = 0.04) and hospitalisation (HR 0.49; 95% CI 0.08-2.29; p = 0.009).

Comment: In recent times, mucosal healing and increasingly, histological healing, have been proposed as treatment targets for UC. Acknowledging that the deeper the level of remission, the greater the improvement in outcomes, targets of therapy have become more ambitious. This study examined the impact of disease clearance, defined as a combination of endoscopic and histological healing on clinical outcomes. A total of 502 patients were included, with a mean follow-up of 33 months. Disease clearance was detected in 13% of patients. As would be expected, disease clearance was associated with reduced hospitalisation at 7% compared to 25% in those who did not achieve disease clearance (p < 0.01). On Kaplan Meier analysis, there was a 31% increased risk of hospitalisation at 5 years in those who did not achieve disease clearance. Surgery was also higher in those without disease clearance at 10% versus 1% with disease clearance (p = 0.02). On Kaplan Meier, there was a 14% reduced risk of surgery at 5 years in those achieving disease clearance. This study demonstrates long-term benefits of disease clearance. The authors conclude by arguing it should be considered as a new target. However, there is no discussion regarding whether this disease clearance improves outcomes above that of endoscopic healing alone or histological healing alone, although previous studies have demonstrated benefit with histologic healing above that of mucosal healing. In addition, current treatments have a low rate of achieving disease clearance and hence if it was to be adopted as a treatment target, we run the risk of burning through different classes of medicine very quickly. Overall though this study adds to the literature supporting histological activity assessment in UC which can be utilised as a prognostic marker even when it is not used as a treatment target. In those who also have not achieved disease clearance, if there is a simple in-class medication optimisation that can occur, then one might consider this. Otherwise, at this stage we await the results of prospective studies examining the benefit of targeting clinical, endoscopic, histological or any combined outcomes before determining the optimal treatment target.

Reference: J Crohns Colitis 2021;15(Suppl 1):S118-S119
Abstract

Independent commentary by Associate Professor Britt Christensen

Britt holds a senior medical staff appointment at the Royal Melbourne Hospital, where she is the Head of the Inflammatory Bowel Disease Unit and is a Clinical Associate Professor at the University of Melbourne. Britt studied Medicine at the University of Melbourne, graduating with honours in 2006 and has completed a Masters of Public Health at Monash University, for which she was awarded a Medal of Academic Excellence. After completing her gastroenterology training at St Vincent's and Alfred Hospital, she was awarded the Joseph B. Kirsner fellowship and spent over 2 years undertaking advanced training in IBD at the prestigious University of Chicago Medicine, one of the largest and most prominent IBD centres in the world. Whilst there, she undertook research toward a PhD looking at histological outcomes and novel therapies in IBD. She is currently supervising multiple PhD students, is the principle investigator on large international clinical trials and has presented her research at numerous national and international conferences and has been published widely. In addition, Britt is a co-founder of the Victorian Immune Diseases Bio Bank and is the author of several book chapters on IBD and is a reviewer for a number of the top journals in the field of gastroenterology.

OP30 Lyophilised orally administered faecal microbiota transplantation for active ulcerative colitis (LOTUS study)

Authors: Haifer C et al.

Summary: In a multicentre, randomised, double-blind, placebo-controlled trial, researchers trialled lyophilised oral FMT from healthy donors in 37 patients with mild-moderately active UC (Mayo score 4-10) after 2-weeks of pre-FMT antibiotic therapy. Week 8 steroid-free clinical remission with endoscopic remission or response (Mayo score ≤2 with subscores ≤1 for rectal bleeding, stool frequency and endoscopic appearance, and ≥1-point reduction from baseline in endoscopy subscore) was achieved by 8 (50%) of 16 FMT recipients versus 3 (16%) of 19 placebo recipients (OR 4.63; 95% CI 1.74-12.30; p = 0.002); steroid-free clinical remission rate was 69% versus 26% (p = 0.012) and endoscopic remission rate was 44% vs 16% (p = 0.074).

Comment: There is evidence that FMT delivered via colonoscopy and enemas is effective for the induction of remission in UC. This results in clinical remission in over 30% of patients. The main concerns with this treatment are that the majority will relapse, there is no maintenance therapy and repeated colonoscopy is not well tolerated. This study looked at whether an orally administered encapsulated FMT could lead to clinical, biochemical, and endoscopic healing in patients with mild or moderate UC. Patients received 2 weeks of antibiotics (amoxicillin, metronidazole, doxycycline) and were randomised to placebo or oral FMT. At week 8, those that responded were re-randomised to placebo or FMT. Treatment consisted of 24 capsules per day in week 1, 12 per day in week 2 and 6 capsules daily for 6 weeks. Maintenance was 2 capsules daily. Patients were able to stay on oral mesalamine, prednisolone and biologics. The primary week 8 outcome was steroid-free clinical remission and endoscopic remission or response. The aim was to enrol 64 patients, but the study had to be stopped at 37 due to the COVID-19 pandemic. There were no adverse events above that of placebo described. FMT lead to significantly greater chance of meeting the primary outcome at week 8 of clinical remission and endoscopic remission or response with FMT versus placebo. FMT also led to greater rates of clinical remission. Continued FMT was well tolerated and was associated with maintenance of clinical and endoscopic remission and the development of histological remission by week 52. Among 10 of 15 FMT recipients who responded to treatment and were re-randomised, 4 continued FMT maintenance and all maintained clinical, endoscopic and histologic healing. The 6 patients randomised to FMT withdrawal all flared. Limitations of this study include the lack of a calprotectin assessment and the low numbers at enrolment. However, overall, this is an exciting project with exciting outcomes. Further research is needed but it looks like this is where the future of FMT lies.

Reference: J Crohns Colitis 2021;15(Suppl 1):S029
Abstract

OP05 Association of ultra-processed food intake with risk of inflammatory bowel disease from the Prospective Urban Rural Epidemiology (PURE) study: A prospective cohort study

Authors: Narula N et al.

Summary: Data from the multinational, Prospective Urban Rural Epidemiology (PURE) study were analysed to examine the association between ultra-processed food intake and risk of developing IBD among 116,087 participants aged 35-70 years. Over a median 9.7 years of follow-up there were 467 incident IBD cases (90 CD, 377 UC). After adjustment for potential confounding factors, greater intake of ultra-processed foods was associated with a greater risk of incident IBD; compared to <1 serving/day, participants with an intake of ≥5 servings/day had an HR of 1.82 (95% CI 1.22-2.72) and those with an intake of 1-4 servings/day had an HR of 1.67 (95% CI 1.18-2.37; p_{trend} = 0.006). Soft drinks, sweets, salty snacks, and processed meat were each associated with a higher HR for IBD.

Comment: This study looked at the association of proceed food intake with risk of developing IBD. Detergents and emulsifiers that are frequently added to foods may have a detrimental impact on the gut barrier. Carboxymethylcellulose has been shown to increase bacterial adherence to intestinal epithelium and may lead to bacterial overgrowth and infiltration of bacteria into the spaces between intestinal villi. Polysorbate 80 is an emulsifier commonly found in processed foods. It has been demonstrated to increase translocation of bacteria like *Escherichia coli* across M cells and Payer's patches in patients with CD. This study aimed to determine if these things increase the risk of developing IBD, which has significantly increased in incidence and prevalence in the industrialised world in recent history. This was an observational cohort study that has been ongoing for more than 20 years. The original study was focused on cardiovascular risk and hence the age group of patients at recruitment was between 35 and 70. Participants completed food frequency questionnaires (FFQ) and donated blood. Processed food intake was determined using the FFQ and included all types of packaged and formulated foods and beverages which contain food additives, artificial flavourings colours or other chemical ingredients. IBD diagnosis was based on a self-report which the team had validated. 116,037 patients were followed for a decade and there were 467 incident cases of IBD. This skewed diagnosis was hypothesised to be due to the age of patients, as diagnosis of CD is more frequent when patients are younger than 35 years. Patients who consumed ≥5 servings per day of processed food were at almost twice the risk of developing IBD. This was more pronounced in those diagnosed with CD. ≥1 per day of processed meat intake and ≥3 soft drink servings per week and salty foods and snacks ≥100 g/day also almost doubled the risk of IBD and was similar in both UC and CD. Intake of foods high in refined sugar (≥100 g/day) were seen to increase the risk for UC but not CD. Finally, fried food also increased the risk of developing IBD (but these are likely processed foods and salty). Exploratory analysis looking at white meat, red meat, dairy, starch, and fruit and vegies did not find any association. In conclusion, higher processed food intake was associated with increased risk of developing IBD, and the risk is seen with all categories of processed foods. This study was limited as it was not set up to measure for IBD and there was no direct measurement of emulsifiers or specifics. However, it is the first large study that does give weight to the hypothesis that a Western diet is associated with IBD. This study demonstrates that there is a stronger signal for CD, but it was still there for UC. In high-risk patients it may be prudent to council on a low-processed Mediterranean style diet to reduce the risk of IBD onset.

Reference: J Crohns Colitis 2021;15(Suppl 1):S006
Abstract

DOP36 Non-invasive assessment of postoperative disease recurrence in Crohn's Disease: A multicenter, prospective cohort study

Authors: Furfaro F et al.

Summary: This Italian blinded study compared colonoscopy versus non-invasive measures, including bowel ultrasound, C-reactive protein and faecal calprotectin (FC), for assessment of post-surgical management and treatment in 70 patients. At 6 months post-surgery, 45 (64%) patients had experienced endoscopic recurrence (Rutgeerts' score >2); 13 were symptomatic (Harvey-Bradshaw Index >4). Endoscopic recurrence was found to be independently associated with bowel wall thickness (1 mm increase OR 2.63; 95% CI 1.13-6.12; p = 0.024), the presence of lymph-nodes (OR 23.24; 95% CI 1.85-291.15; p = 0.014) and FC >50 µg/g (OR 11.86; 95% CI 2.60-54.09; p = 0.001).

Comment: The majority of patients with CD will require a surgical resection at some point in their lifetime. Prevention of recurrence of disease following resection is critical as 90% of patients will have endoscopic recurrence by 12 months without medical treatment. Currently guidelines that come off studies like POCER (Post-operative Crohn's Endoscopic Recurrence Study) performed here in Australia recommend endoscopic assessment within 12 months of disease. However, this is expensive and poorly tolerated by patients. Calprotectin has been demonstrated to be associated with endoscopic recurrence but lacks both sensitivity and specificity. Therefore, it is critical to look for non-invasive and patient friendly monitoring tools. This study looked at a non-invasive combination of calprotectin and bowel ultrasound and compared this to endoscopy to identify recurrence. Following ileocecal resection, a colonoscopy and ultrasound was performed at 6 months. Bowel wall thickness, mesenteric lymph nodes, mesenteric fat hypertrophy and FC were all associated with endoscopic recurrence. On multivariate analysis, bowel wall thickness, lymph nodes and FC all were associated with endoscopic recurrence. A combined endpoint of FC ≥50, or increased bowel wall thickness or presence of lymph nodes had high sensitivity at predicting recurrence with a sensitivity of 95% and negative predictive value of 87% for identifying recurrence. Furthermore, combining abnormal FC and ultrasound bowel wall thickness gave a specificity and positive predictive value of 100% for identifying recurrence, but had a low sensitivity of 58%. Overall, these findings demonstrate that combining calprotectin and ultrasound results in a very accurate screening tool to identify endoscopic recurrence and can be used as an alternative for post-op monitoring. Personally, I use intestinal ultrasound and FC to monitor post-op patients every 3-6 months. I also do an ileocolonoscopy within or at 12 months and if findings match the ultrasound and FC I then rely on these for ongoing follow-up and monitoring.

Reference: J Crohns Colitis 2021;15(Suppl 1):S074-S075
Abstract

DOP75 Loss-of-response and immunogenicity following immunomodulator withdrawal from anti-tumour necrosis factor alpha combination therapy: Results from a large retrospective cohort study

Authors: Mahmoud R et al.

Summary: This multicentre, retrospective cohort study examined real-world outcomes after immunomodulator discontinuation during maintenance in 543 IBD patients (615 episodes) receiving combination therapy with anti-TNF compounds (infliximab or adalimumab) and immunomodulators (thiopurine or methotrexate). Over a median of 0.9 years, immunomodulators were discontinued in 296 (48%) episodes, while 85% of patients were in clinical remission, as part of a de-escalation strategy (53%), for intolerance (29%) or for other reasons (18%). During a median follow-up of 1.7 years after withdrawal, 46 (16%) patients experienced a loss-of-response; 79 (32%) required dose-escalation and 31 (10.3%) had anti-drug antibodies. Withdrawal did not increase loss-of-response risk (adjusted HR [aHR] 1.10; 95% CI 0.74-1.64), but more withdrawal patients required dose escalations (aHR 1.42; 95% CI 1.02-1.97) or developed anti-drug antibodies (aHR 2.22; 95% CI 1.21-4.08). Among withdrawal patients, clinical remission at withdrawal was the only predictor of loss of response (aHR 0.48; 95% CI 0.23-0.99). Risk of immunogenicity was increased by higher BMI (aHR 1.09; 95% CI 1.01-1.17) and shorter duration of combination therapy (aHR 0.57/year; 95% CI 0.33-0.96). Trough levels of infliximab, but not adalimumab, decreased after immunomodulator withdrawal.

Comment: Combining anti-TNF therapy with immunomodulators is more effective at achieving clinical and endoscopic remission than either agent alone. However, the combination is associated with increased side effects including increased risk of infection and increased risk of lymphoma when compared to anti-TNF monotherapy. Therefore, it is often advised to induce remission with combination therapy and then de-escalate by withdrawing the immunomodulator once remission is achieved. Small studies have looked at this, with most demonstrating no difference in clinical relapse or anti-TNF discontinuation; however, these studies have been underpowered and there have been some studies that have demonstrated worse pharmacokinetics following immunomodulator withdrawal. This study was a large retrospective study on patients on infliximab or adalimumab for at least 4 months with azathioprine or methotrexate. 615 episodes of combination therapy followed for a median 2.1 years were included. 296 had monomodal withdrawal and were followed for a median 1.7 years. Those that stopped immunomodulators were more likely to have been on their first anti-TNF therapy and had been on therapy longer. 85% were in remission at time of withdrawal. At withdrawal, loss of response occurred at a rate of 6.6% per patient year and anti-drug antibodies developed at a rate of 4.5% per patient year. After immunomodulator withdrawal there was no increased risk of loss of response, but there were significantly higher rates of antibody formation and dose escalation and lower infliximab trough levels. On multivariate analysis, longer duration of combination therapy was protective against anti-drug antibody development and higher BMI predicted development. In those that used combination therapy for at least 2 years before withdrawal there was significantly less likelihood of developing anti-drug antibodies. These findings need to be confirmed ideally in a prospective randomised study but suggest that currently we should wait for 2 years of combination therapy before attempting immunomodulator withdrawal.

Reference: J Crohns Colitis 2021;15(Suppl 1):S109
Abstract

