ABSTRACT
Management of ulcerative colitis is determined by disease severity, extent of disease, frequency of relapses, prior drug therapy and presence of complications. A step-up approach in treatment is usually followed with algorithmic use of aminosalycilates, corticosteroids, azathioprine and biological or surgery. The concept of mucosal healing and advent of effective biologicals is bringing about a paradigm shift in our treatment goals and approach to ulcerative colitis. There is emerging evidence that early use of biological can induce rapid and sustained mucosal healing leading to a favourable alteration in natural course of the disease. There are strong limitations to this step-down approach including definition and assessment of mucosal healing, opportunistic infection with biological and prohibitive cost of these drugs. There is a strong need for further studies to establish that step-down approach with early use of biologicals can alter the course of ulcerative colitis can be recommended for all cases. At this stage it is best reserved for severe and predicted severe cases of ulcerative colitis.

INTRODUCTION
Ulcerative colitis (UC) is a chronic disease characterized by diffuse inflammation of the large gut. Rectum is involved in over 95% of patients with variable proximal progression in a symmetrical, circumferential and continuous manner to involve either part or entire colon. Treatment goals in UC have been to establish and maintain remission, improve quality of life, prevention of hospitalisation and colectomy. Conventional, step-up therapy with sequential and algorithmic use of steroids, aminosalicylic acid and immunomodulators like azathioprine is able to achieve this in only 60-80% of cases. The concept of mucosal healing has brought a paradigm shift in therapeutic goals and clinical endpoints in management of UC. There is growing evidence that mucosal healing can change the natural course of UC resulting in sustained remission and even prevention of colorectal carcinoma. In other words, if mucosal healing can be induced before irreversible mucosal damage due to chronic inflammation, natural course of UC can be altered for the better. Biologicals have the potential for early induction of mucosal healing. Whether its early use as in step-down therapy can alter the natural course of disease is a subject of intensive study in UC at this time.

ULCERATIVE COLITIS IN INDIA
Contrary to general perception, UC is relatively common with a reported incidence of 6.02/104/year and prevalence of 44.3/105 population. The incidence and prevalence is highest in for the Asian subcontinent and similar to prevalence in the West. The disease is limited to rectum in 18.3%, the left colon in 38.8% and involves the entire colon in 43.8%. The corresponding figures from the West are 30-60%, 16-40% and 18-35% respectively. The peak median age of onset is 2nd-3rd decade in India. The second peak in 6th decade as seen in the west has not been reported in Indian literature.

The clinical course in UC is characterized by exacerbations and remissions, often spontaneous and sometimes triggered by intercurrent infections, drugs or in response to treatment. This intermittent disease course is seen in 47.2% and a chronic continuous inflammatory course is seen in 35.5% of patients. Extension of disease, frequent relapses, acute severe colitis at onset and colectomy imply a severe disease. Predictive factors for severity include younger age of onset, female gender, early relapse, higher endoscopy score and non-smokers.

MUCOSAL HEALING – REALISTIC OR AN IDEAL GOAL
There is no universally accepted and validated definition of mucosal healing (MH). It usually denotes absence of mucosal lesions of UC on sigmoidoscopy or colonoscopy (loss of vascularity, erythema, erosions and ulcerations). International Organisation of IBD (IOIBD) Task Force defined mucosal healing in UC as the absence of friability, blood, erosions, and ulcers in all visualized segments of the colonic mucosa. Many clinicians accept MH even in presence of mild friability and erythema. Different endoscopic indices for determining MH in UC have been used in clinical trials. Mayo Endoscopy Score is the most widely used tool in clinical studies, however, Ulcerative Colitis Endoscopic Index of Severity (UCEIS) that takes into account vascularity, blood in lumen and erosions or ulcerations is the only score that has been validated clinically (Table 1).

It is accepted that clinical remission does not imply MH in UC. Clinical assessment underestimates disease activity as assessed by endoscopy or histology. Active endoscopic and histologic disease has been noted in 39% - 60% and 63% -90% of patients with UC in clinical remission respectively.

Recent studies have demonstrated conclusively that MH in UC results in decrease in corticosteroid use, decrease in hospitalisation rates, increase in sustained clinical
remission, decrease in colectomy rates and decrease in development of colorectal carcinoma. A recent meta-analysis that included 13 studies comprising 2073 patients with active UC showed that patients with MH had pooled odds ratio of 4.50 for achieving long-term clinical remission (95% CI, 2.12–9.52), 4.15 for remaining free of colectomy (95% CI, 2.53–6.81), 8.40 for achieving long-term MH (95% CI, 3.13–22.53), and 9.70 for achieving long-term corticosteroid-free clinical remission (95% CI, 0.94–99.67), compared with patients without MH. There was no difference in outcomes if patients achieved MH while receiving biologic versus non-biologic therapy.

MH is a logical end-point in treatment of UC. It can be conveniently assessed by endoscopy and biopsy. Since rectum is usually involved and the lesions are mucosal as well as continuous, a sigmoidoscopic examination is sufficient in most cases of UC to determine MH. Limitation is in developing a universally accepted and validated definition of MH.

CONVENTIONAL STEP-UP THERAPY
Management of UC is determined by severity and extent of disease, prior response to therapy and quality of life indices. A sequential algorithmic step-up treatment with 5-aminosalicylate (topical or systemic), corticosteroids (topical or systemic) and immunomodulators like azathioprine or methotrexate constitute the conventional therapy (Figure 1). Biologicals are added if conventional therapy fails to induce remission or maintain sustained remission. Surgery is reserved for patients with medical failure, complications and in fulminant acute colitis.

Mucosal healing by conventional treatment is 20% -71% depending on severity of disease, clinical end-point, choice of drug and dosage used. The wide variation in mucosal healing rates is largely due to heterogeneity of the studies with respect to subjects studied, definition of mucosal healing and inter observer variation.

BIOLOGICALS AND MUCOSAL HEALING
Advent of biologicals (Table 2) has brought in a paradigm shift in management of ulcerative colitis. The efficacy of these drugs in inducing clinical remission has prompted change in clinical end-points in therapy of UC. The concept of mucosal healing as a therapeutic end-point that can alter the natural course of the disease has gained ground with the introduction of these monoclonal antibodies.

Biologics (naive proteins, cytokines, growth factors, and antibodies) interfere with molecules that are involved in the disease pathogenesis. Initially, biologics targeting tumor necrosis factor-α (TNF α ) were approved for patients with persistent active disease despite conventional treatment. Subsequently, many novel biological therapies targeting different immunological pathways were introduced. All showed significant success in achieving sustained clinical remission or mucosal healing (Table 3).

<table>
<thead>
<tr>
<th>Descriptor (Score Most Severe Lesions)</th>
<th>Likert Scale Anchor Points</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular pattern</td>
<td>Normal (0)</td>
<td>Normal vascular pattern with arborization of capillaries clearly defined, or with blurring or patchy loss of capillary margins</td>
</tr>
<tr>
<td>Patchy obliteration (1)</td>
<td></td>
<td>Patchy obliteration of vascular pattern</td>
</tr>
<tr>
<td>Obliterated (2)</td>
<td></td>
<td>Complete obliteration of vascular pattern</td>
</tr>
<tr>
<td>Bleeding</td>
<td>None (0)</td>
<td>No visible blood</td>
</tr>
<tr>
<td>Mucosal (1)</td>
<td></td>
<td>Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away</td>
</tr>
<tr>
<td>Luminal mild (2)</td>
<td></td>
<td>Some free liquid blood in the lumen</td>
</tr>
<tr>
<td>Luminal moderate or severe (3)</td>
<td></td>
<td>Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa</td>
</tr>
<tr>
<td>Erosions and ulcers</td>
<td>None (0) Erosions (1)</td>
<td>Normal mucosa, no visible erosions or ulcers Tiny (&lt;5 mm) defects in the mucosa, of a white or yellow color with a flat edge</td>
</tr>
<tr>
<td>Superficial ulcer (2)</td>
<td></td>
<td>Larger (&gt;5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared with erosions, but remain superficial</td>
</tr>
<tr>
<td>Deep ulcer (3)</td>
<td></td>
<td>Deeper excavated defects in the mucosa, with a slightly raised edge</td>
</tr>
</tbody>
</table>
Fig. 1: Treatment of Ulcerative Colitis (Step-up approach)

**Table 2: Biologics in Ulcerative Colitis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TNF Inhibitors</td>
<td>Infliximab, Adalimumab, Golimumab</td>
</tr>
<tr>
<td>Anti-adhesion molecules</td>
<td>Natalizumab (recombinant IgG4 monoclonal antibody to α4 integrin)</td>
</tr>
<tr>
<td></td>
<td>Vedolizumab (anti α4β7 integrin antibody)</td>
</tr>
<tr>
<td></td>
<td>Etrolizumab</td>
</tr>
<tr>
<td>Janus kinase inhibitors</td>
<td>Tofacitinib</td>
</tr>
<tr>
<td>Others</td>
<td>Abatacept, Tocilizumab</td>
</tr>
</tbody>
</table>

Experience in India with biologicals is limited and is restricted to infliximab in published literature. Sood has reported reduction in colectomy in his patients with steroid refractory UC treated with infliximab. Adalimumab has been reportedly used in some centres.

Two randomized, double-blind, placebo-controlled trials, Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2), evaluated the efficacy of infliximab for induction and maintenance therapy in adults with moderate to severe ulcerative colitis. In each study, 364 patients with concurrent medications received placebo or infliximab (5 mg or 10 mg per kilogram of body weight) intravenously at weeks 0, 2, and 6 and then every eight weeks through week 46 (in ACT 1) or week 22 (in ACT 2). Patients were followed for 54 weeks in ACT 1 and 30 weeks in ACT 2. In ACT 1, 69% and 61% of patients who received 5 mg and 10 mg of infliximab respectively had a clinical response at week 8, as compared with 37% of those who received placebo (P<0.001 for both comparisons with placebo). In ACT 2, 64% and 69% of patients who received 5 mg and 10 mg of infliximab respectively had a clinical response at week 8, as compared with 29% of those who received placebo (P<0.001 for both comparisons with placebo). In both studies, patients who received infliximab were more likely to have a clinical response at week 30 (P<0.002 for all comparisons). In ACT 1, more patients who received 5 mg or 10 mg of infliximab had a clinical response at week 54 (45% and 44% respectively) than did those who received placebo (20%, P<0.001 for both comparisons). In the ACT-1 and ACT-2 trials, the proportion of patients in clinical remission at week 30 of therapy was 4-fold greater for patients with MH at week 8 (48.3 vs. 9.5%, respectively).

ULTRA 1 study concluded that ADA160/80 was safe and effective for induction of clinical remission in patients with moderately to severely active ulcerative colitis failing treatment with corticosteroids and/or immunosuppressants. It was an 8-week, multicentre, randomised, double-blind, placebo-controlled study in patients with moderate to severe UC non-responsive to conventional therapy. 390 patients were randomised (1:1:1) to ADA160/80, ADA80/40, or placebo. At week 8, 18.5% of patients in the ADA160/80 group (p = 0.031 vs placebo) and 10.0% in the ADA80/40 group (p = 0.833 vs placebo) were in remission, compared with 9.2% in the placebo group.

ULTRA 2 was a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of adalimumab in induction and maintenance of clinical remission in 494 patients with moderate-to-severe ulcerative colitis who received concurrent treatment with oral corticosteroids or immunosuppressants. Patients were stratified based on prior exposure to TNF-α antagonists (either had or had not been previously treated with anti-TNF-α) and randomly assigned to groups given adalimumab 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week or placebo. Primary end points were remission at weeks 8 and 52. Overall rates of clinical remission at week 8 were 16.5% on adalimumab and 9.3% on placebo (P =
Table 3: Efficacy of Biologics in Ulcerative Colitis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Protocol</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>ACT 1 (N=364) Mod-Severe</td>
<td>5mg/kg 0,2,6 weeks, every 8 weeks x 46 weeks</td>
<td>69% at week 8 (Placebo 37%)</td>
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<td></td>
<td></td>
<td></td>
<td>45.5% at week 54 (Placebo 20%)</td>
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<tr>
<td></td>
<td>ACT 2 (N=364) Mod-Severe</td>
<td>5mg/kg x 22 weeks</td>
<td>64% at week 8 (Placebo 29%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>47.1% at week 30</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>ULTRA 1 (n= 390) Mod-severe</td>
<td>160/80, 80/40, Placebo S/C every 2 weeks</td>
<td>18.5% at week 8 (160 mg) vs 9.2%</td>
</tr>
<tr>
<td></td>
<td>ULTRA 2</td>
<td>40 mg s/c every 2 weeks after induction</td>
<td>16.5% at week 8 (Placebo 9.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.3% at week 52 (Placebo 8.5%)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>PURSUIT N=1065 Mod-Severe</td>
<td>200 mg week 0, 100 mg week 2</td>
<td>51% week 6</td>
</tr>
<tr>
<td></td>
<td>PURSUIT MAINT. N=464 Mod Severe</td>
<td>100 mg every 4 weeks after induction</td>
<td>49.7% week 52</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>GEMINI N=895 Mod-Severe</td>
<td>300 mg IV at 0 and 2 weeks, then 4 or 8 weekly IV</td>
<td>47.1% at week 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>41.8-44.8% at week 52</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Sandborn et al N=194 Mod-Severe</td>
<td>15 mg BD x 8 weeks</td>
<td>78% at week 8</td>
</tr>
</tbody>
</table>

**STEP-UP OR STEP-DOWN – CLINICAL PERSPECTIVE**

Whilst the Step-Down approach may seem to be logical and exciting given its potential for achieving sustained mucosal healing and potential to favourably alter the natural course of disease, a critical analysis will reveal the following limitations:

1. Mucosal healing is achieved in a sizable number of patients even with conventional step-up therapy. It may be presumed that step-down approach may achieve this more rapidly, however, no such hard evidence exists.
2. Our experience with biologicals in rheumatology tells us that these drugs are capable of changing the natural history of immune mediated disorders. There is emerging evidence of similar effect in ulcerative colitis, nevertheless more data and validation is required before step-down approach can be adopted for all cases.
3. A universally acceptable definition of mucosal healing is still elusive. Assessing mucosal healing is equally worrisome. Endoscopy is invasive and patients are reluctant to submit themselves for repeated endoscopic and histologic assessment.
4. Cost of biologicals is prohibitive and out of reach of most patients in India.
5. Risk of developing tuberculosis and opportunistic infection is significant and meticulous pre-treatment and during the course of treatment surveillance is mandatory.

Further clinical trials conclusively establishing the superiority of biological over aminosalicylates, steroids

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**STEP-DOWN APPROACH: CLINICAL RATIONALE**

Mucosal inflammation damages mucosa and begets further inflammation giving rise to persistent disease activity, complications and risk of developing colorectal carcinoma in ulcerative colitis. To favourably change the natural course of the disease it is necessary to interrupt this vicious cycle of mucosal inflammation during the early stage of the disease before irreversible mucosal damage takes place. Biologicals, with their efficacy to induce MH, quick onset of action, ability to maintain remission have the potential to meet this target.

Once remission is achieved, it can be maintained with continuing biological or stepping down to immunomodulators like azathioprine. If biological fail to induce or maintain remission patient can be taken up for colectomy (Figure 2).
and immunomodulators is required to strengthen the protocols of step-down therapy in UC. Mucosal healing needs to be better defined and validated with clinical outcome. Identification of surrogate biochemical markers of mucosal healing is warranted to avoid repeated invasive endoscopies. Lastly, affordable biological need to be introduced in the market for wider clinical use.

In conclusion, step-down therapy may be an exciting approach to treat ulcerative colitis but at this stage it may be restricted to patients with severe or predicted severe disease.

REFERENCES


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In conclusion, step-down therapy may be an exciting approach to treat ulcerative colitis but at this stage it may be restricted to patients with severe or predicted severe disease.

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