HOW TO IMPROVE YOUR SUCCESS IN TREATING MILD AND MODERATE INFLAMMATORY BOWEL DISEASE

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Chairperson
Geert D'Haens[1]

Speakers
Ailsa Hart,[2] Pieter Hindryckx[3]

1. Academic Medical Centre-IBD Unit, University of Amsterdam, Amsterdam, Netherlands
2. Director, IBD Unit, St Mark's Hospital, London, UK
3. Research Gastroenterologist, Department of Gastroenterology, University Hospital of Ghent, Ghent, Belgium

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MEETING SUMMARY

Inflammatory bowel disease (IBD) describes two inflammatory conditions of the gastrointestinal tract: ulcerative colitis (UC) and Crohn's disease (CD). For patients with UC, chronic inflammation of the rectum and colon results in faecal urgency, recurring diarrhoea, and abdominal pain. For patients with CD, mucosal inflammation may occur anywhere along the gastrointestinal tract and common symptoms may include diarrhoea, abdominal pain, fatigue, and weight loss. The vast majority of patients with IBD have mild-to-moderate disease at diagnosis: 85% of patients with UC and 70–80% of patients with CD. Evidence-based guidelines for the management of UC recommend 5-aminosalicylic acid (ASA) treatment (mesalazine) as a first-line therapy. There is evidence to suggest that 5-ASA treatment can be optimised in patients with mild-to-moderate UC by optimising the dose, combining oral with rectal therapy, and increasing treatment duration. For ileocaecal CD, guidelines recommend budesonide as a first-line treatment for mildly and moderately active disease. Systemic corticosteroids may be prescribed as an alternative to budesonide in patients with moderately active disease and as initial therapy in severely active disease. As with all chronic therapies, poor adherence impacts treatment efficacy in IBD as a result of a number of patient and treatment-related factors. Approaches to improve adherence include boosting patient motivation and education and reducing treatment complexity. Key factors for ensuring successful treatment of both UC and CD include understanding predictors of outcome, selection of the right drug, at the right dose, at the right time, and having well-informed and motivated patients.

Success Factors in the Treatment of Mild-to-Moderate Ulcerative Colitis

Doctor Ailsa Hart

UC is a chronic inflammatory condition that begins in the rectum and may extend to the proximal colon. It is characterised by the presence of blood in stools and faecal urgency. UC can be categorised by severity as mild, moderate, or severe, with the majority of patients (85%) having mild-to-moderate disease.[1]

DEFINING MILD-TO-MODERATE ULCERATIVE COLITIS

A number of factors are used to assess the severity of UC, including bowel movement frequency, extent of colonic involvement, and impact on patients' lives. The definition of severe UC is generally well understood: patients with six or more bowel movements per day plus signs of systemic involvement (elevated heart rate, low haemoglobin, and an erythrocyte sedimentation rate of 30 mm/hour or more).[2,3] The distinction between mild and moderate UC, however, may be less clear. Classically, mild disease has been defined as up to four stools per day with no systemic illness, and moderate disease as more than four stools per day with minimal signs of systemic toxicity.[2,3]

Systems for determining UC severity include the Mayo score. This system is based on bowel movement frequency (relative to what is normal) but also incorporates assessment of the presence of blood in stools, endoscopic activity, and impact of disease on patients' lives.[4]

Assessment of the impact of UC on patients' lives is an important component that can be underestimated by physicians. A survey that compared patients' and physicians' perception of quality of life found that gastroenterologists underestimated the proportion of UC-related difficulties reported by patients. Patients were asked to comment on whether their disease made life more stressful, made it difficult to live a normal life, was embarrassing, and/or had ruined important moments, and the results were consistently higher than gastroenterologists had estimated. For example, gastroenterologists estimated that 36% of patients would find it difficult to lead a normal life but 62% of patients reported this to be the case.[5]

PREDICTORS OF OUTCOME

The clinical course of UC is typically described as having recurring periods of exacerbation and remission. However, stable remission after an initial period of activity has been observed to be a more common pattern than chronic intermittent disease during the first 5 years after diagnosis (55% versus 37%, respectively) in a European cohort study (N=519).[6]

Young age and female gender have been associated with a trend towards more frequent relapses, and the relationship between sustained non-smoking status and less active disease has been well established.[7] Perhaps more crucially, extensive or complete colitis at diagnosis has been associated with increased risk of colectomy and cancer; endoscopic lesions and extension of disease (progression from proctitis to total colitis) have been associated with increased risk of colectomy.[7]

TREATMENT GOALS

Treating mild-to-moderate UC involves finding the right balance between undertreatment of difficult disease and overtreatment of minimal disease. The ultimate goal is to have patients who are well: clinically, endoscopically, histologically, psychologically, and without side effects of therapies. This involves alleviation of symptoms and aiming to achieve steroid-free remission, mucosal healing, improved patient quality of life, reduced need for operations, and prevention of cancer.

Patient Case Example One: Ulcerative Proctitis

An 18-year-old male presented with a 2-month history of faecal urgency, rectal bleeding, and abdominal pain. Stool analysis showed no infection and blood tests showed that the patient was anaemic. Endoscopic and histologic findings were consistent with ulcerative proctitis.

How should this patient be treated?

Evidence-based guidelines from the European Crohn's and Colitis Organisation (ECCO) recommend 5-ASA 1.0 g suppository once daily (QD) as an initial treatment for mild or moderately active proctitis.[8] As an alternative, 5-ASA foam enemas may be used, although delivery may be less effective compared with suppositories. The guidelines note that combining topical 5-ASA with oral 5-ASA or topical steroids is more effective than either alone and should be considered for

escalating treatment.[8] For patients with refractory proctitis, treatment with immunosuppressants and/or biologics may be required.[8]

Patient Case Example Two: Left-Sided Ulcerative Colitis

A 30-year-old female had suffered from left-sided UC for 5 years. She was taking oral 5-ASA 2.4 g/day (with good compliance) and used topical 5-ASA occasionally. She had previously received a course of prednisolone but "hates steroid side effects". She was experiencing a flare following a Mediterranean holiday.

How should this patient be treated?

ECCO guidelines recommend that mild-to-moderate left-sided UC should initially be treated with an ASA enema 1.0 g/day combined with oral 5-ASA 2.0 g/day.[8] Systemic corticosteroids are appropriate if symptoms of active colitis are unresponsive to 5-ASA. If left-sided UC is severe, hospital admission for intensive systemic therapy is usually indicated.[8]

IMPROVING OUTCOMES

Factors that may influence outcomes include: early diagnosis, appropriate therapy selection, well-informed patients, appropriate monitoring, and treatment escalation where required.

Avoiding Delays in Diagnosis

Delayed diagnosis of UC (median: 4 months) is a problem in paediatric and adult patients.[9] Thus, there is a need for increased awareness of IBD, education for primary care and other specialties, and systems in place to support rapid initiation of treatment.

Appropriate Therapy Selection

There are a number of different ways in which 5-ASA-based treatments can be delivered, including rectal systems (enemas and suppositories), pH-triggered (delayed release) and sustained-release systems, and prodrugs.

It is important to consistently choose the correct therapy, at the right time, with the correct dose, and correct mode of delivery. Regarding dose, evidence from a randomised, controlled trial in 386 patients with mild-to-moderate UC (ASCEND II) suggests that treatment with oral 5-ASA at a dose of 4.8 g/day may provide greater overall improvement than a dose of 2.4 g/day after 6 weeks (success rate: 72% versus 59%, respectively; p=0.036).[10] In terms of delivery, enemas may not provide effective delivery of 5-ASA to the rectum but their combination with oral therapy may be effective. Significantly higher improvement rates were achieved after 4 weeks of treatment with a combination of oral 5-ASA 2.0 g twice daily (BID) and an enema of 5-ASA 1.0 g each evening versus monotherapy (89% versus 62%, respectively; p=0.0008) in a randomised study in ambulatory patients with mild-to-moderate UC (n=127).[11] Finally, there is some evidence that an extended duration of 5-ASA treatment is beneficial. In a single-arm study that enrolled patients with UC who had previously failed to achieve remission after 8 weeks in two Phase III trials (N=304), 59% achieved remission after a further 8 weeks of treatment with mesalazine 4.8 g/day, regardless of initial treatment assignment (Figure 1).[12]

Addressing the Problem of Non-Adherence

The World Health Organization (WHO) has estimated that approximately 50% of medicines prescribed for long-term illnesses are not taken as directed.[13] Adherence to 5-ASA therapy can be suboptimal outside of clinical trials, especially in patients in symptomatic remission. Average adherence rates have been reported as 80% in clinical trials compared with 40–60% in community-based trials.[14] Non-adherence to prescribed therapy has a clinical and economic impact: an approximate 4 to 5-fold increased risk of relapse and higher overall medical costs have been reported with non-adherence compared with good adherence in a systematic review of randomised controlled trials.[15]

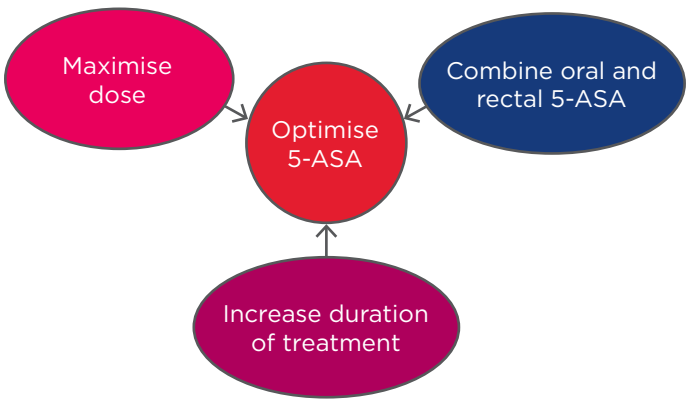

Figure 1: Optimising 5-ASA treatment in patients with mild-to-moderate ulcerative colitis.[10-12]
5-ASA: 5-aminosalicyic acid.

Predictors of non-adherence in chronic disease include patient beliefs, lack of perceived necessity, perceived therapeutic effects (or a lack of), tolerability concerns, and depression.[13] Consequently, approaches to improve adherence involve motivating and educating patients to change their behaviour (e.g. by informing them about their disease and the benefits of maintaining remission), treatment of depression, and efforts to reduce treatment complexity.[15,16] The long-term benefits of simplifying dosing regimens in UC are not yet clear. In a small pilot study, patients with UC were randomised to mesalazine QD (n=12), or mesalazine BID or thrice daily (TID [n=10]). At 3 months, adherence was significantly higher in the QD dosing group versus the conventional BID/TID dosing group (100% versus 78%; $p<0.05$); however, at 6 months, there was no significant difference in adherence between the two groups (75% versus 70%, respectively).[17]

Ongoing Monitoring

Appropriate monitoring, treatment escalation where required, and having a suitable care system for the practice setting are also critical factors for effective management of UC. With increasingly busy clinics, remote monitoring systems (telephone, internet) and the utilisation of IBD nurses can help to address the challenges of face-to-face consultations.

Fatigue, pain, and faecal urgency remain significant issues for patients with UC even when in remission. Faecal urgency or incontinence is experienced by 66% of patients in remission but often goes unreported and physicians may not always ask.[18] It is important to clarify what symptoms are a priority for the patient as part of ongoing monitoring, so that they can be managed appropriately.

It is important to note that not all symptoms are due to inflammation; other causes (e.g. bile salt malabsorption) should be considered and investigated following a clear algorithm. Ideally, all available tools should be employed in the ongoing management of UC, including diet counselling, loperamide, anti-depressants, and psychological therapy, where required.

In conclusion, if healthcare professionals managing patients with UC raise their expectations of what can be achieved, patients' expectations will in turn be increased.

Success Factors in Treatment of Uncomplicated Crohn's Disease

Doctor Pieter Hindryckx

CD is a relapsing, inflammatory disease affecting the mucosa and tissue of the gastrointestinal tract that can be broadly classified as complicated or uncomplicated. Uncomplicated disease is generally defined in the literature as CD without bowel damage (no stricture, abscess, or fistula) that does not require surgery.[19] This definition corresponds with the B1 behaviour phenotype of the Montreal classification system, which also assesses disease location and age of onset.[2] Uncomplicated CD accounts for the majority (70–80%) of cases at diagnosis, however CD is a progressive disease and some patients will develop strictures and/or penetrating disease over time.[20,21]

IDENTIFYING PREDICTORS OF COMPLICATED DISEASE

When tailoring a therapeutic strategy for CD, the aim should be to avoid both undertreatment of patients at risk of complications, and overtreatment of patients with uncomplicated disease, which may pose an unnecessary risk of side effects and be associated with unnecessary expense. It is therefore helpful to be able to identify patients at risk of a complicated disease course.

Age at Onset

Disease course differs by age at diagnosis. For patients with elderly-onset CD, disease behaviour is stable over time, whereas for patients with paediatric-onset CD, the likelihood of progressing to complicated disease is higher. In a French registry study that followed more than 8,000 patients with CD, the proportion of elderly-onset patients (n=367) with an inflammatory phenotype (uncomplicated) was 78% at diagnosis and remained over 60% throughout the observation period (68% after 15 years). In contrast, in the paediatric-onset patients (n=689), the proportion with a stricturing or penetrating phenotype increased from 23% and 4% (at diagnosis), respectively, to 39% and 32%, respectively, after 20 years.[22]

Disease Location

The relationship between disease location, ileal involvement in particular, and risk of complications has been established in several studies,

including an American cohort study (N=248).[23] Researchers found that the risk of developing an intestinal complication increased by approximately 6-fold in patients with ileocolonic disease, 9-fold in patients with ileal disease alone, and 12-fold in patients with upper gastrointestinal involvement when compared with patients with colonic disease.[23] Ileal involvement has also been shown to increase the likelihood of requiring surgical treatment.[24]

Smoking Status

Smoking is a well-known risk factor for CD. A recent meta-analysis of 33 prospective studies has confirmed that smoking is associated with increased risks of flares, surgery, relapse after surgery, and requirement for a second surgery.[25]

Colonic Ulcers

The presence of deep colonic ulcers at diagnosis has been shown to be associated with increased risk of penetrative complications and colectomy over time in a retrospective study, which included 102 patients with CD.[26]

Predicting Uncomplicated Disease

It is also helpful to identify predictors for uncomplicated CD. As part of a retrospective study including 162 newly diagnosed patients, a multi-parameter scoring system for predicting uncomplicated CD (based on age, mean C-reactive protein concentration, endoscopic severity, perianal lesions, and combined risk of complications) has been developed by Kruis et al.[27] Such a scoring system could potentially help to avoid overtreatment of patients who do not require aggressive therapy. However, prospective studies are needed to confirm predictors of uncomplicated CD.

USING THE CORRECT DRUGS AT THE RIGHT DOSE AND TIME

Using the correct drugs at the right dose and time is a fundamental principle in the management of IBD, including CD. Treatment of CD with conventional corticosteroids (e.g. prednisone) can be associated with poor tolerability. Budesonide, a corticosteroid with high topical activity but low systemic activity, is associated with a lower risk of corticosteroid-related adverse events than conventional corticosteroids.[28] While unsuitable as a maintenance therapy for CD,[29] a volume of clinical data support budesonide as an effective treatment for induction of remission.

Clinical Data on Budesonide

Early trials demonstrated superior efficacy for induction of remission of budesonide compared with placebo[30] and 5-ASA,[31] and similar efficacy to prednisone.[32] More recently, a meta-analysis confirmed a trend towards superior efficacy of budesonide over 5-ASA for active ileocaecal CD, with no significant difference between the efficacy of budesonide and conventional steroids.[28] However, this meta-analysis also confirmed that conventional steroids have superior efficacy to budesonide in the subgroup of patients with severe ileocaecal CD.

Regarding dosing frequency, budesonide 9.0 mg QD has been demonstrated to provide comparable efficacy in terms of clinical remission to 3.0 mg TID dosing, with similar tolerability over 8 weeks in a randomised, controlled trial that included patientswith mild-to-moderately active ileocaecal CD (n=471).[33]

Evidence-Based Treatment Guidelines

Treatment guidelines prepared by ECCO for different CD severities reflect the published literature. These guidelines recommend budesonide 9.0 mg daily as a first-line treatment for mildly active ileocaecal CD. Patients with moderately active ileocaecal CD can also be treated with budesonide 9.0 mg/day or, alternatively, with systemic corticosteroids. Initial treatment with systemic corticosteroids is recommended for severely active ileocaecal CD. For colonic disease, ECCO recommends systemic corticosteroids or, if only mildly active, sulfasalazine.[34]

Therapeutic Strategy Based on Risk Stratification

When deciding on a treatment strategy for an individual patient, it is important to consider risk stratification (Table 1). Patients with a low risk of complications can probably be treated conservatively based on symptoms, while patients with a high risk of complications may be treated more aggressively with maintenance therapy to prevent further complications.

Patient Case Example One: Uncomplicated Crohn's Disease

A 45-year-old female was diagnosed with ileal CD in 1996 and received treatment with budesonide. Two years later, the patient experienced a flare and again received budesonide. She was also started

on azathioprine as a maintenance therapy. In 2002, she experienced another flare, which was treated with budesonide as previously. Poor adherence to the maintenance therapy was noted. Ten years later, the patient presented as an outpatient with abdominal cramps and watery diarrhoea (>6 bowel movements per day in the past month). She was not taking maintenance therapy and reported two episodes of similar complaints in the past 5 years. Ileocolonoscopy showed isolated aphthous ileitis. Applying risk stratification, the conclusion would be that the patient is at low risk of complications and treatment should focus on addressing her symptoms.

Patient Case Example Two: Complicated Crohn's Disease

In 2012, a 22-year-old female was diagnosed with ileal CD with an intra-abdominal abscess and immediately underwent ileocaecal resection. One year later, results from a postoperative ileocolonoscopy were reassuring and no maintenance therapy was prescribed. However, in 2014, the patient presented with abdominal cramps and watery diarrhoea (>6 bowel movements per day in the past month). Ileocolonoscopy showed isolated aphthous ileitis. Applying risk stratification in this case, the conclusion would be that based on the patient's previous surgery, she is at high risk of further complications and should be prescribed a maintenance therapy.

PATIENT EMPOWERMENT

Communicating with patients and obtaining their commitment to a therapeutic approach is key to ensuring success. It is important to educate patients and their families on why they are receiving a particular drug and what the expected effects are. Patients' own ideas, expectations, and concerns should also be explored in order to empower them to feel involved in their treatment. In addition to pharmacotherapy, patients' emotional and psychological well-being should be supported, as necessary.

A study of risk-benefit preferences in patients with CD has reported improved daily symptom severity to be the main determinant of treatment satisfaction, while effect on complications and time to next flare were less important.[35] Interestingly, patients in this study were willing to accept some increase in risk of adverse events in favour of clinical efficacy. These findings highlight the importance of factoring patient perspectives and preferences in decision-making.

A useful mnemonic is COPE: Communicate with patients; Obtain commitment to therapeutic objective; Promote emotional/psychological/physical support; Educate the patient and their family.

Identifying Patients Likely to be Non-Adherent

As with many chronic diseases, poor adherence is a problem in IBD, reported in approximately 30–40% of patients on maintenance therapies.[36] For successful management of CD, it is important to identify patients likely to be non-adherent and the drivers of their non-adherence. These may include: young age, diagnosis more than 5 years ago, outpatient status, patient attitudes, and concerns regarding side effects.

There are many practical strategies to tackle non-adherence and the IBD nurse can play an important supporting role in this area.

Table 1: Therapeutic strategy according to risk stratification.

Low probability of complications	High probibility of complications
Mild disease	Severe disease
Non-smoking	Smoking
Elderly onset	Early onset
Long-term inflammatory disease behaviour	Previous surgery
Pure colonic disease (L2)	Stricturing of penetrating disease behaviour
	Ileal disease (L1, L3)
Conservative treatment (symptom-based)	**Aggressive treatment**

L1: ileal location; L2: colonic location; L3: ileocolonic location (Montreal classification system).

Educational interventions to improve patients' knowledge of IBD, the benefits of treatment, potential side effects, and consequences of non-adherence is one strategy. Other approaches include behavioural interventions such as simplified medication regimens or reminder systems, cognitive behavioural interventions to address barriers to adherence, and motivating patients to seek help and individually identify their own priorities and goals.[37]

Smoking Cessation

A clear effect of smoking cessation on the course of CD has been demonstrated in a cohort study of 474 patients. Over a median follow-up period of 29 months, the risk of a flare in patients who had stopped smoking for 1 year was similar to that of non-smokers, and significantly less than in continuing smokers ($p<0.001$). Similarly, stopping smoking was associated with reduced need for steroids and immunosuppressive therapy.[38]

A separate study has shown that most patients with CD may not be aware of the impact of smoking on their disease.[39] Therefore, there is room to improve education of patients and their families on the risks of smoking.

CONCLUSIONS

In summary, to optimise treatment of uncomplicated CD, the correct drugs must be used in the right way and at the right time; patients must be treated according to risk stratification with the dual aim of preventing damage by undertreating and minimising harm associated with overtreatment; and lastly, all patients should be empowered to take an active role in their disease, identifying and addressing their individual concerns and expectations.

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