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Inflammatory Bowel Disease (G Lichtenstein, Section Editor)

Novel Therapies and Treatment Strategies for Patients with Inflammatory Bowel Disease

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Abstract

Purpose of review This article reviews current treatment options and strategies and provides an update on the status of drug development programs of new therapeutic agents for inflammatory bowel diseases (IBD).
Recent findings In the past two decades, tumor necrosis factor antagonist therapy has given clinicians better treatment options. However, not all patients respond to induction therapy with these agents, and of those initially responding, up to 40% ultimately lose response due to suboptimal drug exposure (e.g., caused by immunogenicity), side effects,

or other poorly characterized mechanisms. Recently, additional therapies, such as vedolizumab, an integrin blocker that prevents T cell trafficking to the gut, and ustekinumab, an antibody blocking the common p40 subunit of interleukin (IL)-12 and 23, were introduced to the market. In addition, other agents including novel anti-trafficking therapies (e.g., anti-β7 and sphingosine-1-phosphate receptor modulators), antibodies against p19 (unique to IL-23), and small molecules including Janus kinase inhibitors are under investigation in phase II and III trials.
Furthermore, the management of IBD has evolved from targeting control of symptoms to suppression of mucosal inflammation. This shift in thinking has been accompanied by the early use of highly effective therapy in poor prognosis patients, accelerated treatment escalation and utilization of a treat to target paradigm approach, and adoption of therapeutic drug monitoring.
Summary The treatment landscape for IBD is rapidly evolving with the recent approval of novel biologics as well as several other agents in late phase of clinical development. Moreover, we have started to use agents more intelligently with a focus on risk stratification and early use of highly effective therapy in high-risk patients, treat to target using patient-reported outcomes (PROs), biomarkers, endoscopy, and therapeutic drug monitoring.

Introduction

The idiopathic inflammatory bowel diseases (IBD), Crohn's disease (CD), and ulcerative colitis (UC) are characterized by chronic inflammation of the intestine [1]. Symptoms include frequent bloody bowel movements, abdominal pain, weight loss, and fatigue. Complications include stricture formation, abscesses, fistulas, extra-intestinal manifestations and colorectal cancer [2]. Current therapy consists of 5-aminosalicylates (5-ASA), corticosteroids, immunosuppressives, and biologics. While tumor necrosis factor (TNF) antagonists have dominated the treatment of IBD for almost two decades [3], the advent of novel biologics such as anti-integrins and IL-12/IL-23 antagonists offer new alternatives. In parallel, treatment paradigms have evolved from purely control of symptoms to mucosal healing [4••]. We summarize key data for existing and novel compounds and speculate upon evolving treatment paradigms in IBD.

Current therapies

5-ASA and corticosteroids

Treatment of IBD should be individually tailored by risk stratification, taking into account disease severity, location, behavior, complications, and previous response to therapies. Treatment with 5-ASA is effective for both induction [5] and maintenance [6] of remission in patients with mild to moderate UC. In contrast, only sulfasalazine, but not mesalamine or its derivatives, has shown to be modestly effective for induction of remission, but not for maintenance therapy in CD [7]. Corticosteroid formulations, composed of both conventional (prednisone and prednisolone) and second-generation glucocorticosteroids (e.g., ileal-release budesonide in CD and colonic-release budesonide MMX in UC), are effective induction agents. Although second-generation corticosteroids have a better safety and tolerability profile [8–11], long-term corticosteroid use with either conventional corticosteroids or budesonide is not recommended [12, 13].

Immunosuppressives

Thiopurines and methotrexate (MTX) have been used in the conventional step-up approach to treatment [14]. MTX is used for induction and maintenance of clinical remission in CD. A relatively high dose of parenteral methotrexate (25 mg subcutaneous/week) is effective for induction of clinical remission in CD [15], albeit with 17% withdrawal rates due to adverse events [16], chiefly nausea. There is no good evidence to support the use of methotrexate in UC. More recently low dose oral methotrexate has gained popularity for prevention of immunogenicity to biologics [17]. Although azathioprine is not effective as monotherapy to induce clinical remission in patients with CD [18, 19], it is frequently used for maintenance of remission in both UC and CD and in combination with a biologic to prevent immunogenicity. Common adverse events are myelosuppression, hepatoxicity, and pancreatitis, requiring frequent routine laboratory monitoring [20]. Thiopurine use is associated with an approximately 4-fold increased risk for the development of lymphoma and nonmelanoma skin cancer [21, 22]. However, the absolute risk for lymphoma with thiopurine therapy in IBD patients is very low; being 1 in 2000 per year in a patient younger than 50 (except for men younger than 30 for which the absolute risk is 1 per 500–1000 person-years), it increases markedly to 1:350 in those older than 50 [22, 23].

TNF antagonists

TNF antagonists (infliximab, adalimumab, golimumab, and certoluzimab pegol) have greatly improved disease management [24–27] and are effective for both induction and maintenance therapy, decrease exposure to corticosteroids, and promote sustained mucosal healing [28, 29]. However, up to one third of patients do not respond to induction therapy, and of those initially responding, up to 40% ultimately lose response due to suboptimal drug exposure (e.g., caused by immunogenicity or high drug clearance), intolerance, or other poorly characterized mechanisms [30, 31].

The relatively high costs of TNF antagonists and patent expiration have triggered the development of biosimilar monoclonal antibodies. Multiple regulatory agencies have approved the use of biosimilars in IBD based upon trial data that showed similar safety and efficacy to originator infliximab in patients with rheumatoid arthritis [32] and ankylosing spondylitis [33]. Recently, the first controlled trial on switching from an originator to biosimilar has been published [34••]. The NOR-SWITCH trial included 482 patients with six different inflammatory diseases (155 with CD and 93 with UC) who were in remission and receiving infliximab. Patients were randomized 1:1 to either continue infliximab originator or to switch to CT-P13. The primary outcome was occurrence of clinical disease worsening at 1 year. The authors found that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator based upon a prespecified noninferiority margin of 15%. However, the overall point estimate favored the originator. There are some limitations to this study [35]. Firstly, it is questionable if the noninferiority margin of 15% that was used is not clinically relevant. Secondly, the study was not powered to assess efficacy in the individual diseases. However, a subgroup analysis in the CD population showed a

risk difference of 14.3% (95% confidence interval (CI), – 29.3 to 0.7) in favor of the originator, suggesting that the biosimilar may be less effective. Furthermore, NOR-SWITCH did not evaluate the possible risk of immunogenicity that could result from switching patients back and forth between different biosimilars and originator. As recently outlined in a Food and Drug Administration (FDA) draft guidance, well-designed randomized interchangeability studies are necessary to address this question [36]. Nevertheless, switching is quickly coming into widespread clinical practice across the globe.

Anti-integrins

New biologics have become available (Table 1). The α4β7 integrin antibody vedolizumab (Entyvio; Takeda) inhibits trafficking of subpopulations of T cells to the gut mucosa [38]. Vedolizumab was shown to be effective and safe in phase III trials and was subsequently approved for induction and maintenance therapy in both UC and CD. In UC, 47.1% (vs 25.5% in the placebo group) had clinical remission after 6 weeks of induction therapy and at week 52, 41.8 and 44.8% of patients who received vedolizumab every 8 and 4 weeks, respectively (vs 15.9% in the placebo group, $p < 0.001$ for both groups compared to placebo) [39]. Corresponding data were obtained in CD; at week 6, 14.5% (vs 6.8% in placebo, $p = 0.02$) and at week 52, 39.0 and 36.4% of patients who received vedolizumab every 8 and 4 weeks, respectively, were in clinical remission (vs 21.6% in the placebo group, $p < 0.001$ and $p = 0.004$ respectively) [40]. A separate study showed that in patients previously exposed to TNF antagonist, clinical remission rates were significant in the vedolizumab group at week 10 (26.6 vs 12.1% placebo, $p = 0.001$), whereas no beneficial effects was seen yet at week 6 (15.2 vs 12.1%, $p = 0.433$) [41]. CD is likely to require a longer time horizon; therefore, response to induction therapy should be evaluated at approximately 14 weeks. For both UC and CD, vedolizumab is more effective in patients naive to TNF antagonists. The efficacy of vedolizumab for the treatment of extra-intestinal manifestations is unclear[42]; ongoing phase IV trials will determine its effectiveness for treatment of fistulizing disease (NCT02630966) and pouchitis (NCT02790138). Vedolizumab is an attractive choice as a first-line biologic because of the favorable safety profile and lack of systemic immune suppression.

IL-12/23 antagonists

Interleukin (IL)-12 and IL-23 are pro-inflammatory cytokines regulating the T_H1 and T_H17 pathway, respectively [43, 44]. These heterodimeric cytokines share a common p40 subunit [45]. Ustekinumab (Stelara; Janssen Biotech), a fully human IgG_K monoclonal antibody that blocks the common p40 subunit, was recently approved for the treatment of moderate to severely active CD on the basis of demonstrated efficacy in induction (UNITI-1 and UNITI-2) and maintenance (IM-UNITI) in both TNF antagonist naïve and failure patients [46••]. Clinical efficacy was greatest in TNF naïve patients. The adverse events observed were consistent with 5 years of cumulative data acquired in patients with psoriasis, including a large registry that demonstrated no increased risk of serious infection, malignancy or mortality [47•, 48]. Ustekinumab is highly effective for the treatment of psoriasis and thus could be considered a treatment

Table 1. New agents for IBD and their current status in development

Drug	Other names	Type	Target	Mode of administration	Status[a] CD	UC	Comments
Vedolizumab	Entyvio	Humanized mAb	Anti-integrin (α4β7 subunit)	IV	Approved	Approved	
Natalizumab	Tysabri	Humanized mAb	Anti-integrin (α4 subunit)	IV	Approved	–	Only approved by FDA, not by EMA[b]
Etrolizumab	RG7413	Humanized mAb	Anti-integrin (β7 subunit)	IV/SQ	Phase III	Phase III	
Ozanimod	RPC1063	Small molecule	S1P modulation	Oral	Phase II	Phase III	
Etrasimod	APD334	Small molecule	S1P modulation	Oral	–	Phase II	
Ustekinumab	Stelara	Fully human mAb	Anti-IL-12/IL-23(p40)	IV/SQ	Approved	Phase III	
Risankizumab	ABBV-066/BI655066	Fully human mAb	Anti-IL-23(p19)	IV/SQ	Phase III	–	Not yet recruiting
Brazikumab	AMG 139/MEDI2070	Fully human mAb	Anti-IL-23(p19)	IV/SQ	Phase IIb	–	
Mirikizumab	LY3074828	Humanized mAb	Anti-IL-23(p19)	IV/SQ	Phase II	Phase II	
Tofacitinib	Xeljanz	Small molecule	JAK1/JAK3	Oral	–	Accepted for filing by FDA	
Filgotinib	GLPG0634, GS-6034	Small molecule	JAK1	Oral	Phase III	Phase III	
Upadacitinib	ABT-494	Small molecule	JAK2	Oral	Phase II	Phase II	

CD Crohn's disease, *UC* ulcerative colitis, *mAb* monoclonal antibody, *IV* intravenous, *FDA* Food and Drug Administration, *EMA* European Medicines Agency, *SQ* subcutaneous, *IL* interleukin, *S1P* sphingosine-1-phosphate, *JAK* Janus kinase

[a]The highest level of clinical status, obtained from www.clinicaltrials.gov October 2017

[b]Risk of PML in approximately 1 in 100 patients who are JC virus antibody positive, had prior immunosuppressive exposure, and ≥ 2 years use [37]

of choice in CD patients who have both conditions or those who develop psoriasiform lesions as an adverse effect of TNF antagonist therapy [49, 50].

Current status of agents in late-phase development

Anti-trafficking therapies

Anti β-7

Etrolizumab (rhuMAb Beta7, RG7413; Genentech) is a humanized IgG1 monoclonal antibody directed against the β7 subunit of the α4β7 and αEβ7 integrins. These interact with mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) and E-cadherin, respectively. MAdCAM-1, which is primarily expressed in high endothelial venules, is responsible for lymphocyte recruitment into the intestine [51]. E-cadherin, expressed on the basolateral surface of epithelial cells in the gut mucosa, plays an important role in homing of intestinal intraepithelial lymphocytes. Accordingly, by targeting both α4β7:MAdCAM-1 and αEβ7:E-cadherin interactions, mucosal lymphocyte trafficking is reduced and intraepithelial leukocyte retention is inhibited. Etrolizumab was evaluated in a randomized, controlled, phase II trial (EUCALYPTUS, NCT01336465) [52••]. UC patients were assigned to receive subcutaneous etrolizumab 100 mg ($n = 39$) at weeks 0, 4, and 8 or a 420 mg loading dose followed by 300 mg at weeks 2, 4, and 8, or placebo ($n = 41$). At week 10, no patients in the placebo group were in clinical remission compared with 21% of patients in the etrolizumab 100-mg group ($p = 0.004$) and 10% of patients in the 300 mg plus loading dose group ($p = 0.048$). Interestingly, in a post-hoc analysis, more patients with high αE integrin gene expression in baseline colon biopsies achieved clinical remission compared to patients with low αE integrin gene expression. The proportion of patient with adverse events was similar in patients who received active drug and those who received placebo. Based on these results, etrolizumab is undergoing evaluation in placebo controlled phase III trials for UC (NCT02136069, NCT02100696) and CD (NCT02394028).

Sphingosine-1-phosphate receptor modulators

The sphingosine-1-phosphate (S1P) receptor is expressed on lymphocytes and endothelial cells in lymph nodes. Lymphocytes follow an S1P concentration gradient in their migration from regional lymph nodes into the blood. Modulation of the S1P receptor results in internalization and degradation of the target receptor. Consequently, lymphocytes are unable to follow the S1P1 gradient on the lymphatic endothelium, functionally trapping them in lymph nodes and preventing their participation in pathological processes at sites of inflammation [53].

Fingolimod, a first-generation S1P receptor modulator developed and approved for the treatment of multiple sclerosis (MS), is a nonselective small-molecule agonist to four of the five S1P receptors (S1P1,3–5) [54]. Although it is highly effective for the treatment of MS, fingolimod has important side effects including bradycardia, increased risk of herpes infection, macular edema, and interstitial lung disease [55]. Next-generation S1P

receptor modulators with greater selectivity were subsequently developed to overcome this limitation. Ozanimod (RPC1063; Celgene), a S1P receptor 1 and 5 agonist, demonstrated efficacy phase II clinical for the treatment of UC (TOUCHSTONE, NCT01647516) [56••]. In this study, 197 patients were randomly assigned to either placebo, 0.5, or 1 mg of oral ozanimod daily. The 1-mg dose showed an increased rate of clinical remission as compared to placebo (16 vs 6%, $p = 0.048$ at week 8 and 21 vs 6%, $p = 0.01$ at week 32). Ozanimod was well tolerated; the most common adverse effects were headache and anemia. Ozanimod is currently being tested in a phase III trial in UC (NCT02435992) and a phase II trial in CD (NCT02435992). Another selective S1P modulator, etrasimod (APD334; Arena), is being evaluated, as placebo-controlled phase II trial in UC (NCT02447302, NCT02536404).

Anti-cytokine antibodies

IL-23 (p19)

IL-12 p35-p40 and IL-23 p19-p40 are heterodimeric, proinflammatory cytokines found in increased concentrations in the inflamed mucosa of patients with CD [57]. These cytokines, which share a p40 subunit, are expressed by dendritic cells and tissue-resident macrophages and play a key role in T cell immune responses [58]. IL-12 and IL-23 induce T_H1 and T_H17 differentiation, respectively [59].

The humanized IgG1 monoclonal antibody risankizumab (BI655066; AbbVie), directed against the p19 subunit of Il-23, was tested in a randomized, double-blind, placebo-controlled phase II study [60••] that evaluated 121 patients with moderately-to-severely active CD. Patients were randomized equally to intravenous 200-mg, 600-mg risankizumab, or placebo at weeks 0, 4, and 8. The primary outcome was clinical remission (CDAI < 150) at week 12. The 600-mg risankizumab dose achieved significantly higher clinical (37 vs 15.0% $p = 0.0252$) and endoscopic remission (20 vs 3.0% $p = 0.0107$) rates. It is noteworthy that these results were obtained in a patient population in which 69% of patients had previously been exposed to at least two TNF antagonists. Adverse events were similar between risankizumab- and placebo-treated patients; the most common adverse event was nausea. Phase III development programs have been initiated (NCT03105128, NCT03104413).

Another humanized monoclonal antibody directed against IL-23p19 is brazikumab (AMG 139/MEDI2070; Allergan). A recent double-blind, placebo-controlled phase II trial evaluated brazikumab in 119 adults with moderate to severe CD who had failed a TNF antagonist. Patients were randomly assigned to either brazikumab (700 mg) or placebo intravenously at weeks 0 and 4 [61••]. Clinical response at week 8 was achieved in 49.2% of patients who received brazikumab compared with 26.7% of those assigned to placebo ($p = 0.010$). The most common adverse events were headache and nasopharyngitis.

Mirikizumab (LY3074828; Eli Lilly and Company) is currently being studied in two phase II trials including patients with CD (SERENITY, NCT02891226) and UC (NCT02589665). Two other Il-23p19 antibodies, tidrakizumab (Merck) and guselkumab (Janssen), which are currently in

development for the treatment for psoriasis, are also likely to be studied for IBD in the future.

Janus kinase inhibitors

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is involved in vital cellular processes, such as cell growth, development, proliferation, differentiation, and regulatory immune functions. Genome-wide association studies have demonstrated the importance of the JAK/STAT pathway in the pathogenesis of IBD [62]. The JAK family consists of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) [63]. JAK/STAT pathways regulate signaling for multiple immune-relevant mediators, including type I interferon, interferon-γ, and IL-2, 4, 6, 7, 9, 12, 15, 21, 23, and 27 [64].

Tofacitinib

Tofacitinib (Xeljanz, Pfizer), FDA approved for rheumatoid arthritis, is an orally administered small molecule that predominantly inhibits JAK1 and JAK3. Recent phase III data showed a significant treatment effect in three clinical trials in UC [65••]. In the identical induction trials OCTAVE 1 and OCTAVE 2, 598 and 541 patients respectively were randomly assigned in a 4:1 ratio to receive induction therapy with tofacitinib (10 mg twice daily) or placebo for 8 weeks. Clinical remission at week 8 occurred in 18.5% of the patients in the 10 mg tofacitinib group versus 8.2% in the placebo group ($p = 0.007$) in the OCTAVE 1 trial and in 16.6 versus 3.6% ($p < 0.001$) in the OCTAVE 2 trial. Similar results were obtained in patients who had received previous treatment with a TNF antagonist and those who were naïve to these agents. Patients who completed the induction trials with a clinical response were eligible to participate in the OCTAVE SUSTAIN trial. In the OCTAVE SUSTAIN trial, remission at week 52 occurred in 34.3% (5 mg), 40.6% (10 mg) versus 11.1% in the placebo group ($p < 0.001$ for both comparisons to placebo). Similar to findings from earlier studies in rheumatoid arthritis, lipid and creatine kinase levels were increased in tofacitinib treated patients though the clinical relevance of these abnormalities is uncertain. Infections, including herpes zoster, and cardiovascular events occurred at higher rates in tofacitinib treated patients than those who received placebo. Tofacitinib is currently under regulatory review in both Europe and the USA.

Filgotinib and upadacitinib

Additional JAK inhibitors are under development. The JAK1-selective inhibitor filgotinib (Galapagos; GLPG0634, GS-6034) has positive phase II data in CD showing that at week 10 47% of patients treated with 200 mg filgotinib daily achieved clinical remission versus 23% treated with placebo ($p = 0.0077$) [66••]. Further trials in fistulizing CD (NCT03077412) and small bowel disease (NCT03046056), as well as phase III trials in UC (NCT02914535, NCT02914522) and CD (NCT02914561, NCT02914600), are underway. The preliminary results of a phase II study in CD with JAK1-selective inhibitor upadacitinib (ABT-494; AbbVie) showed endoscopic improvement and clinical benefit. Compared with placebo, more patients achieved clinical response with 6 and 24 mg twice daily (57 and 61% respectively), versus 32% placebo ($p =$

0.05), and endoscopic remission with 24 mg at week 16 (22 vs 0% in the placebo group, $p = 0.01$) [67]. The drug is being evaluated for UC (NCT02819635) and in an upcoming phase III trial for CD.

Defining an optimal treatment strategy

Risk stratification, early intervention, and combination treatment

Although the availability of new drugs is a major factor in the journey toward highly effective therapy, our experience with the TNF antagonists has taught us that a great deal can be achieved by optimizing conventional agents before switching out of class. Although no fully validated predictive model currently exists, several studies have proposed classification of disease using the following criteria [68]. First, the impact of the disease on the patient needs to be assessed, based upon clinical symptoms and quality of life. Second, inflammatory burden should be quantified using objective measures, such as C-reactive protein (CRP), fecal calprotectin (FCP), endoscopy, and cross-sectional imaging. Finally, disease manifestations and course need evaluation. Predictive factors for a severe course of CD have been identified in population-based cohort studies, including perianal disease, fistulas, deep ulceration on endoscopy, prior surgery, early and repetitive corticosteroid use, cigarette smoking, diagnosis before the age of 40 years, and extra-intestinal manifestations [69–73]. In the case of UC, patients with pancolitis, presence of deep ulcers, and nonsmoking status are at higher risk for both colectomy and development of colon cancer [74].

It is important to recognize that approximately 20% of patients with IBD have an indolent disease course [75, 76] and are at low risk for disease-related complications. Risk stratification guides early introduction of highly effective therapy in patients with a poor prognosis and prevention of overtreatment in low-risk patients. In CD, several studies have demonstrated the benefits of the early introduction of combination therapy [77]. Specifically, the TOP-DOWN [14] and SONIC [78] trials showed superiority of early combined immunosuppression to conventional management. The REACT-1 study compared the use of combination therapy to conventional management early in the induction treatment algorithm in community gastroenterology practices. This study demonstrated that use of highly effective therapy resulted in a reduction in major adverse outcomes, such as surgery, hospital admission, or serious disease-related complications, without an increase in risk of serious infection or mortality [79•].

Treat to target

Assessment of treatment strategies are shifting from subjective targets, such as patient-reported outcomes (PROs), toward more objective targets including biomarkers, endoscopy, cross-sectional imaging, and histology (Table 2).

Patient-reported outcomes

A PRO is a report coming directly from a patient about the status of their health condition and/or response to therapy. In the absence of a well-characterized instrument, the Selecting Therapeutic Targets in IBD (STRIDE) program recommends that the primary PRO for CD should be resolution of abdominal pain and normalization of bowel habit, and in the case of UC, resolution of rectal

Table 2. Recommendations for treating to target in IBD by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD)

Crohn's disease	
Clinical target[a]	Resolution of abdominal pain and normalization of bowel habit.
Endoscopic target	Absence of ulceration.
Histologic target	Histologic remission is not a target.
Imaging	When endoscopy cannot adequately evaluate inflammation, resolution of inflammation as assessed by cross-sectional imaging is a target.
Biomarkers[b]	Available biomarkers including CRP and fecal calprotectin are not targets.
PRO	Resolution of abdominal pain and normalization of bowel habit.
Ulcerative colitis	
Clinical target[a]	Resolution of rectal bleeding and normalization of bowel habit.
Endoscopic target	A Mayo endoscopic subscore of 0 is the optimal target. A Mayo endoscopic subscore of 1 should be a minimum target.
Histologic target	Histopathology is a sensitive measure of inflammation but is not a target due to lack of evidence of clinical utility.
Imaging	Cross-sectional imaging is not a target in UC.
Biomarkers[b]	Available biomarkers including CRP and fecal calprotectin are not targets.
PRO	Resolution of rectal bleeding and normalization of bowel habit.

Source: [4••]
CD Crohn's disease, *UC* ulcerative colitis, *IBD* inflammatory bowel disease, *CRP* C-reactive protein, *PRO* patient-reported outcome, *Mayo 0* normal mucosa or inactive disease, *Mayo 2* mild activity (erythema, decreased vascular pattern, mild friability)
[a]Resolution of symptoms alone is not a sufficient target. Objective evidence of inflammation of the bowel is necessary when making clinical decisions
[b]CRP and fecal calprotectin are adjunctive measures of inflammation for monitoring in IBD. Failure of CRP or fecal calprotectin normalization (below lab-specific cutoff) should prompt further endoscopic evaluation, irrespective of symptoms

bleeding and normalization of bowel habit [4••]. Interim PROs for use in clinical trials have been developed [80, 81]. However, control of symptoms alone is insufficient and more objective treatment targets are necessary to prevent complications related to uncontrolled inflammation.

Mucosal healing

In observational studies, mucosal healing has been consistently associated with improved outcomes, including clinical remission, hospitalization, and abdominal surgery [4••, 82]. In patients with CD, mucosal healing (absence of ulceration [4••]) predicts sustained, steroid-free remission 3 and 4 years after therapy initiation [28] and is associated with fewer hospitalizations and disease related surgeries [83]. In patients with UC, early mucosal healing (endoscopic Mayo subscore of 0 or 1 [4••]) is also associated with improved long-term clinical outcomes, glucocorticoid-free clinical remission, mucosal healing, and lower colectomy rate [84•, 85]. Based upon these observations, it is highly likely

that endoscopy will ultimately prove to be a robust treatment target; however, at this time, it has not been shown a valid surrogate, in that no controlled trial demonstrating that treating to endoscopic remission results in better outcomes has been performed.

Histologic healing

Histologic healing may ultimately provide an objective measure for use as an endpoint in clinical trials and patient management which provides more robust information than that provided by endoscopy. In UC, histopathology has consistently demonstrated prognostic value with better precision than either endoscopic or using relapse-free survival, corticosteroid use, and hospitalization as outcomes of interest [86, 87•]. The importance of this topic is likely to increase due to the recent development of validated histopathology indices. Traditionally, the empirically derived Geboes and modified Riley scores were the most commonly used measures to evaluate microscopic inflammation; however, two new instruments, the Robarts Histopathologic Index and Nancy Index, have been shown to be valid and reproducible [88]. The situation in CD is more complex. Although the Global Histologic Disease Activity Score (GHAS) has been extensively used as an outcome measure in clinical trials, it has not undergone extensive validation testing [89, 90]. Nevertheless, it has been demonstrated that fewer clinical flares occur in patients with lower histologic disease activity based upon GHAS scoring [91]. Our opinion is that despite very compelling observational data histopathology cannot yet be considered a treatment target in either UC or CD.

Biomarkers

Both endoscopy and histology are problematic as treatment targets because an invasive and expensive intervention (endoscopy) is required. On this basis, interest has grown in less invasive surrogate markers. The most widely used noninvasive measurements are serum CRP and FCP. CRP is an acute-phase protein produced by the liver in response to IL-6 secretion by macrophages and T cells. In general, elevated CRP in CD is associated with clinical disease activity and endoscopic and histologic inflammations [92]. However, CRP is not specific for intestinal inflammation with an overall specificity in IBD of 0.49 (95% CI 0.72–0.98) [93]. Moreover, approximately 20% of CD patients do not mount a CRP response during flares [94]. Many ambulatory patients with UC do not have elevated concentration of CRP; however, serial measurement is very useful for assessment of treatment response in patients with severe colitis undergoing infliximab therapy. Calprotectin is a 36-kDa calcium- and zinc-binding protein that is the predominant cytosolic proteins in granulocytes. The concentration of FCP reflects neutrophil influx to the intestine. FCP is a highly sensitive marker (0.88 (95% CI 0.84–0.90)) of endoscopically active disease in symptomatic IBD patients. FCP has shown better specificity in UC (0.79 (95% CI 0.68–0.87)) than CD (0.67 (95% CI 0.58–0.75)) [93].

The CALM trial was designed to prospectively study the impact of a treat to target approach based on serial monitoring of CRP and FCP in CD

patients. In the intervention arm, treatment intensification was made according to biomarker defined targets whereas the patients assigned to control were managed according to symptom management. The primary endpoint of endoscopic healing at week 48 was met in 45.9% (56/122) of patients in the treat to target group versus 30.3% (37/122) in the symptom-based management group ($p = 0.01$) [95•].

Tight disease control based on therapeutic monitoring

Therapeutic drug monitoring (TDM) provides insights into the pharmacokinetics of the individual patient and can be used to guide treatment decisions [20, 96•]. In general, TDM is not recommended in patients with quiescent IBD due to the lack of sufficient evidence. In patients starting thiopurine treatment, routine thiopurine methyltransferase (TPMT) testing is recommended (either enzyme activity or genotype) for potential dosing adjustments[20]. In patients treated with azathioprine or 6-MP, measurement of 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP) concentrations can aid in treatment decisions [96•, 97]. With regard to TNF antagonists, optimal trough serum concentrations are associated with higher rates of clinical and endoscopic remission[98, 99]. In practice, the use of TDM is valuable for assessment of patients who lose response to a TNF antagonist. First, the trough concentration is measured. In the case, a patient has active disease despite an adequate level, in which switching to a different drug class can be considered. In the case of low serum concentrations, anti-drug antibodies (ADAs) are determined. In the case of low trough levels with no detectable ADAs, the drug should be optimized (by increasing the dose, shortening dose interval and/or adding immunomodulator). In the case of no detectable drug in the presence of ADAs, it can be considered to switch to another drug within the same class (or to another drug class). A decision support tool on when to perform and interpret TDM in patients starting or taking thiopurine or a TNF antagonist is available [].

Predicting response to therapy

As new drug classes become available, it would be attractive to be able to predict which drug is optimal for an individual patient. Preliminary data illustrating the potential of the concept comes from a post-hoc analysis of the EUCALYPTUS trial, a phase II induction trial with etrolizumab. In a post-hoc analysis, patients with higher integrin αE gene expression in baseline colonic biopsy samples were more likely to achieve clinical remission compared to patients with low αE gene expression [52••]. Another example of this concept has recently been published. Inflamed intestinal tissues from IBD patients contain high amounts of the cytokine oncostatin-M (OSM) [101, 102•]. OSM is part of the IL-6 cytokine family and is mainly produced by activated T cells, monocytes, and dendritic cells. Recently, it was demonstrated in five independent cohorts that high OSM expression in intestinal mucosa of patients before TNF integrin therapy is strongly associated with a decreased responsiveness to therapy (complete mucosal healing therapy was achieved in 69–85% of patients with low OSM expression compared to 10–15% of patients with high OSM expression)

[102•], suggesting that OSM measurement before therapy could predict response to therapy.

Development of clinical prediction models which enable prediction of response to a specific treatment in an individual patient is essential as the armamentarium for IBD expands.

Conclusion

Multiple new classes of drugs have become available for IBD, and many promising agents are in late-stage development. Moreover, we have started to use agents more intelligently with a focus on risk stratification and early use of highly effective therapy in high-risk patients, treat to target using PROs, biomarkers, endoscopy, and therapeutic drug monitoring.

Compliance with Ethical Standards

Conflict of Interest

Robert Battat declares no conflict of interest.

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administration (New Zealand patent 306062; Singapore patent 45647; Australia patent 707168; Czech patent 290428) issued, a patent Intestinal absorption of nicotine to treat nicotine responsive conditions (Australia patent 718052; US 6,238,689) issued, a patent The use of topical azathioprine and thioguanine to treat colorectal adenomas (US 6,166,024) issued, a patent Enema and enterically coated oral dosage forms of azathioprine (US 6,432,967) issued, a patent A pharmaceutical composition for the treatment of inflammatory bowel disease (US 7,341,741) issued, a patent Intestinal absorption of nicotine to treat nicotine responsive conditions (Canada patent 2,260,909) issued, and a patent Obesity treatment and device (US 7,803,195 B2) licensed to Enteromedics.
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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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