BEYOND THE GUT: THE IMPORTANCE OF CONTROLLING SYSTEMIC INFLAMMATION IN INFLAMMATORY BOWEL DISEASE

Summary of presentations from the AbbVie-Sponsored Symposium on Inflammatory Bowel Disease, held at the 11th Congress of the European Crohn's and Colitis Organisation (ECCO) in Amsterdam, Netherlands, on 17th March 2016

Chairperson

Geert D'Haens[1]

Speakers

Yehuda Chowers,[2] Remo Panaccione,[3] Geert D'Haens[1]

1. Academic Medical Centre-IBD Unit, University of Amsterdam, Amsterdam, Netherlands

2. Gastroenterology Institute, Rambam Health Care Campus, Haifa, Israel

3. Inflammatory Bowel Disease Group, University of Calgary, Calgary, Canada

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MEETING SUMMARY

Inflammatory bowel disease (IBD) management goals have recently focussed on gastrointestinal symptom resolution and mucosal healing. IBD causes systemic disorder, with inflammation occuring both within and outside the gut, with associated morbidity, disability, and quality of life (QoL) impairment. Thus, there is a need to reduce the overall burden of chronic inflammation in IBD.

Environmental factors, genetics, gut microbiota, and the immune system significantly impact IBD and its extraintestinal manifestations (EIMs). T cells play a crucial role in immunity, and certain subsets are associated with several chronic inflammatory disorders, including IBD. Targeting such cells and/or key inflammatory cytokines (e.g. interleukins [IL], and tumour necrosis factor [TNF]) provides a basis for several IBD therapies.

Systemic inflammation in IBD can involve the development of fistulae and/or EIMs. Common EIMs include musculoskeletal pain, dermatological and ocular lesions, and primary sclerosing cholangitis (PSC). Early diagnosis of fistulae and EIMs should help guide IBD therapy and reduce overall morbidity. Many EIM treatment options are currently available with varying degrees of efficacy e.g. sulfasalazine, COX-2 inhibitors, certain antibiotics, immunomodulators, anti-TNFs, corticosteroids, and ursodeoxycholic acid. However, fistulae and most EIMs respond well to anti-TNFs, such as adalimumab and infliximab.

Prognostic markers aid disease treatment. C-reactive protein (CRP) is a valuable marker of systemic inflammation in IBD (particularly Crohn's disease [CD]). Current anti-TNF agents (e.g. adalimumab) markedly reduce CRP levels in IBD and have a significant effect on IBD and various EIMs. Numerous novel agents for IBD are under development; examples include Janus kinase (JAK) inhibitors, IL inhibitors, SMAD-7 blockers, sphingosine 1-phosphate receptor 1 (S1P1) inhibitors, and anti-adhesion molecules.

Examining the Inflammatory Burden of Inflammatory Bowel Disease

Professor Yehuda Chowers

THE IMMUNE SYSTEM AND INFLAMMATORY BOWEL DISEASE

IBD is a complex, heterogeneous disease with a multifactorial pathogenesis.[1] Environmental factors, genetics, gut microbiota, and the immune system all impact this disease.[1] Several immune cell types secrete soluble cytokines and chemokines, which act on intestinal epithelial cells and can markedly affect the inflammatory process.[1] The immune system is complex and the maturation of T cells includes many positive and negative feedback loops involving numerous cytokines such as IL, interferon, and TNF.

T cells have a crucial role within the immune system. Typically, various $CD4^+$ T cells are induced under distinct conditions and undergo reinforcement of their role. However, there is plasticity within T cell subsets. Certain $CD4^+$ subsets can also be destabilised under certain conditions, for example, during a simple viral infection.[2] This process of reinforcement and destabilisation of T cell subsets leads to a mixed cell population. This T cell plasticity can impact IBD treatment. For example, a trial found that in moderate-to-severe CD, placebo resulted in a better response than the anti-IL-17A monoclonal antibody, secukinumab.[3] Compared with placebo, unfavourable responses to secukinumab occurred in patients with elevated inflammatory markers (CRP ≥10 mg/dL or faecal calprotectin [FCP] ≥200 ng/mL, p=0.054), whereas no differences between treatments were seen in patients with non-inflammatory disease (p=0.81).[3] This was a seemingly contradictory finding given that T helper (T_h)17 cells are associated with several chronic inflammatory disorders, including IBD. However, in intestinal mucosal samples from patients with inflamed CD, the proportion of IL-17-$Foxp3^+$ regulatory cells was significantly higher when compared with samples from patients with slightly or non-inflamed CD, and healthy controls.[4] Thus, although IL-17 is overexpressed in inflamed CD, poor outcomes resulted from the elimination of T_h17 regulatory cells.

Extraintestinal Manifestations

IBD is a heterogeneous disease and it's clinical manifestation can be characterised by numerous EIMs. Through protein-protein mapping, IBD and several EIMs have been linked, including colorectal carcinoma, ankylosing spondylitis, bone mineral density, PSC, gallstones, deep venous thrombosis, and kidney stones.[5]

Arthritis is a common EIM; it occurs in ~30% of IBD patients and includes peripheral and axial types.[6] Several studies have identified T cell markers in arthritic and intestinal tissues.[7-9] For example, in a patient with spondyloarthropathy (SpA), certain T cell clones were found to be similar in samples from inflamed intestinal mucosa and inflamed synovium.[7] Evidence of possible cross-talk between the synovium and the intestine is provided by a study in patients with SpA. Increased expression of leukocyte adhesion molecules (e.g. CD11a) were seen in gut samples from such patients versus controls.[8] In addition, TNF-alpha is also a common mediator in both IBD and joint inflammation.[9]

Psoriasis is another EIM associated with IBD. An analysis of several genome-wide association studies identified seven shared susceptibility loci between CD and psoriasis.[10] Environmental factors also

impact psoriasis, such as bacteria and smoking (which is also a risk factor for CD).

Perianal Disease

IBD can also result in perianal fistulising disease, a severe complication. A long-term evaluation of CD patients demonstrated that 50% had any fistula and 26% had perianal fistulae when assessed 20 years after diagnosis.[11] Recently, a study evaluated the mechanism of formation of CD-associated perianal fistulae;[12] expression of two genes, *ETS-1* and *β6-integrin*, was associated with fistula formation. TNF and muramyl dipeptide (a bacterial wall component) induced expression of these genes resulting in epithelial-to-mesenchymal transition of gut cells (Figure 1).[12] Another study showed accumulation of T_h1, T_h17, and T_h17/T_h1 cells in tissue samples from the perianal fistulae of CD patients.[13]

Overall, common genes, inflammatory pathways, and environmental factors may be involved in EIMs, related immune-mediated diseases, and perianal disease. However, tissue-specific factors may dominate the final pathophysiology and clinical manifestation.

Effective Management of Extraintestinal Manifestations and Fistulae

Professor Remo Panaccione

OVERVIEW OF EXTRAINTESTINAL MANIFESTATIONS

EIMs are systemic and occur in severe forms of IBD.[14] They significantly impact QoL, and can be more debilitating than the IBD itself. The latter is particularly relevant when EIMs evolve independently of IBD with resistance to IBD treatments. In IBD patients with EIMs, these EIMs can be present in 25% of patients before IBD diagnosis.[15] The development of various EIM types at different times of the IBD course will impact treatment decisions. Thus, early recognition of EIMs should help guide therapy decisions, thereby reducing overall morbidity in affected patients.

IBD-associated EIMs include many conditions occurring within the following areas: musculoskeletal, skin and mucous membranes, ocular, bronchopulmonary, cardiac, endocrine and metabolic, haematological, renal and genitourinary, hepato-pancreato-biliary, and neurological.[14,16] Thus, clinicians need to consider the whole spectrum of EIMs when considering IBD therapies. Several EIMs are common in IBD, i.e. musculoskeletal pain (9–53% of IBD patients), dermatological EIMs (2–34% of patients) and ocular lesions (0.3–5% of patients).[14] Ocular lesions need to be differentiated.[17] The most common ocular EIM is episcleritis; it has mild symptoms and a close association with IBD and disease flare-ups. Scleritis and uveitis are more serious conditions, however they are less common in IBD, and are therefore often overlooked in IBD. Importantly, uveitis requires emergency treatment, however as uveitis is not associated with IBD activity, its treatment is often delayed. It is important to involve an ophthalmologist in the management of ocular EIMs, as these could result in vision loss. One of the most serious EIMs in IBD is PSC, which is a chronic, progressive disorder. As the course of PSC has no relationship to active IBD, its management is particularly challenging.[14]

Treatment of Extraintestinal Manifestations

Several questions need to be considered when evaluating treatment options for EIMs in IBD. Firstly, is the EIM associated with active bowel disease? If so, treating the IBD may heal the EIM. However, if the EIM is not responding then adaptation of the gut therapy may help the EIM. Secondly, does the EIM need specific treatment, and if so, does this treatment actually alter the EIM course or just treat the symptoms?

Many treatment options are available for EIMs. For example, sulfasalazine and COX-2 inhibitors (for arthropathies); cyclosporine or an immunomodulator (for dermatological EIMs); topical and systemic corticosteroids (for ocular lesions); and endoscopic retrograde cholangiopancreatography or ursodeoxycholic acid (for PSC).[18] However, the majority of EIMs, regardless of their relationship with the underlying IBD, will also respond to anti-TNFs such as adalimumab and infliximab (Table 1).[19-27]

A pooled analysis of 10 open-label or double-blind adalimumab studies in patients with moderate-to-severe CD evaluated the impact of this anti-TNF on the resolution of EIMs.[28] For patients with any EIM at baseline, EIMs were resolved in 31% of placebo patients and 54% of patients receiving adalimumab at Weeks 20–26, and in 42% and 60% of placebo and adalimumab patients, respectively, at Weeks 52–54. Considering only musculoskeletal EIMs, resolution was also higher with adalimumab (53% at Weeks 20–26 and 60% at

Weeks 52–54) versus placebo patients (30% and 42%, respectively). For any EIM, the median time-to-resolution was 43 days with adalimumab (95% confidence interval [CI]: 45–57) versus 155 days with placebo (95% CI: 57–225) (p<0.001). For musculoskeletal EIMs, the median time-to-resolution was 43 days with adalimumab (95% CI: 32–57) versus 155 days with placebo (95% CI: 57–244) (p<0.001).[28]

Focus on Fistulae

Unfortunately, many CD patients will develop perianal disease:[29-31] 25–80%, dependent on the definition used. This is a complex disease, and as many as 9–17% of patients with perianal disease will undergo proctocolectomy. Patients with perianal fistulising disease have a poor prognosis, and many clinicians would see this as a need to use anti-TNF-α therapy.

Three factors are key to fistula(e) treatment: correct and proper diagnosis, management of the underlying disease, and specific management of the fistula(e). In a landmark study, a combination of techniques was identified as the best approach to characterising perianal fistulae. In patients with this condition, magnetic resonance imaging, ultrasound examination, and examination under anaesthesia were found to be 87%, 91%, and 91% accurate for diagnosis, respectively; combining any two of these techniques was 100% accurate.[32]

The goals of treatment for fistulising CD are drainage of sepsis, reducing frequency of abscess formation, sphincter preservation, reducing drainage symptoms, and improving QoL.[33] While it is possible to reduce or eliminate the symptoms of fistulising CD, imaging will usually reveal that the condition is still present. These treatment goals are best achieved using a multidisciplinary team approach. Such a team would consist of a radiologist (for diagnosis, surgical 'road map', and response monitoring), a gastroenterologist (to understand the disease course, know when to recommend surgery, or when to use a biological agent), and a surgeon (for draining and diversions, as appropriate). Treatment algorithms will vary between institutions. The algorithm used by the University of Calgary involves diagnosis of perianal fistula(e) and subsequent characterisation into simple or complex disease. Simple disease is treated with an antibiotic, and in the event of no response either a fistulotomy or a seton with antibiotics. If the latter fails, most patients receive anti-TNF agents. Complex disease is further characterised anatomically, which guides surgical or medical therapy, following which patients are treated with an anti-TNF agent (supplemented with other agents, if required) and an antibiotic.

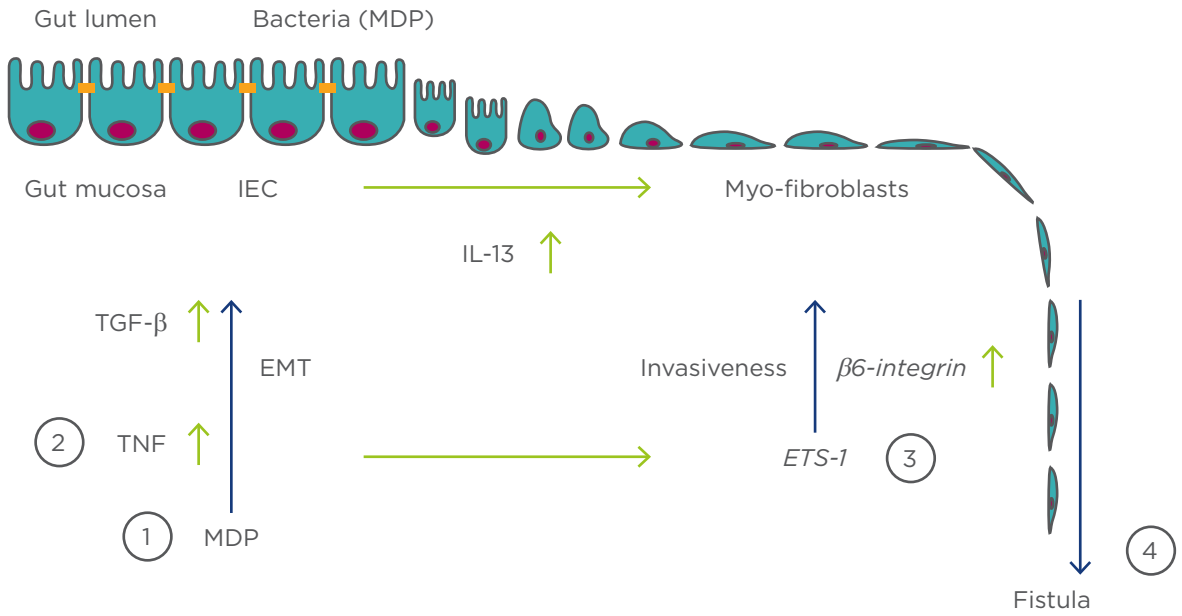

Figure 1: Key role of tumour necrosis factor in fistula formation.
MDP: muramyl dipeptide; TNF: tumour necrosis factor; TGF: transforming growth factor; EMT: epithelial–mesenchymal transition; IL: interleukin; IEC: intestinal epithelial cells.
Adapted from Frei et al.[12]

Table 1: Anti-tumour necrosis factor successfully treats many of the common extraintestinal manifestations of inflammatory bowel disease.

EIM	Prevalence in IBD patients	Parallel course of IBD	Anti-TNF treatment response	Anti-TNF agent
Musculoskeletal				
Ankylosing spondylitis	3–10%[19]	Not necessarily	Yes	Infliximab;[20] adalimumab[31]
Peripheral arthritis	10–20%[19]	Yes	Yes	Infliximab;[22,23] adalimumab[21]
Sacroiliitis	20–25%[19]	Not necessarily	Yes	Adalimumab[21]
Dermatological				
Erythema nodosum	3–20%	Yes	Yes	Adalimumab[21]
Pyoderma gangrenosum	0.5–20%	No	Yes	Infliximab[24]
Ocular				
Uveitis	6%	No	Yes	Adalimumab;[25] infliximab[26]
Episcleritis	2–6%	Yes	Yes	Infliximab[26]
Hepatobiliary disease				
Primary sclerosing cholangitis	7.5–18%	No	No, but no worsening of condition in IBD patients treated with adalimumab[27]	

EIM: extraintestinal manifestation; IBD: inflammatory bowel disease; TNF: tumour necrosis factor.

Agents available for the medical treatment of mucosal disease in CD perianal fistulae include:[33-35] 5-aminosalicylic acids and corticosteroids (poor activity); antibiotics, calcineurin inhibitors, thiopurines (short-term efficacy with little/no long-term feasibility), and anti-TNF agents (excellent short-term efficacy and long-term feasibility). In the ACCENT 2 study, patients who responded to infliximab by Week 14 were randomised to receive either placebo or infliximab.[36] At Week 54, a fistula response was seen in 23% and 46% (p=0.001) of patients, respectively, and a complete fistula response occurred in 19% and 36% (p=0.009) of patients, respectively.[36] In the CHARM study, a subset of CD patients with fistulae initially received adalimumab (one of two regimens) for 4 weeks.[37] These patients were then randomised to either placebo or adalimumab for a 56-week extension. From Week 16 onwards, significantly more patients (31–33%) on adalimumab had complete fistula healing over time versus those on placebo (13–15%) (p<0.05).[37] In CHARM, rates of fistula healing (>30% of patients) were maintained with adalimumab treatment for up to 4 years.[38] Most patients (54%) with fistula remission at 1 year maintained at this endpoint 4 years.[38]

Patients with IBD may also experience hidradenitis suppurativa, suggestive of a shared pathogenesis. Adalimumab has been evaluated in two Phase III studies (PIONEER I and PIONEER 2) in patients with hidradenitis suppurativa. Interestingly, integrated data from the first 12 weeks of these studies showed a significant increase in the proportion of patients achieving complete elimination of draining fistulae versus placebo (33% versus 19%, p<0.001).[39]

Targeting Inflammation: Benefits of Current and Emerging Inflammatory Bowel Disease Therapies

Professor Geert D'Haens

C-REACTIVE PROTEIN AND CURRENT BIOLOGICS IN INFLAMMATORY BOWEL DISEASE

CRP is produced in the liver as part of the acute phase systemic inflammatory response to various cytokines (e.g. IL-6, TNF-α, and IL-1-β).[40] Due to its short half-life, CRP is easy to measure. CRP is thus a valuable marker of disease activity in CD, although ulcerative colitis (UC) has a modest-to-absent CRP

response despite active inflammation.[40] Serum CRP levels correlate with CD activity, and with other inflammation markers (e.g. Crohn's Disease Activity Index score, serum amyloid, IL-6, and FCP).[40]

Importantly, CRP is also a prognostic factor in IBD, as high CRP levels (>45 mg/L) are predictive of the need for colectomy in patients with severe, uncontrolled gut inflammation,[40] including those with severe UC.[41] In asymptomatic CD patients, those with elevated CRP levels were significantly more likely to require hospitalisation versus those with normal CRP values ($p<0.01$).[42] However, CRP is not an absolute measure of active disease, as in CD patients examined by ileocolonoscopy, 54% had active disease with elevated CRP, whereas 25% had elevated CRP levels in the absence of active CD.[43] In CD patients, FCP significantly correlated with serum CRP, and endoscopic disease scores (all $p<0.001$).[44] However, this marker did not correlate with clinical symptoms (e.g. Crohn's Disease Activity Index).[44]

Anti-TNF agents used to treat systemic inflammation can markedly reduce CRP levels in IBD patients, as would be expected. For example, in UC patients with acute, severe disease, infliximab markedly and rapidly reduced CRP levels, whilst having no effect on calprotectin.[45] In the CLASSIC I and CHARM studies in CD patients, median CRP levels were significantly decreased in response to adalimumab.[46,47] Adalimumab treatment for 2 years in CD patients resulted in early clinical remission in the majority of patients, with CRP normalisation as a predictive marker.[48] However, CRP is not necessarily a marker of response for other categories of drugs in current use. For example, the anti-integrin, vedolizumab, did not normalise CRP levels at Week 6 in CD patients; although mean CRP concentrations were significantly decreased with vedolizumab versus placebo at Week 52, the magnitude of this effect was small.[49] These findings are not unexpected as vedolizumab blocks lymphocyte trafficking to inflamed gut tissue rather than affecting systemic inflammation.

Ulcerative Colitis and Crohn's Disease Pathogenesis

UC and CD have different pathogeneses, particularly regarding inflammation. Histological evidence shows that inflammation is limited to the mucosa and submucosa in UC, whereas in CD the inflammation is deeper within the intestinal tissue in any part of the gastrointestinal tract. Thus, CD is more likely to have an impact on systemic inflammation than UC. This hypothesis is borne out by the efficacy of current biologics in these diseases. The anti-TNF agent adalimumab had a significant effect versus placebo at Week 4 on clinical remission (36% versus 12% of patients, $p=0.004$) and clinical response (54% versus 25% of patients, $p<0.05$) in the CLASSIC I trial in CD patients.[46] In the CHARM trial in CD patients, the proportion of patients in remission from Week 4 to Week 56 was significantly higher in both the 40 mg adalimumab weekly and every other week groups compared with placebo (41%, 36%, 12%, respectively, at Week 56).[50] In contrast, compared with placebo, vedolizumab had a slight effect on clinical remission (7% versus 15% of patients, $p=0.02$) and no effect on clinical response (26% versus 31% of patients, $p=0.23$) in CD patients after 6 weeks of treatment.[49] From Week 6 to Week 52, the proportion of patients in clinical remission was generally similar between vedolizumab and placebo from Weeks 6 to 52, and was significantly higher at Week 52 (39% versus 22%, $p<0.001$), although this increase was small.[49]

Emerging Therapies

The development of new drugs, which have more marked effects on CRP reduction than current agents, may possibly lead to new treatments for systemic inflammation. Numerous novel agents are under development for IBD.[51] These potential drugs are distinct in their class and mode of action. Examples include JAK inhibitors (tofacitinib), IL inhibitors (ustekinumab, an anti-IL-12/23 agent), SMAD-7 blockers (mongersen), S1P1 receptor inhibitors (ozanimod), and anti-adhesion molecules (etrolizumab). Many ongoing clinical trials with such agents are expected to report results over the next few years.

Four JAK receptors are activated by multiple cytokines thereby regulating many cellular functions, including inflammation.[52] The JAK inhibitors (e.g. ABT-494, baricitinib, filgotinib, VX-509 [decernotinib], and tofacitinib) potently inhibit one or more of the JAK receptors, and, due to different mechanisms, may have different effects on clinical outcomes. Tofacitinib has shown promising results in UC patients. In a Phase II trial, at Week 8 the proportions of patients with a clinical response, in clinical remission, or with endoscopic remission were significantly higher with one or more doses of tofacitinib versus placebo. There was also evidence of reduced CRP levels with tofacitinib.[53]

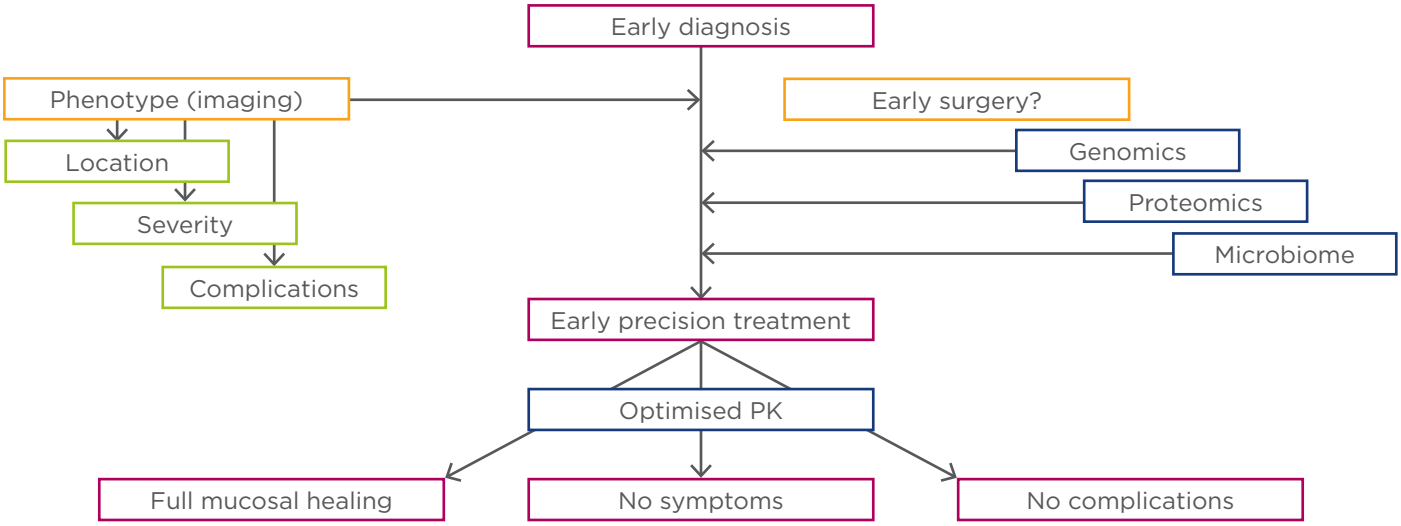

Figure 2: The ideal diagnosis and treatment of inflammatory bowel disease.
PK: pharmacokinetics.

Ustekinumab, an antibody to IL-2 and IL-23, is a highly effective drug in treating psoriasis (a common EIM of IBD). This agent has shown promising results in CD patients. In the UNITI-2 study, there was a significant increase in the proportion of patients with a clinical response, and those with clinical remission in response to ustekinumab versus placebo through Week 8 (all data points were significant).[54] Furthermore, CRP levels were also significantly reduced at all time points with ustekinumab versus placebo.[54] Ozanimod, the next generation oral sphingosine-1-phosphate receptor inhibitor, significantly increased the proportion of UC patients in remission at Week 8 versus placebo (16% versus 6%, p=0.0482).[55]

The Future: Personalised Medicine for Inflammatory Bowel Disease

The key to future IBD treatments is to identify which drug should be given to which patient, i.e. precision medicine (which has been achieved for some cancer therapies). However, this goal requires the identification of specific markers predictive of response to certain drugs. Some encouraging progress has been made in this direction; for example, the presence of the high-risk allele of the single nucleotide polymorphism *rs2241880* in the *ATG16L1* gene was predictive of response to thiopurines in patients with CD.[56] For UC patients, high levels of *alphaE* (*αE*) gene expression and high numbers of αE^+ cells at baseline in colonic biopsies were predictive of clinical remission after treatment with etrolizumab compared with placebo.[57]

The future positioning of new drugs in the treatment paradigm for IBD will depend on many factors, such as the balance between efficacy and safety, monotherapy versus combination therapy, administration route, rapidity of effect, mucosal and/or fistula healing, the availability of convenient biomarkers, and cost. Ideally, the future of IBD treatment will involve early diagnosis including work-up of many factors (e.g. phenotype, genomics, proteomics, and microbiome). These data will then feed into early precision treatment for an individual patient, which, via optimised drug pharmacokinetics, will result in full mucosal healing, and no symptoms or complications (Figure 2).

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