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- IBD genetic risk variants influence gut microbiome
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Abbreviations used in this review:

- 6MP = 6-mercaptopurine; AZA = azathymidine; ADA = azathioprine;
- CD = Crohn’s disease; CDAI = Crohn’s disease activity index;
- eASC = expanded allogeneic adipose-derived mesenchymal stem cells;
- GI = gastrointestinal; HR = hazard ratio; IBD = inflammatory bowel disease;
- IFX = infliximab; IL = interleukin; IV = intravenous; OR = odds ratio;
- PSC = primary sclerosing cholangitis; SNP = single nucleotide polymorphism;
- TNFI = tumour necrosis factor inhibitor; UC = ulcerative colitis.

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Welcome to this review of the 11th Congress of the European Crohn’s and Colitis Organisation (ECCO), which took place in Amsterdam, The Netherlands.

The meeting aims to advance the understanding of the causes of Crohn’s disease and Ulcerative Colitis, to share and discuss top-line results of therapeutic agents and algorithms, to stimulate and promote the implementation of guidelines, to ultimately further improve patient care. For 2016, the theme of the congress was “IBD innovations driving clinical practice”.

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

Kind Regards,
Professor Ian Lawrance
ian.lawrance@researchreview.com.au

Gene-microbiome interactions underlying the onset and the clinical phenotypes of inflammatory bowel disease

Presenter: Floris Imhann, University of Groningen and University Medical Centre Groningen, Groningen, The Netherlands

Summary: This analysis of the luminal gut microbiome, host genome and clinical phenotypes of IBD involved 313 patients with IBD comprising Crohn’s disease (CD) and ulcerative colitis (UC), as well as 582 healthy controls. All participants were genotyped. IBD was associated with significant dysbiosis: 28% of the bacterial taxa, including 16 families, were significantly altered in the CD cohort, as compared with healthy controls, whereas 12% of the analysed taxa, including 9 families, were significantly altered in patients with UC (FDR <0.05). CD disease activity was associated with an increase in the Enterobacteriaceae family (FDR=0.036). The gut microbiome differed markedly between patients with colonic and those with ileal CD, with significantly decreased alpha diversity in ileal CD (p=3.28×10^{-13}). Significant alterations of the gut microbiome were observed among healthy individuals with a large genetic risk for IBD; the abundance of the Roseburia genus decreased as the IBD genetic risk score increased (FDR=0.03).

Comment: This study proposed that interactions between the host genome and the gut microbiome could impact on IBD disease location, activity and behaviour. They analysed stool samples, serum and the phenotypes of 313 IBD (188 CD, 107 UC, 18 IBDU) patients and 582 healthy controls (taking no systemic medication with no known disease and not having IBS using the ROME III criteria). Stool examination identified a large dysbiosis between the IBD and control samples, with the gut flora related to disease location (PCoA1 rho=0.63, 7.39×10^{-13}, Spearman correlation) and reduced bifidobacteria and faecalibacterium and increased gammaproteobacteria and bacteroides species identified in CD. Microbial diversity was also related to disease location (p=3.28×10^{-13}). Examining the presence of the NOD2, CARD9, FUT2, ATG16L1 and IRGM gene variants associated with IBD, the greater number of these variants that an IBD patient had, the fewer Roseburia species they had. As Roseburia species are acetate-to-butyrate converters, functionally, this can lead to a reduction in short-chain fatty acid production and levels of propionate and butyrate. This study highlights the importance of ongoing studies into the interaction between the genomes of a patient, their microbiota and the clinical presentation of their disease. Only by understanding this further will we more likely have the potential to impact the disease process at its source.


Abstract

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Genotype-phenotype analysis across 130 422 genetic variants identifies RSPO3 as the first genome-wide significant modifier gene in primary sclerosing cholangitis

Presenter: Rudi Alberts, University of Groningen and University Medical Centre Groningen, Groningen, The Netherlands

Summary: This review of clinical data from 3402 patients in the International PSC Study Group sought to identify genetic variants that play a role in PSC subphenotypes. A genetic variant next to RSPO3 was found to be associated with liver transplant-free survival (SNP rs853974, p=2.87 × 10^-10). The association remained significant when cholangiocarcinoma was used as an endpoint (p=2.04 × 10^-7). RNA sequencing revealed significantly elevated expression of RSPO3 in cholangiocytes from control and DDC–treated mice, as well as multiple murine tissues. RSPO3 was also highly expressed in cholangiocyte-like cells as compared with human induced pluripotent stem cells. The study researchers confirmed previously published associations of classical HLA alleles for autoimmune hepatitis (AIH) in patients with PSC-AIH overlap syndrome. The authors proposed that the use of low-dose thiopurine can maintain the IFX trough levels and favourable IFX pharmacogenetics, which should translate into better patient outcomes with lower potential complications.


Abstract

Azathioprine dose reduction in patients with inflammatory bowel disease on combination therapy: a prospective study

Presenter: Emilie Del Tedesco, University Hospital, Saint-Etienne, France

Summary/Comment: Combination therapy with a thiopurine and infliximab (IFX) is the best strategy in IBD but has safety concerns that include opportunistic infections, lymphomas and skin cancers. This study aimed to determine if azathioprine (AZA) can be reduced without loss of disease control. It was a prospective study with all patients receiving IFX (5 mg/kg 8-weekly)/AZA (2–2.5 mg/kg/d) for ≥1 year and if they were in complete remission (clinical and endoscopic and/or biomarkers remission) for ≥6 months and had an IFX ≥2 μg/mL they either continued therapy unchanged, had the AZA halved or ceased. Of the 81 patients (45 CD, 36 UC) there was no difference in disease relapse between the groups. The IFX trough in the AZA continuation group remained stable from week 0 to 52 as it did in patients on half-dose AZA, despite a 6-TGN drop (310 to 128 pmoles p=0.03). The IFX trough, however, dropped significantly in the no-AZA group (4.2 to 2.1 μg/mL; p=0.02). The development of an unfavourable change in IFX pharmacogenetics at week 52 occurred significantly more often in the no-AZA patients than in the other groups (p=0.01) with a 6-TGN threshold of <105 pmoles identified as predictive (Sensitivity 67%, Specificity 92%). These findings suggest that the use of low-dose thiopurine can maintain the IFX trough levels and favourable IFX pharmacogenetics, which should translate into better patient outcomes with lower potential complications.


Abstract

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Comparison of adalimumab monotherapy and a combination with azathioprine for patients with Crohn’s disease: a prospective, multicentre, open-labelled clinical trial (DIAMOND study)

Presenter: Takayuki Matsumoto, Iwate Medical University, Morioka, Japan

Summary: In this study, 176 biologic- and thiopurine-naïve Japanese patients with moderate-to-severe Crohn’s disease (a Crohn’s disease activity index [CDAI] of 220–450) were randomised to subcutaneous adalimumab (160 mg at week 0, 80 mg at week 2, and subsequently 40 mg every other week; monotherapy group; n=85) or to the same schedule of adalimumab with azathioprine (25–100 mg/day; combination group; n=91) for 52 weeks. The primary endpoint was clinical remission at 26 weeks (CDAI <150). Endoscopic improvement was determined as simple endoscopic severity (SES)-capsule endoscopy (CE) ≤4 points or a decrease in SES-CD ≥8 points. Thirty-three patients in the monotherapy group (74.1%) and sixty-two patients in the combination group (68.1%) completed the study. Combination therapy was associated with more withdrawals due to active disease (21.2% vs 7.7% on monotherapy). At 26 weeks, remission rates did not differ significantly between the groups (68.1% combination, 71.8% monotherapy; OR 0.84, p=0.63), although the rate of endoscopic improvement was significantly higher with combination therapy (84.2% vs 62.8%; p=0.019). Pharmacokinetic analyses at 26 weeks showed trends towards higher trough levels of adalimumab (7.56 µg/mL vs 6.50 µg/mL; p=0.084) and a lower prevalence of adalimumab antibodies (4.0% vs 13.2%; p=0.078) with combination therapy versus monotherapy.

Comment: The combination of AZA and IFX is more effective than monotherapy. It is unclear if the same is true for AZA combined with adalimumab (ADA). This prospective, open-labelled Japanese study examined the efficacy of monotherapy with ADA and in combination with AZA in CD. The primary endpoint was clinical remission at 26 weeks and this was achieved in 71.8% of patients on monotherapy compared with 68.1% on combination therapy (p=0.63). Medication side effects resulted in patient withdrawal in 15 combination therapy patients (16.5%) and 2 monotherapy patients (2.4%). Endoscopic improvement at week 26, however, was greater in the combination group (84.2%) compared to the monotherapy group (63.8%) (p=0.019). ADA trough levels, however, were not significantly higher. This study was small and may have been underpowered to identify a beneficial effect of combination therapy. Adverse effects were certainly higher but as endoscopic improvement was greater with combination therapy it would appear that the evidence is still unclear as to if combination therapy could be of benefit, particularly in CD patients with worse disease.

The TOPPIC Trial: a randomised, double-blind parallel-group trial of mercaptopurine versus placebo to prevent recurrence of Crohn’s disease following surgical resection in 240 patients

Presenter: Ian Arnott, NHS Lothian, Edinburgh, UK

Summary: This study enrolled 240 patients with a confirmed diagnosis of CD undergoing intestinal resection and randomly assigned them to receive a daily oral dose of 6-mercaptopurine (6MP; n=128) or placebo (n=112), for a maximum of 36 months. The primary endpoint was defined by clinical recurrence of CD (CDAI >150 plus 100 point rise) and the need for anti-inflammatory rescue therapy or primary surgical intervention.

Comment: CD is not cured by surgical resection and many patients require subsequent surgeries. This randomised, placebo-controlled, double-blind, parallel-group trial aimed to determine if 6MP can prevent, or delay, postoperative recurrence in CD. 240 patients were randomised to receive 6MP (1 mg/kg) or placebo 4–6 weeks after surgical discharge for a maximum of 36 months. Colonoscopies were undertaken at weeks 49 and 156. Primary outcome was clinical CD recurrence and reached by 26 placebo (23%) compared to 16 6MP (12.5%) patients (HR 0.535; 95% CI, 0.27 to 1.06; adjusted p=0.073). Smokers were more likely to reach the primary endpoint than non-smokers (p=0.018), the NNT to prevent recurrence was 3. A higher proportion of 6MP patients had to on endoscopy at weeks 49 (29.7 vs 14.4%; p=0.006) and 157 (22.5% vs 12.5%; p=0.041) and it was noted that faecal calprotectin <100 µg/g had a predictive value of 75.5% for endoscopic i2 disease (Sensitivity 72.2%, Specificity 62.1%). Unfortunately, 61 of 102 6MP-treated patients were subtherapeutic (6TGN <235 mmol/L) at week 49. Thus, it would appear that 6MP is beneficial in the postoperative management of CD, but monitoring and maintaining patients in the therapeutic range could potentially improve this efficacy.


Abstract

Anti-tumour necrosis factor therapy is associated with increased risk of postoperative morbidity after surgery for ileocolonic Crohn’s disease: outcome analysis in a prospective nationwide cohort of 592 patients

Presenter: Antoine Brouquet, Bicètre Hospital - Université Paris Sud, France

Summary: This group of researchers analysed data from 592 patients who underwent surgery for ileocolonic CD at 19 French academic centres between September 2013 and September 2015. Data were obtained from the RICCO registry held by the GETAID chirurgie group. Univariate and multivariate logistic regression analyses were used to examine the possible associations between tumour necrosis factor (TNF) inhibitor therapy and postoperative overall morbidity. A propensity score was calculated and used to estimate the effects of treatment on outcomes based on the inverse probability of treatment weighting ( IPTW).

Comment: Surgical and postoperative complications in CD are not uncommon and there is debate as to if anti-TNF therapy at the time of surgery increases this risk. This study prospectively included 592 consecutive patients undergoing ileocolonic CD surgery and assessed the postoperative morbidity at 30 days. There were no deaths. Anti-TNF therapy was received by 137 (23%) patients <6 months before surgery. Overall emergency surgery was 10% of all cases; 73% were laproscopic surgery and perforating disease was found intra-operatively in 43%. A primary anastomosis was undertaken in 79% of surgeries. Intra-abdominal sepsis morbidity rates in patients with or without preoperative anti-TNF were 13% versus 7% (p=0.03). Overall morbidity was also higher with anti-TNF use (41% vs 26%; p=0.001). On multivariate analysis, anti-TNF therapy before surgery was an independent risk factor of overall morbidity (OR 1.99; p=0.01), as was preoperative Hb <10 g/dL (OR 4.77; p=0.017), operative time >180 mins (OR 2.71; p=0.0006), and recurrent CD (OR 1.95; p=0.017). Having one of these risk factors increased the risk of morbidity from 19% to 32% (p=0.02) and in patients with 2 or more of these risk factors the risk increased further to 52% (p=0.0001). The increased morbidity risk of anti-TNF, however, may not be a function of the medication but a marker of disease severity as is a low Hb, longer operating time and disease recurrence. Despite this, the use of anti-TNF medication is associated with an increased morbidity risk and its use should be taken into account when deciding surgical treatment strategies, including the need for a temporary stoma.


Abstract
Risk factors for colorectal neoplasia in ulcerative colitis: results from the largest and longest-running colonoscopic surveillance programme

Presenter: Chang-Ho Ryan Choi, St Mark’s Hospital, London, UK

Summary/Comment: It is well documented that UC patients have an increased risk of colorectal cancer (CRC). The overall risk, however, is low and while surveillance does not prevent dysplasia, it can be detected earlier and a patient’s risk for dysplasia can be stratified. This study examined risk factors of colorectal neoplasia (CRN) development in UC from a single-centre surveillance programme from 2003–2012. 987 UC patients with extensive colitis underwent 6985 colonoscopies (minimum 2, median 6) over 12,305 patient-years. Severity of inflammation, endoscopic and histological, were determined from the worst bowel segment (0, normal/quiescent; 1, mild; 2, moderate; 3, severe active). The mean histological inflammation severity was the average inflammation score across all endoscopies. The average score was the strongest predictive factor (HR 3.1 for every increase of 1 unit; p<0.001), although the level of inflammation on the most recent colonoscopy showed similar predictive effect (mild HR 2.4, moderate HR 3.2 and severe HR 4.5). Both the severity and chronicity of microscopic inflammation impacted on the CRN risk. Macroscopic features of chronicity (tubular/featureless/shortened colon HR 1.8, or stricture HR 3.2) and PSC (HR 2.3) also helped to identify high-risk patients. This study highlights the need to stratify patients according to risk and also the importance of reducing the inflammatory burden on the colon by controlling inflammation, not just endoscopically but also microscopically.


Abstract

A phase III randomised controlled trial of Cx601, expanded allogeneic adipose-derived mesenchymal stem cells (eASC), for complex perianal fistulas in Crohn’s disease

Presenter: Julià Panés, Hospital Clinic Barcelona, Barcelona, Spain

Summary: Patients recruited to this study had non- or mildly active luminal CD (CDAI ≤220) and complex active perianal fistulas (high tract, active drainage during the prior 6 weeks, with ≤2 internal and ≤3 external openings assessed clinically and with pelvic MRI). They were refractory to antibiotics, immunosuppressants, and/or TNF inhibitor therapy. Current medical treatment was permitted to continue without modification throughout the study treatment period.

Comment: Up to 25% of CD patients have perianal disease and the current management of complex perianal fistulas often does not result in fistulae healing but more the control of ongoing sepsis. Mesenchymal stem cells have immunomodulating effects and can promote T Reg cells and promote tissue repair. This paper presented a phase III investigation of the injection of 120 million expanded allogeneic adipose-derived mesenchymal stem cells (eASC to all tracts) or placebo in a 1:1 randomisation to actively draining complex perianal CD fistulae patients who had failed at least one medical therapy. About 80% of patients had failed anti-TNF therapy. All patients underwent fistula curettage and seton placement (if indicated) ≥2 weeks before study treatment. The primary endpoint was remission at 24 weeks with closure of all external openings without MRI-identifiable collections. Of 212 patients randomised, 103 were actively treated and 102 received placebo. Active treatment induced the primary endpoint in 51.5% versus 35.6% receiving placebo (p=0.02), with a clinical remission achieved by 55.3% versus 42.6%, respectively (p=0.057). There were no differences in any adverse events or serious adverse events. Overall, the therapy appeared to have some efficacy but patient response to surgical management alone was very high, considering that patients had failed medical therapies. This suggests that the surgical management for these patients may not have been optimal prior to their recruitment into this study and highlights the importance of colorectal surgical involvement in these patients.


Abstract

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A multicentre, double-blind, placebo-controlled phase 3 study of ustekinumab, a human interleukins-12/23p40 mab, in moderate-severe Crohn’s disease refractory to anti-tumour necrosis factor α: UNITI-1

Presenter: Paul Rutgeerts, University Hospital Gasthuisberg, Leuven, The Netherlands

Summary: The main inclusion criteria for this study stipulated the presence (and duration of ≥3 months) of moderate-to-severely active CD as measured by a CDAI score of 220–450, and prior failure or intolerance to ≥1 TNF inhibitor. 741 patients were randomised to ustekinumab 130 mg, weight-based tiered ustekinumab at approximately 6 mg/kg or placebo. For the weight-based tiered group, ustekinumab 260 mg was administered to patients weighing ≤55 kg, 390 mg if weight was >55 kg to ≤85 kg, and 520 mg for those weighing >85 kg. Administration for all 3 treatment groups was one single intravenous dose. Participants had a history of anti-TNF failure, with a baseline median CDAI of 317, C-reactive protein (CRP) of 9.9 mg/L, and prior disease duration of 10.1 years. A total of 51% of enrolled patients had previously failed ≥2 TNF inhibitors.

Comment: Interleukin (IL)-12 and IL-23 are involved in the inflammatory cascade in CD. Ustekinumab (UST) is a fully humanised IgG1 monoclonal antibody that binds the p40 subunit of IL-12 and IL-23 and is already in clinical use for psoriasis. This phase III study examined the efficacy and safety of IV UST induction of 130 mg (n=245) or weight-based tiered UST dosing (6 mg/kg for placebo [n=249]) to placebo (n=247) in CD refractory to anti-TNF therapy. The primary endpoint was clinical response at week 6 (CDAI reduction ≥100 points). 975 patients were randomised to ustekinumab. The primary endpoint was achieved in 33.7% (6 mg/kg) and 34.3% (120 mg) versus 21.5% on placebo (p<0.003 and 0.002, respectively). Clinical remission (CDAI <150) at 8 weeks was also better in both UST groups (20.9% for 6 mg/kg, p<0.001; 15.9% for 120 mg, p=0.003 vs placebo 7.3%). Patient response to UST was also significantly better than placebo at 8 weeks and 6. CRP was suppressed in all active treatment groups. There was 1 death from postoperative respiratory failure (50 mg), 2 GI perforations (50 mg and 200 mg) and 4 serious GI abscesses (2 with the 10-mg dose, 2 with the 50-mg dose). Although there may be some efficacy of this medication in refractory CD, the number of serious complications would appear to be high and further consideration as to the risk:benefit ratio needs to be undertaken before any further studies are conducted.

Results of ANDANTE, a randomised clinical study with an anti–IL6 antibody (PF-04236921) in subjects with Crohn’s disease who are anti-tumour necrosis factor inadequate responders

Presenter: Silvio Danese, Humanitas University Clinical and Research Hospital, Rozzano, Milan, Italy

Summary: Study eligibility required patients to be aged 18–75 years with active moderate-severe CD (CDAI 220–450), a history of failure or intolerance to TNF inhibitor therapy, a CRP ≥5.0 mg/L and ulcers on colonoscopy. They were randomised to placebo or PF-04236921 at a dose of 10, 50, or 200 mg, administered on days 1 and 28.

Comment: Interleukin (IL)-6 is a proinflammatory cytokine that is increased in CD and induces the liver production of CRP. This is a phase ll study investigating the effect of subcutaneous administration of a fully human IgG2 monoclonal antibody that binds to human IL-6 in CD. There were 4 groups: 10 mg (n=67); 50 mg (n=71); 200 mg (n=40); and placebo (n=69), but dosing in the 200-mg arm was terminated because of safety concerns. The primary endpoint was a CDAI reduction of ≥70 points at week 6 or 12. Placebo and 10 mg efficacy were not different at any time point. For 50 mg, the response was 49.3% versus 30.6% for placebo (p=0.04) at week 6 and 47.4% vs 28.6% (p<0.04) at week 12. CRP levels were suppressed in all active treatment groups. There was 1 death from postoperative respiratory failure (50 mg), 2 GI perforations (50 mg and 200 mg) and 4 serious GI abscesses (2 with the 10-mg dose, 2 with the 50-mg dose). Although there may be some efficacy of this medication in refractory CD, the number of serious complications would appear to be high and further consideration as to the risk:benefit ratio needs to be undertaken before any further studies are conducted.