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Ulcerative colitis: STRIDE-ing beyond symptoms with new standards

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ABSTRACT

The landscape of ulcerative colitis has changed in the last two decades. Advancements in pharmacotherapeutics have heralded the introduction of new treatment options, with many agents in development. Better clinical outcomes are seen with tighter disease control, made possible with greater understanding of inflammatory pathways and their blockade with drugs. There has been a resultant shift in treatment targets, beyond symptoms to endoscopic and histological healing. Controlling the burden of disease activity also lowers the risk of developing colorectal cancer. Colorectal cancer screening now requires the use of dye-based agents and high definition colonoscopy to improve detection of colonic neoplasms.

Keywords: biologic therapy, biosimilars, inflammatory bowel disease, treat to target, ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) is an idiopathic chronic inflammatory bowel disease (IBD) characterised by a chronic relapsing clinical course that runs a spectrum from asymptomatic histological remission to florid macroscopic inflammation of the colon. The plethora of translation research and new pharmacotherapies in the last two decades has dramatically changed the landscape of UC. Over the course of 20 years, we have moved beyond symptom resolution to endoscopic remission as a treatment goal, and beyond immunomodulators to biologics to achieve mucosal healing. In this narrative review, we look at the current landscape of UC and recent updates that will be useful for practising gastroenterologists who care for these patients.

BEYOND SYMPTOMS

The therapeutic goal has shifted towards mucosal healing, with the hope of preserving long term gut function. This evolution of endpoints has paralleled other immune mediated diseases such as rheumatoid arthritis. Continuous subclinical inflammation that is not well controlled increases risk of developing disease related complications.

The natural history of UC is varied among patients, but most will experience disease flares or progression during their clinical course. Approximately a third of patients with UC will have extension during their disease course. A recent meta-analysis reported 21-34% of patients with left sided colitis will go on to develop extensive colitis. Cumulative 5-year risk of anatomical progression is approximately 13%.⁽¹⁾ Approximately 15% of patients will go on to require surgery 10 years after diagnosis,⁽²⁾ although lower figures have been quoted in Asian studies.⁽³⁾ Several studies have demonstrated the importance of looking beyond clinical symptoms, to achieve and maintain endoscopic healing.⁽⁴⁾ A recent retrospective analysis showed discordance between symptoms and mucosal inflammation on endoscopy, highlighting the importance of objective documentation of remission on both aspects.⁽⁵⁾ Endoscopic remission has been shown to predict better long term outcomes⁽⁶⁾ (Fig. 1).

This has motivated a shift towards a treat-to-target (T2T) strategy, for long-term prevention of disease complications such as hospitalisations, colorectal neoplasia and colectomy. In T2T, therapeutic targets of both symptomatic remission and endoscopic healing were proposed by the Selecting Therapeutic Targets in IBD⁽⁷⁾ (STRIDE) committee in 2015 and updated to STRIDE-II in 2021.⁽⁸⁾ The update proposed a change to a spectrum encompassing short term, intermediate and long term goals in the care of IBD patients. In the STRIDE-II recommendations, short term targets include symptomatic response and remission in patient reported outcomes (PRO), with normalisation of C-reactive protein (CRP) to under the upper limit of normal. Intermediate targets are decrease in faecal calprotectin (FC) to

acceptable range (100-250 $\mu\text{g/g}$), and in paediatric patients, the restoration of normal growth. Long term treatment goals are endoscopic healing (Mayo endoscopic subscore [MES] =0 or Ulcerative Colitis Endoscopic Index of Severity [UCEIS] ≤ 1), normalisation of quality of life (QoL) and the absence of disability. (Fig. 2) The concept of complete endoscopic healing (MES=0) (Fig. 3a-3d) has been proposed as the new treatment target in STRIDE II. It has been associated with superior disease outcomes⁽⁹⁾, better PRO scores⁽¹⁰⁾ and lower FC levels.⁽¹¹⁾

STRIDE-II introduced serum and faecal inflammatory biomarkers as intermediate treatment targets. FC, CRP and erythrocyte sedimentation rate (ESR) have all been employed in monitoring of disease activity in IBD. The ease of collection and low cost of these non-invasive markers position them as ideal modalities for monitoring of response post induction and during the disease course. Although all three investigations can predict endoscopic activity in UC, FC appears to be more sensitive than CRP or ESR.^(12,13) The correlation of FC with disease activity, endoscopic and histological indices has been reported in both adult and paediatric populations. The interval increase between two measurements of FC may predict flares before the development of clinical symptoms.⁽¹⁴⁾ However, the role of FC in predicting complete clinical remission still requires further evaluation⁽¹⁵⁾. Various studies have proposed differing cut-offs for both endoscopic and histological healing,^(16,17) with some showing utility of FC level of ≤ 168 $\mu\text{g/g}$ for predicting sustained clinical response at 1 year (83% sensitivity and 74% specificity) and ≤ 121 $\mu\text{g/g}$ for predicting endoscopic healing (79% sensitivity and 57% specificity). Thus, the STRIDE-II recommends a normalisation of FC to 100-250 $\mu\text{g/g}$ as an intermediate treatment target.

Patients in histologic remission tend to have a more favourable disease course with better quality of life. They are more likely to be symptom-free, with lower risk of relapse, hospitalisation, surgery and colorectal cancer. However, the evidence to support its utility in regular clinical practice is lacking and there are obstacles to applying histologic remission as a

target. Difficulties in application include the lack of a uniform, validated histologic scoring system, wide inter-observer variability⁽¹⁸⁾ and microscopic heterogeneity.⁽¹⁹⁾ Additionally, histological remission is a high bar to achieve, and has to be balanced against cost and risk of therapy escalation to attain this. Future research is also needed to determine if this stringent target justifies the increased utilisation of medical treatment. Considering these factors, histologic remission may be a goal in the foreseeable future, but not at present. It has thus, been included in the STRIDE-II as target to consider but not a formal treatment target (Fig. 2). Precision medicine in UC is a developing field, with the hopes of identifying patients who are likely to benefit from aggressive treatment and sparing those who would not require escalation of therapy.

The T2T concept has been introduced into clinical practice and patient education is pivotal. The traditional objective of therapy has been clinical remission, which is immediately appreciable by patients. However, a recent study showed one-third of patients remain unconvinced on the need for a treat to target approach. Patients with better adherence to therapy were more likely to accept this strategy, whereas age, disease phenotype or patient-reported state of disease did not affect acceptance.⁽²⁰⁾ In a time when information is readily available with instantaneous Internet searches, patient engagement will go a long way towards achieving these new targets set by STRIDE-II.

BEYOND IMMUNOMODULATORS – BIOSIMILARS, ANTI-INTEGRIN AND ORAL SMALL MOLECULES

With the increasing relevance of the T2T strategy and focus on histological remission, physicians rely on an ever-growing armamentarium of therapeutic advancements to achieve this. For most patients with UC, anti-inflammatory and immunosuppressive agents such as

aminosalicylates and thiopurines are still cost effective and efficacious. There remains a group of patients for whom more aggressive pharmacotherapeutic agents are required.

In 1998, United States Food and Drug Administration (FDA) approved the first biologic for IBD, anti-tumour necrosis factor α (anti-TNF) infliximab, which heralded the biologic era. Subsequent anti-TNF agents such as adalimumab and golimumab have since become available.⁽²¹⁾ The recent decade also saw the introduction of biosimilar agents. Biosimilar therapies are defined by the FDA as a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and for which there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product.⁽²²⁾ Multiple clinical studies have compared the anti-TNF biosimilar CT-P13 with infliximab with both controlled trials and observational studies showing non-inferiority and comparable safety profiles, supporting its use in IBD.⁽²³⁻²⁵⁾ A major push factor for switching from originator biologics to biosimilars is cost reduction, allowing for greater patient access. The decision to switch to a biosimilar should be personalised to the individual patient. In Singapore, the biosimilar for infliximab, Remsima (CT-P13) has been assessed by the Agency of Care Effectiveness (ACE) to be cost-effective and in 2018, has been included in Medical Assistance Fund (MAF) list of subsidised drugs.⁽²⁶⁾ As of September 2020, Amgevita, the biosimilar for adalimumab, has also been approved for use in IBD in Singapore by the ACE under MAF.⁽²⁷⁾

Anti-TNF agents are not without their issues, including loss of response to therapy, infection and malignancy risks.^(28,29) This has led the push towards the development of safer agents with gut selective target receptor inhibition.⁽³⁰⁾ The development and introduction of vedolizumab, a monoclonal antibody which inhibits the gut-selective $\alpha^4\beta^7$, has become a mainstay in the treatment of UC. The GEMINI I study showed evidence supporting efficacy of vedolizumab for inducing clinical remission (placebo[%] vs treatment[%]: 25.5 vs 47.1;

p<0.001) and mucosal healing (placebo[%] vs treatment[%]: 24.8 vs 40.9; p=0.001).⁽³¹⁾ However, in those with prior anti-TNF exposure, a subgroup analysis showed lower rates of clinical remission and mucosal healing. The VARSITY trial compared the efficacies of vedolizumab and adalimumab. It demonstrated higher rates of clinical remission and endoscopic improvement in the patients who received vedolizumab.⁽³²⁾

Ustekinumab is a monoclonal antibody directed at the IL-12/IL-23 pathway. Recent data demonstrates efficacy in moderately severe UC. In the phase III induction RCT (UNIFI trial), ustekinumab met the primary endpoint of clinical remission at 8 weeks, with rates of 15.6% (p<0.001), 15.5% (p<0.001) and 5.3% in the fixed dosing group, body weight based dosing group and placebo group respectively.⁽³³⁾ Of interest, it is the first RCT in UC to include histological remission as a primary endpoint, signalling a shift for therapeutic goals. As of October 2019, Ustekinumab has been licensed for UC by the FDA and is available in Singapore.

Another therapeutic agent available in Singapore is tofacitinib, an oral small-molecule pan-Janus kinase (JAK) inhibitor, which was shown to be effective in both induction and maintenance of remission in UC. The OCTAVE induction trial showed efficacy of tofacitinib in both achieving remission (placebo[%] vs treatment[%] - OCTAVE 1: 8.2 vs 18.5; OCTAVE 2: 3.6 vs 16.6) and mucosal healing (placebo[%] vs treatment[%] - OCTAVE 1: 15.6 vs 31.3; OCTAVE 2: 11.6 vs 28.4).⁽³⁴⁾ A network meta-analysis showed that in biologic experienced patients, there was a greater likelihood of achieving clinical response and endoscopic remission with JAK inhibitors as compared with 2nd line biologic agents.⁽³⁵⁾ Treatment with a JAK inhibitor was associated with significantly increased risk of thromboembolic events and infection, especially herpes zoster. In OCTAVE, there was also elevated serum lipid concentrations reported in patients on tofacitinib but this was deemed unlikely to be of clinical significance. A second meta-analysis from the United Kingdom comparing tofacitinib and

other biologics proposed that it may be a cost-effective option,⁽³⁶⁾ although this needs to be further evaluated in our local context. In particular, the JAK inhibitors may find favour with patients due to ease of oral administration.

Looking ahead, there are a few therapies on the horizon for ulcerative colitis. Upadacitinib, an oral selective JAK-1 inhibitor, showed promise in a phase 2b trial (U-ACHIEVE), achieving clinical remission in 8.5% ($p=0.052$), 14.3% ($p=0.013$), 13.5% ($p=0.011$) and 19.6% ($p=0.002$) of patients receiving doses of 7.5 mg, 15 mg, 30 mg, and 45 mg once daily respectively, as compared to 0% of patients receiving placebo.⁽³⁷⁾ Another identified target receptor is the p19 subunit of IL-23. Risankizumab and mirikizumab are monoclonal antibodies directed against the p19 sub-unit.⁽³⁸⁾ Phase 2 studies for mirikizumab in patients with moderate to severe ulcerative colitis showed promise, with 15.9% ($p=0.066$), 22.6% ($p=0.004$), and 11.5% ($p=0.142$) of patients in the 50mg, 200mg, and 600mg groups achieving clinical remission respectively, compared to 4.8% of patients given placebo.⁽³⁹⁾ Two new promising oral therapeutic agents have also emerged - filgotinib and ozanimod. Filgotinib is also an oral selective JAK-1 inhibitor which has shown promise, with lower risk of zoster and venous thromboembolism, as compared to tofacitinib. The SELECTION trial, a phase2b/3 trial for filgotinib, involved two cohorts; patients with moderate to severe UC, who were biologic naïve but failed conventional therapy, and those who failed previous biologics.⁽⁴⁰⁾ In both cohorts, a greater proportion of patients who received 200mg/day of filgotinib achieved both clinical, and endoscopic remission at week 10 ([biologic naïve group, treatment vs placebo] 26.1% vs 15.3%, 95% CI 2.1–19.5, $p=0.0157$; [biologic experienced group, treatment vs placebo] 11.5% vs 4.2%, 7.2%; 95% CI 1.6–12.8, $p=0.0103$). In the maintenance phase, subjects on filgotinib 200mg/day also had increased rates of response compared to placebo (6-month corticosteroid-free remission; treatment vs placebo: 27.2% vs 6.4 [$p=0.005$], endoscopic remission; 15.6% vs 6.1% [$p=0.0157$], histological remission; 38.2% vs 13.3% [$p<0.0001$]).

Ozanimod is an oral small molecule agent, a selective sphingosine-1-phosphate receptor modulator. Data on ozanimod in patients with moderate to severe UC was also recently published in the phase 3 True North study.⁽⁴¹⁾ This study included both biologic-naïve and -experienced patients. In the induction phase, there was significantly higher incidence of clinical response ([treatment vs placebo] 47.8% vs 25.9%, $p < 0.001$) and clinical remission ([treatment vs placebo] 18.4% vs 6.0%, $p < 0.001$). In the maintenance phase, there was also increased rates of clinical remission (37.0% vs 18.5%, $p < 0.001$), clinical response (60.0% vs 41.0%, $p < 0.001$) and endoscopic remission (29.6% vs 14.1%, $p < 0.001$).

Further studies are currently ongoing. Even with newer biologic therapies, a large proportion of patients do not achieve endoscopic remission. Although it still eludes us at present, the ideal drug would be affordable, easy to administer and have excellent efficacy along with minimal systemic side effects.

BEYOND STANDARD COLONOSCOPY – IMAGE ENHANCED ENDOSCOPY IN UC

Patients with longstanding IBD with pancolitis have an increased risk of developing colorectal cancer (CRC)⁽⁴²⁾ with an estimated standardised incidence ratio (SIR) of 2.4.⁽⁴³⁾ Most major consensus guidelines recommend that surveillance should be initiated after 8 years of onset of symptoms. Factors increasing risk of CRC include diagnosis at a young age, longer duration of disease, severity and extent of inflammation, family history of CRC and concomitant primary sclerosing cholangitis. Dysplasia in IBD was once difficult to detect, and white light endoscopy (WLE) with random 4-quadrant biopsies for every 10cm of the colon was previously recommended to screen for dysplasia.⁽⁴⁴⁾ Detection of dysplasia should prompt consideration of either endoscopic resection or colectomy. With better endoscopic technology, detection and characterisation of colonic dysplasia is easier and we have moved away from non-targeted random biopsies and colectomy.

The role of random biopsies has been subject to much research and controversy with regards to detection of dysplastic lesions. An RCT comparing dysplasia detection with random versus targeted biopsies found non inferiority between random and targeted biopsy groups, but those undergoing random biopsies had longer procedure times and more specimens passed for histological examination.⁽⁴⁵⁾ Random biopsies were predicated on the concept that invisible dysplasia is common in IBD. Improvements in endoscopic equipment and introduction of high definition (HD) WLE has reduced the additional benefit that random biopsies provided in the era of standard definition (SD) WLE (Fig. 4a & 4b).⁽⁴⁶⁾

In 2015, SCENIC⁽⁴⁷⁾ recommended the use of dye-based chromoendoscopy (DCE) over WLE for surveillance when using either high definition (HD) or standard definition (SD) colonoscopy. Since the introduction of the SCENIC guidelines, more data has emerged comparing benefit of DCE with electronic virtual chromoendoscopy (VCE). Meta-analyses have shown superiority of DCE over SD-WLE, but no difference when comparing DCE to other techniques.^(48,49) Subsequent RCTs in 2018 showed that standard HD-WLE and VCE were non inferior to DCE in detection of dysplasia^(50,51). Further studies are required to ascertain the best and most cost-effective modality for surveillance. We recommend the use of either HD-WLE or DCE over SD-WLE when screening for colitis associated dysplasia.

An initial meta-analysis in 2001 reported cumulative probabilities of development of CRC to be 2%, 8% and 18% at 10, 20 and 30 years from diagnosis respectively.⁽⁴²⁾ A later report in 2013 demonstrated decreasing incidence of CRC, quoting cumulative risks at 1%, 2% and 5% after 10, 20 and > 20 years of disease duration.⁽⁵²⁾ Two large case series have also demonstrated patients who underwent surveillance had improved survival due to early detection of CRC.^(53,54) It is unclear if the reduction in CRC incidence can be attributed purely to surveillance programmes alone, or if other factors such as better disease control may also have a contributing role. Although unequivocal evidence for the benefit of surveillance

colonoscopy is lacking, the practice of screening for CRC in patients with longstanding UC is still recommended by experts.⁽⁵⁵⁾

CONCLUSION

In the last 2 decades, we have moved from clinical remission to endoscopic remission as a treatment target, with the shift culminating in better outcomes for patients with resolution of colonic inflammation. Newer, novel agents lead the push towards more stringent therapeutic endpoints. However, the use of aggressive treatment must always be weighed against the cost and risk of systemic immunosuppression. Finally, standard colonoscopy is no longer sufficient for CRC screening in UC, with high definition white light endoscopy with or without dye based chromoendoscopy being the new standard of care.

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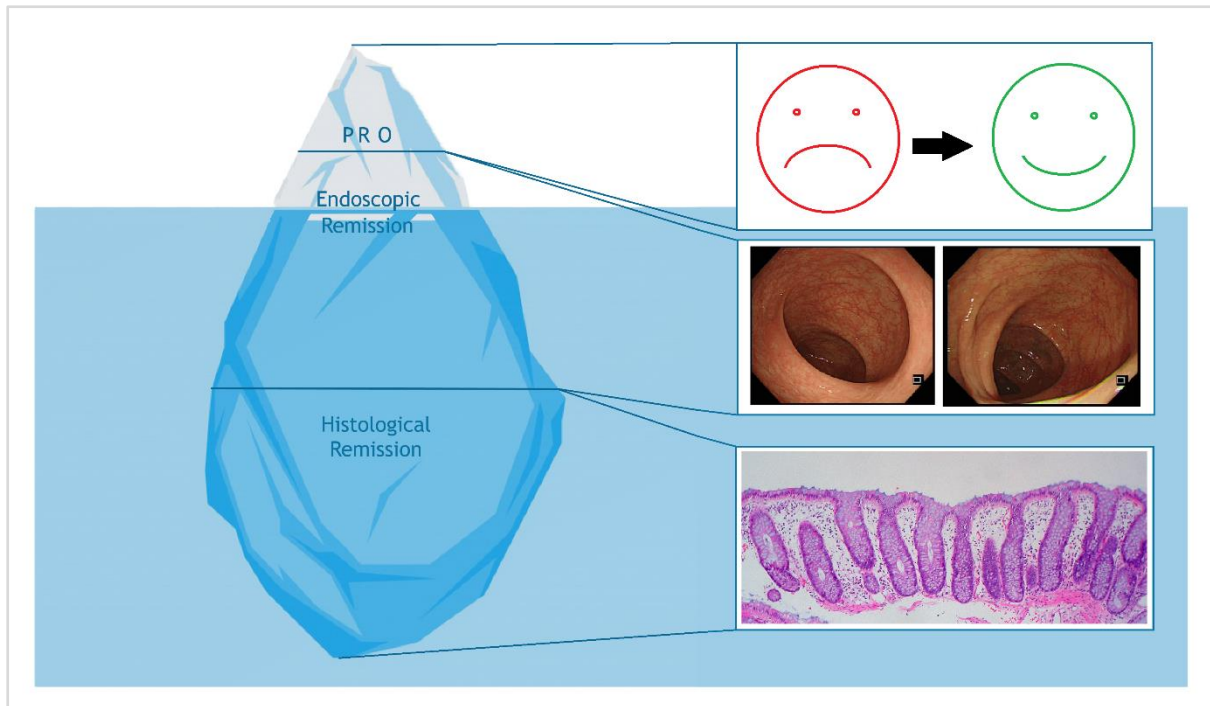


Fig 1. Disease clearance and depth of remissions in ulcerative colitis. Clinical remission using patient reported outcomes (PRO) is only the tip of the iceberg. Achieving endoscopic remission is the current standard of care. Histological remission may be the next defining target in disease management. [Adapted from Danese et al⁽²¹⁾]

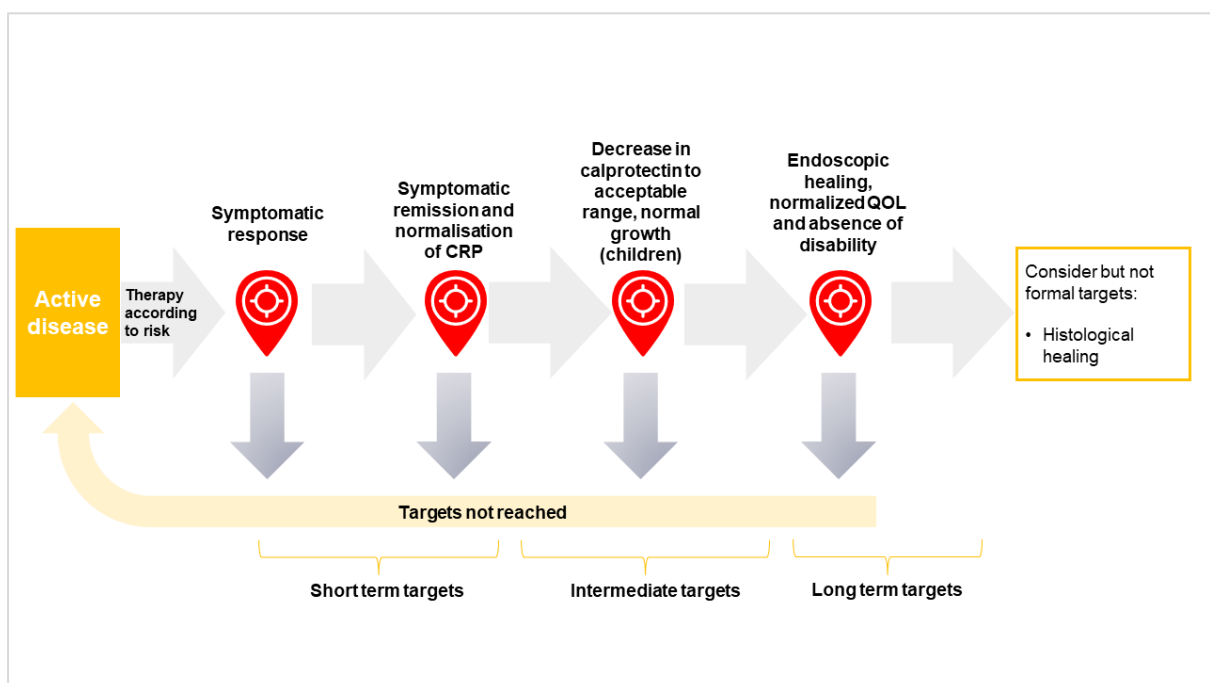


Fig. 2. Summary of STRIDE II recommendations for ulcerative colitis. [Adapted from Turner et al⁽⁸⁾]

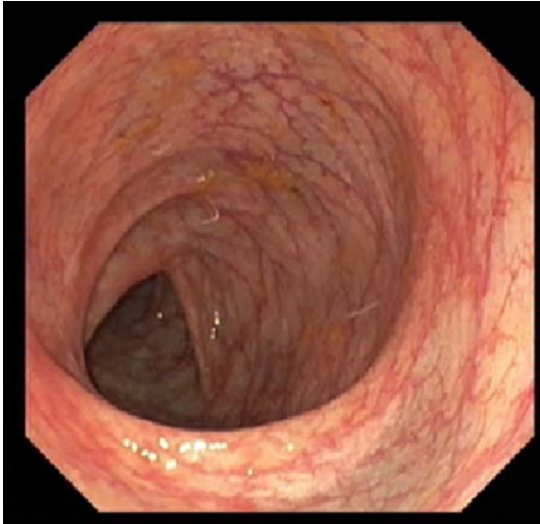


Fig 3a Endoscopic remission: Normal looking mucosa, with preserved vascular pattern, absence of erosions and bleeding. (Mayo sub score 0)



Fig 3b Endoscopic remission: Erythema, decreased vascular pattern and friable mucosa. (Mayo subscore 1)

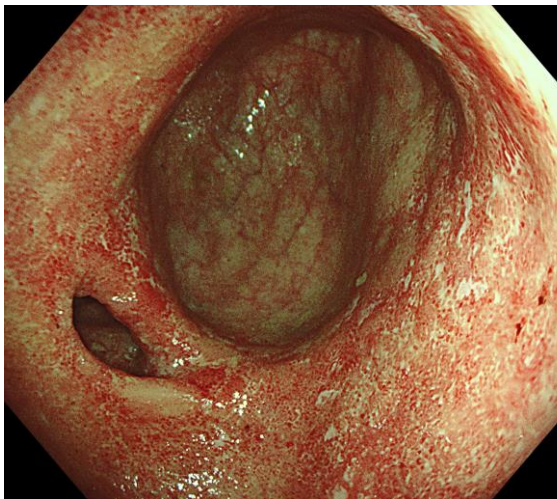


Fig 3c Active disease: Patulous ileocaecal valve from chronic inflammation. Marked erythema, absent vascular pattern, erosions. (Mayo subscore 2)



Fig 3d Acute severe ulcerative colitis, with spontaneous bleeding and deep ulcerations. (Mayo subscore 3)

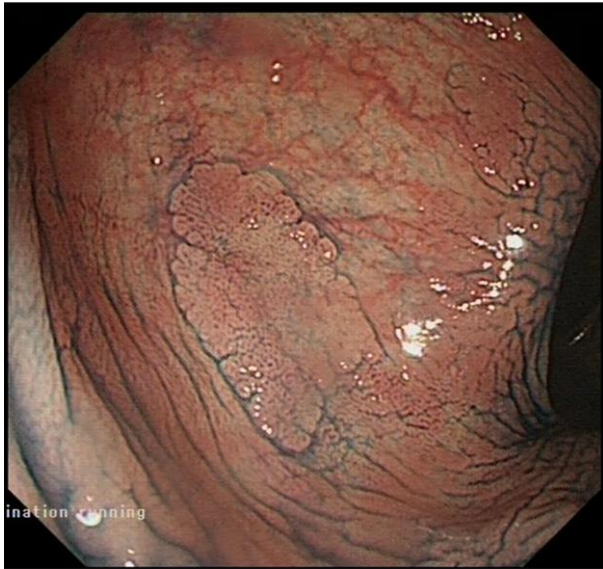


Fig. 4a Dye-based chromoendoscopy with indigocarmine: Well demarcated borders of a flat polyp.



Fig. 4b Virtual chromoendoscopy with NBI: Serrated epithelial changes and low grade dysplasia in a patient with long standing ulcerative colitis.