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SPEAKER SERIES

Collaborative care in IMIDs – part 2

Making Education Easy

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About the Speaker

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After obtaining his BSc, Dr. Jakob Begun completed his MPhil in Biochemistry at Cambridge University, and his MD and PhD in genetics at Harvard Medical School. He completed his clinical training at Harvard University and his advanced training in IBD (inflammatory bowel disease) at Massachusetts General Hospital (MGH). He returned to Australia in 2014 to pursue his interest in clinical and translational IBD research. He is the IBD clinical lead at the Mater Hospital and Queen Elizabeth II Hospital in Brisbane. He is the IBD Group leader and a Senior Research Fellow at the Mater Research Institute – University of Queensland and is a Senior Lecturer at the UQ School of Medicine. He runs a basic and translational laboratory at the Translational Research Institute investigating the interaction between the innate immune functions of the gut and the microbial community with a focus on therapeutic interventions. He also performs clinical research examining the natural history of IBD, endoscopic assessment and interventions in the setting of IBD, and investigating barriers of care for adolescents and young adults with IBD at the Mater Young Adult Health Centre.

Abbreviations used in this review:
CD = Crohn's disease
FMT = faecal microbiota transplantation
GWAS = genome-wide association study
IBD = inflammatory bowel disease
IL = interleukin
IMID = immune-mediated inflammatory disease
SNP = single-nucleotide polymorphism
TNF = tumour necrosis factor

About this review

This publication summarises the presentation 'Collaborative care – don't forget the gut' by Dr. Jakob Begun on the multidisciplinary approach to IMIDs (immune-mediated inflammatory diseases), which was part of the IMID meeting held in Auckland on Sept 29–30. IMID, which was sponsored by AbbVie NZ, was an educational meeting developed by a steering committee for enhancing medical knowledge and scientific exchange. We hope you find the information in the publication helpful. Please also keep an eye on your inbox for publications summarising other presentations from this meeting.

IMID was an educational meeting developed by a steering committee for enhancing medical knowledge and scientific exchange. The IMID meeting was sponsored by AbbVie NZ, and this meeting write up has been commissioned and sponsored by AbbVie Ltd, Wellington. The content of the presentations is entirely independent and based on published studies, unpublished research and the speakers' opinions, and the views expressed are not necessarily those of AbbVie Ltd. Please consult the full datasheet for any of the medications mentioned in this article at www.medsafe.govt.nz before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician. NZ-GAST-0006. December 2017.

COLLABORATIVE CARE – DON'T FORGET THE GUT

Dr. Jakob Begun

Dr. Begun started his talk by expressing the importance of thinking about IMIDs as systemic diseases that require a multidisciplinary approach. This is because the underlying aetiology of IMIDs is an inappropriate immune response to normal tissue components, resulting in the potential for multiple organ involvement.[1] The tissue/organ where an IMID's symptoms are most significant usually determines its nomenclature (e.g. if the gastrointestinal tract is affected, CD [Crohn's disease] could be the cause); however, it is important to remember that other organs can be involved. For example, while 5–10% of patients with spondyloarthropathies have known IBD, 25–49% and 50–60% have macroscopic and microscopic gut inflammation, respectively, thus it is important to assess patients with spondyloarthropathies for the presence of gut inflammation.[2]

Dr. Begun commented that the goals of treatment tend to be similar across specialities and organ systems, specifically the avoidance of disabling disease due to long-standing inflammation that irreversibly damages tissues. The consequences of damage include severe disability, need for more intensive interventions (e.g. surgery) and, in the case of psoriasis, increased risk of suicidality.[3]

Dr. Begun highlighted that because IMIDs are multifactorial diseases affecting multiple health domains, it is important that patients are managed in a collaborative-care setting across disciplines and with allied health professionals, including dieticians, specialist nurses, physiotherapists, occupational therapists and mental health and social workers.

The following case presentation demonstrates the meandering course a patient with an IMID can take, where the prominent symptom(s) at any one time often determines who they will be treated by and how they will be treated, so it is important to keep an open mind when seeing patients to consider other organ involvement.

CASE PRESENTATION

Dr. Begun reported on a 40-year-old woman who was a Russian immigrant to Australia who he saw at his institution in Brisbane. She was initially seen in the ophthalmology clinic for eye pain, for which she twice received a topical steroid for anterior uveitis. Inflammatory back pain was also noted, and she was referred to rheumatology where she revealed a history of intermittent lumbar and thoracic back pain (thought to be reactive arthropathy) before leaving Russia that had worsened since arriving in Australia. Initial conservative treatment with nonsteroidal anti-inflammatory drugs was started by her general practitioner, but was limited by abdominal pain. Her examination was notable for reduced lumbar flexion, chest wall tenderness and sacroiliac discomfort. Magnetic resonance imaging findings and laboratory results were consistent with ankylosing spondylitis.

CASE PRESENTATION (CONTINUED)

The woman was treated with sulfasalazine, a COX-2 inhibitor and a proton-pump inhibitor, and was referred to gastroenterology due to ongoing abdominal pain. Gastroscopy and colonoscopy revealed diverticular disease and mild colonic inflammation with histology consistent with IBD (inflammatory bowel disease; chronic inflammation). Uptitration of sulfasalazine initially resulted in her symptoms settling, an improved C-reactive protein level and normalisation of her faecal calprotectin level.

However, 6 months later, the woman's joint and bowel symptoms flared. Her faecal calprotectin level increased to >1000 µg/g of faeces and flexible sigmoidoscopy revealed moderately severe colitis. She was treated with corticosteroids and ultimately an anti-TNF agent.

IBD around the world

IBD is prevalent in developed countries with incidences among first-generation immigrants mirroring host populations.[4] NZ and Australia have among the highest incidences in the world. While incidence data showed that IBD increased worldwide in developing countries until the 21st century, recent data suggest a plateau in IBD incidence in European countries.[4]

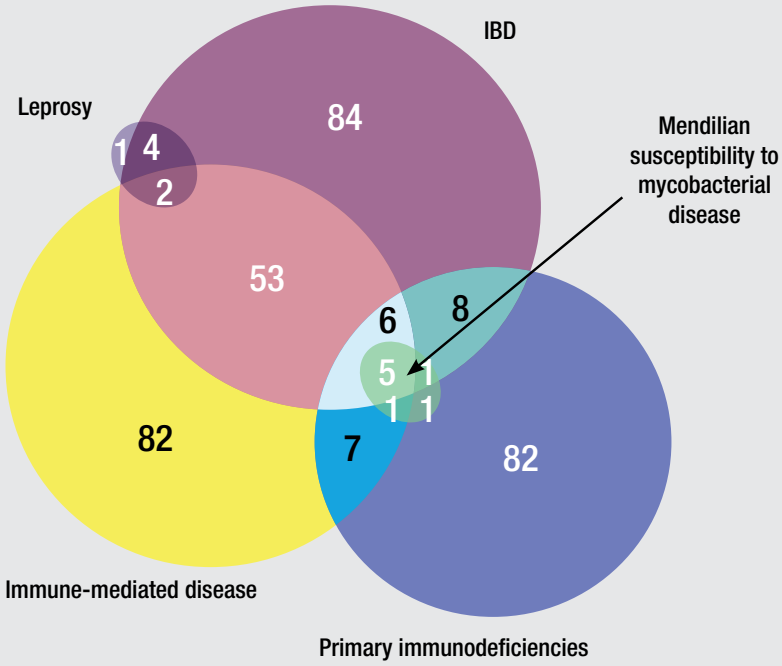
Genetics in IBD

Familial clustering suggests the importance of genetics to IBD pathogenesis, particularly CD.[5] Studies in monozygotic twins have shown that concordance rates for CD range from 20% to 50%, and concordance rates for UC range from 14% to 19%. First-degree relatives of patients with IBD also have an increased risk, further supporting the role of genetics.[5] The first CD-associated gene identified by positional cloning was *NOD2*, but since then the advent of next-generation sequencing has allowed GWASs (genome-wide association studies) to be undertaken. These allow the identification of SNPs (single nucleotide polymorphisms) that occur more frequently in patients with an IMID compared with control patients, and SNPs with probabilities that reach a significance threshold are deemed to be associated with the IMIDs.

Targeting IL pathways

GWASs performed on 10,000s of patients and 100,000s of controls from around the world have yielded a multitude of SNPs associated with a disease. They have also shown that there are a number of SNPs with overlap between IBD and other immune-mediated diseases (Figure 1).[6] Of the 163 known loci associated with IBD, 113 (70%) are also associated with other complex diseases or traits, including 66 of 154 loci previously associated with other IMIDs, which is an 8.6-fold increase of that would be expected by chance. IL-23 is a heterodimer composed of p19 and p40 subunits; the p40 subunit is also found with p35 in IL-12. IL-23 and IL-12 signal through downstream JAK-STAT signalling.[7] The IL-23 pathway exemplifies the synergy that can be seen between genetics and drug development. GWAS studies have identified multiple genes in the IL-23 pathway implicated across a range of IMIDs.[8] This is corroborated by molecules that target this pathway showing activity in a number of IMIDs. In NZ, ustekinumab, which targets the p40 subunits on IL-12 and IL-23, is approved for the treatment of moderately to severely active CD, plaque psoriasis and psoriatic arthritis;[9] ustekinumab is not currently funded in NZ for any of these indications.

Figure 1. Overlap between IBD-associated SNPs and other immune-mediated diseases (adapted from Jostins L *et al.* Nature 2012;491:119–24)[6]

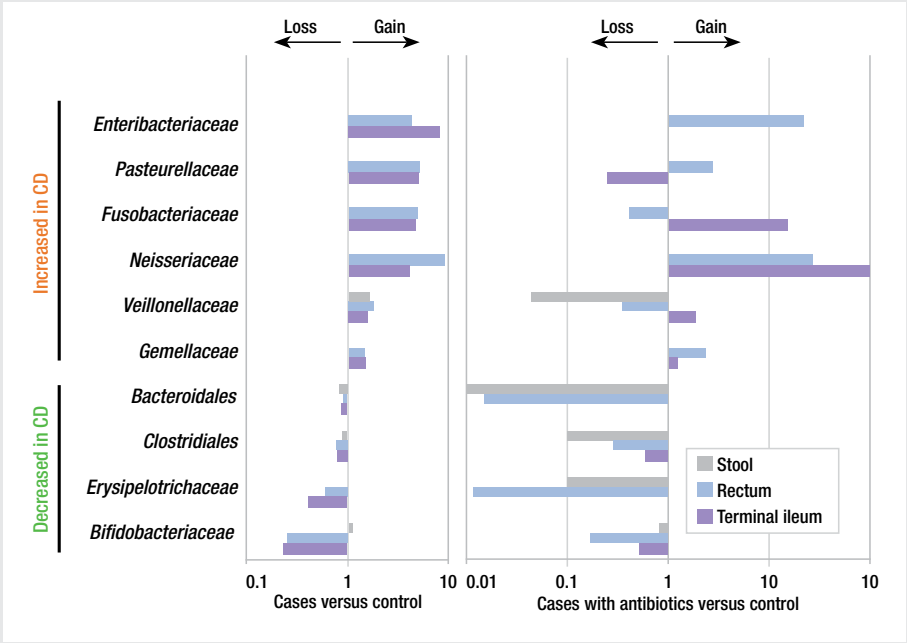


The IL-17 pathway, which is downstream from IL-23, is the focus of drug development for treating a variety of IMIDs, with many agents being actively investigated.[7] The TNF-α pathway has been successfully targeted for the treatment of IMIDs, although etanercept is not effective in IBD, and has lower efficacy for treatment in some forms of uveitis.[1,10–12] Dr. Begun also commented that studies so far have shown that while targeting IL-17 seems to work well for indications such as psoriasis, phase 2 trials in CD have been terminated due to worsening disease.[13] Data from murine research have shown that this difference may be explained by different IL-17 variants driving inflammation in the skin and gut.[13–15]

Association of gut microbiome with IMIDs

The human microbiome has complex interactions with the epithelium, metabolism and the immune system. The gut microbiome may be altered in a number of IMIDs.[16] In IBD, microbial diversity is generally decreased and there are shifts in the distribution of organisms; for example increases in *Firmicute* spp. and decreases in *Bacteriodites* spp. have been detected in paediatric patients with new-onset CD, along with data on antibiotic use driving the microbiome to a state of dysbiosis (Figure 2).[17] Links between rheumatoid arthritis and gut microbiota have been appreciated since 1965, when increased *Clostridium perfinges* was identified.[18] The largest cohort study to date investigating the microbiome in patients with rheumatoid arthritis found increases in *Lactobacillus* spp. and decreases in *Haemophilus* spp.[19] In psoriasis, links have been identified between tonsil infection with group A streptococci and skin superinfection with *Staphylococcus aureus* and *Candida albicans*.[20] Gut sequencing has also revealed decreased diversity and reduced *Akkermansia* spp. and *Faecalibacterium prusnitzii* in psoriasis.[21,22]

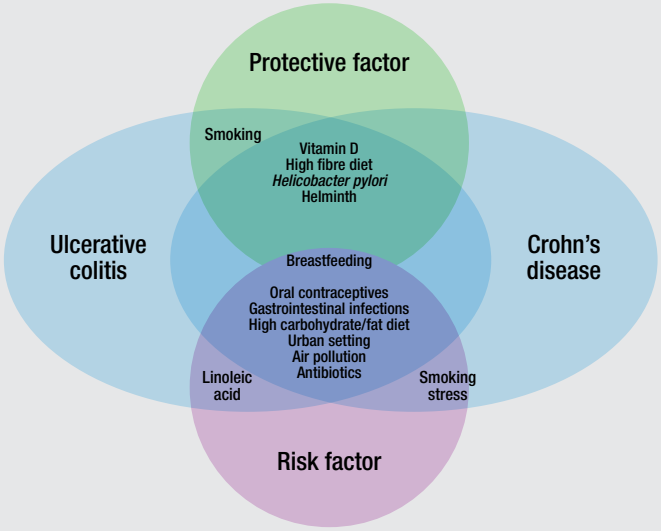
Figure 2. Differences between gut microbiomes of paediatric patients with new-onset CD versus controls (adapted from Gevers D *et al.* Cell Host Microbe 2014;15:382–92)[17]



Changes in the microbiome are intimately related to the metabolic milieu, and research focussing on interactions with the immune system is starting to elucidate the mechanisms of the effects on the immune system.[23] Research has shown that directly targeting the microbiome using FMT (faecal microbiota transplantation) is effective for treating IBD. In one of these studies, 81 patients with ulcerative colitis were randomised to receive FMT or placebo. Steroid-free clinical remission and endoscopic response rates were significantly higher in FMT-treated patients compared with controls, but endoscopic remission did not differ significantly between study groups in this trial.[24]

Diet has also received a great deal of attention, with 'western', high-animal fat and low-fibre diets and processed food linked to IBD, while diets high in fish oils and fibre may be protective.[25] Exclusive enteral nutrition is also effective for treating CD.[26] In an active area of research, a relatively low concentration of emulsifiers that are commonly present in foods (carboxymethylcellulose and polysorbate-80) added to the drinking water of experimental mice over 12 weeks resulted in changes in the microbiome, decreases in mucus layer thickness and increased inflammation.[27] Other environmental exposures appear to have integrating roles for driving inflammation in IBD (Fig 3).[28]

Figure 3. Roles of environmental exposures in driving inflammation in IBD (adapted from Ponder A & Long MD. Clin Epidemiol 2013;5:237–47)[28]



Links with inflammation

Evidence suggests that the mechanisms by which the microbiome and gut and joint inflammation are linked may begin with bacteria attaching to and penetrating the intestinal epithelium.[29] HLA-B27/CARD-15 polymorphisms in patients with spondyloarthropathies can alter the recognition and handling of bacterial antigens, leading to an overexuberant inflammatory response. Activated immune cells carrying bacterial components may migrate to joints or other tissues, including the skin or eye, leading to inflammation at these sites. The exact link between spondyloarthropathies and IBD is unknown, but is thought to involve both microbial and genetic factors.

TAKE-HOME MESSAGES

- IMIDs are multifactorial diseases that affect multiple health domains and require an integrated treatment strategy.
- IMIDs frequently affect multiple tissues and organs, therefore a thorough patient assessment is required.
- Similar pathogeneses, involving genetic predisposition, an altered microbiome and environmental triggers, are thought to underlie IMIDs.
- Not all drugs have efficacy across the various IMIDs.
- Effective management involves collaborative care across medical and allied health disciplines.

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