CHAPTER

64

Management of Ulcerative Colitis: Step-up or Step-down Approach?

Bhaskar Nandi

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.[1-3] The concept of mucosal healing has brought a paradigm shift in therapeutic goals and clinical end-points 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.[4,5] 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 [6-8]. 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.[9]

The incidence and prevalence is highest in for the Asian subcontinent and similar to prevalence in the West. [9,10] The disease is limited to rectum in 18.3%, the left colon in 38.8% and involves the entire colon in 43.8%.[11] The corresponding figures from the West are 30-60%, 16-40% and 18-35% respectively. [12-14] 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.[11] 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.[15]

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.[16] 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.[4] Mayo Endoscopy Score[17] is the most widely used tool in clinical studies, however, Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[18], 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.[19-21]

Recent studies have demonstrated conclusively that MH in UC results in decrease in corticosteroid use, decrease in hospitalisation rates, increase in sustained clinical

Table 1: Ulcerative Colitis Endoscopic Index of Severity

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

remission, decrease in colectomy rates and decrease in development of colorectal carcinoma.[5,22-25] 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.[26]

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-aminosalycilate (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.[27-30] 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).

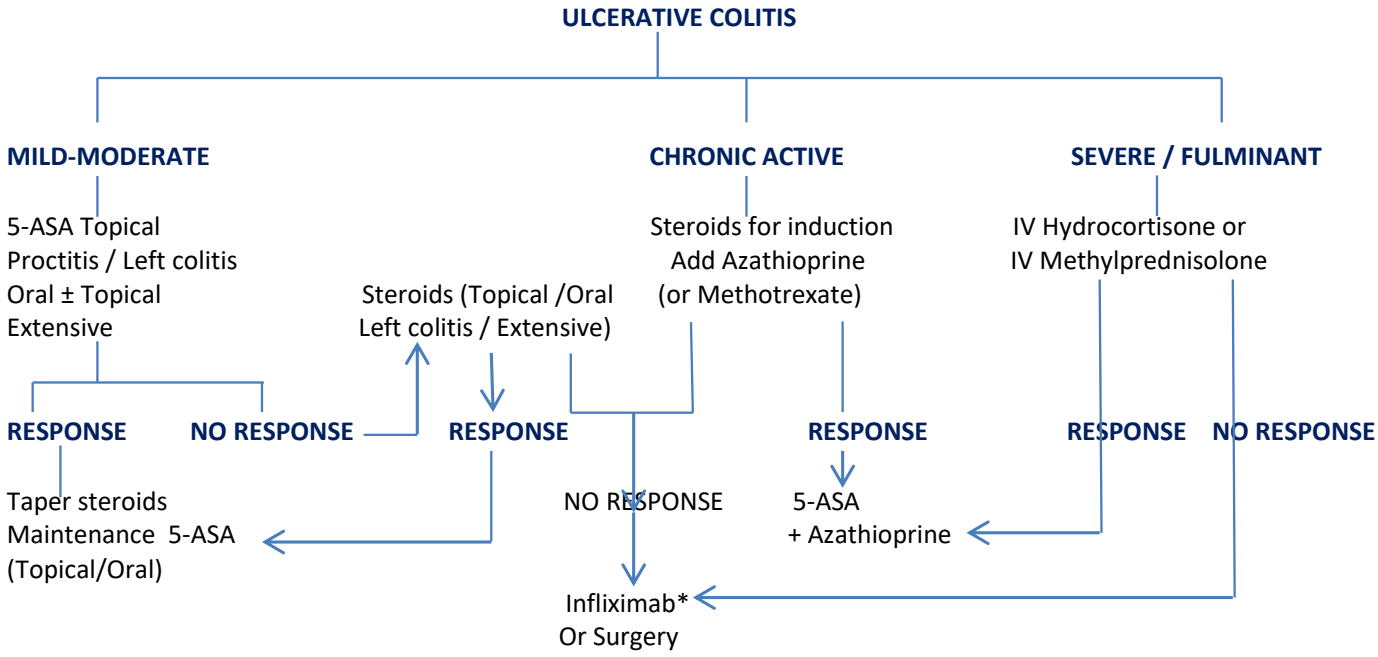

Fig. 1: Treatment of Ulcerative Colitis (Step-up approach)

Table 2: Biologics in Ulcerative Colitis	
Anti-TNF Inhibitors	Infliximab. Adalimumab, Golimumab
Anti-adhesion molecules	Natalizumab (recombinant IgG4 monoclonal antibody to α4 integrin) Vedolizumab (anti α4â7 integrin antibody) Etrolizumab
Janus kinase inhibitors	Tofacitinib
Others	Abatacept, Tocilizumab

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. Adalilumab 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.[31] 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 10mg 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< or =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.[32] It was an 8-week, multicentre, randomised, double-blind, placebo-controlled study in patients with moderate to severe UC non-resposive 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.[33] 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

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

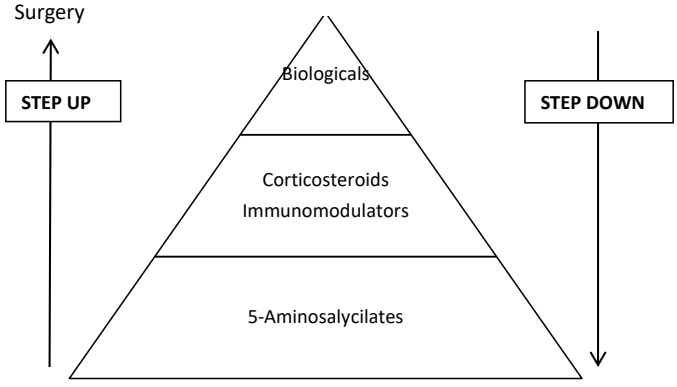

Fig. 2: Step down therapy in Ulcerative Colitis

.019); corresponding values for week 52 were 17.3% and 8.5% (P = .004).

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).

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 biologicasl 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

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

1. Feagen BG, Rutgeerts P, Sands BE. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013; 369:699-710
2. Sandborn WJ, Ghosh S, Panes J. Tofacitinab, an oral Janus kinase inhibitor, in active ulcerative colitis. *N Engl J Med* 2012; 367:616-624.
3. Stidham RW, Lee TC, Higgins PD. Systematic review with network meta-analysis: the efficacy of anti-tumor necrosis factor-alpha agents for the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2014; 39:660-671
4. Osterman MT. Mucosal healing in Inflammatory Bowel Disease. *J Clin Gastroenterol* 2013; 47:212-221.
5. Walsh A, Palmer R, Travis S. Mucosal healing as target for therapy in colonic inflammatory bowel disease and methods to score disease activity. *Gastrointest Endoscopy Clin N Am* 2014; 24:367-378.
6. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; 141:1194e201.
7. Park SC, Jeen YT. Current and emerging biologics for Ulcerative Colitis. *Gut and Liver* 2015; 9:18-27
8. Ghosal UC, Verma A. Biologicals in treatment of acute ulcerative colitis. *Trop Gastroenterology* 2015; 36:80-85
9. Sood A,Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of Ulcerative Colitis in Punjab, North India. *Gut* 2003; 52:1587-1590.
10. Ahuja V, Tandon RK. Inflammatory Bowel Disease in Asia-Pacific area: A comparison with developed countries and regional differences. *J Dig Dis* 2010; 11:134-147.
11. Makharia GK1, Ramakrishna BS, Abraham P, Choudhuri G, Misra SP, Ahuja V, Bhatia SJ, Bhasin DK, Dadhich S, Dhali GK, Desai DC, Ghoshal UC, Goswami BD, Issar SK, Jain AK, Jayanthi V, Loganathan G, Pai CG, Puri AS, Rana SS, Ray G, Singh SP, Sood A; Indian Society of Gastroenterology Task Force on Inflammatory Bowel Disease. Survey of inflammatory bowel diseases in India. *Indian J Gastroenterol* 2012; 31:299-306.
12. Moum B, Ekbom A, Vatn MH, Elgjo K. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. *Am J Gastroenterol* 1999; 94:1564–9.
13. Henriksen M, Jahnsen J, Lygren I et al. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (the IBSEN study). *Inflamm. Bowel Dis* 2006; 12:543–50.
14. Jess T, Riis L, Vind I. Changes in clinical characteristics, course,and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. Inflamm. *Bowel Dis* 2007; 13:481–9.
15. Wanderas MH, Moum BA, Hoivik ML. Predictive factors for a severe clinical course in ulcerative colitis: Results from population-based studies. *World J Gastrointest Pharmacol Ther* 2016; 7:235-241.
16. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. *Gastroenterology* 2007; 132:763–86.
17. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; 317:1625–1629.
18. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the ulcerative colitis endoscopic index of severity (UCEIS). *Gut* 2012; 61:535–42.
19. Truelove SC, Richards WCD. Biopsy studies in ulcerative colitis. *Br Med J* 1956; 1:1315–1318.
20. Matts SGF. The value of rectal biopsy in the diagnosis of ulcerative colitis. *Q J Med* 1961; 30:393–407.
21. Dick AP, Holt LT, Dalton ER. Persistence of mucosal abnormality in ulcerative colitis. *Gut* 1966; 7:355–360.
22. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; 141:1194–201.
23. Rutter MD, Saunders BP, Wilkinson KH, et al. Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. *Gut* 2004; 53:1813–6.
24. Ardizzone S, Cassinotti A, Duca P, et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. *Clin Gastroenterol Hepatol* 2011; 9:483–489.
25. Meucci G, Fasoli R, Saibeni S, et al. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: a prospective, multicenter study. *Inflamm Bowel Dis* 2012; 18:1006–1010.
26. Shah SC, Colombel JF, Sands BE, Narula N. Mucosal Healing Is Associated With Improved Long-term Outcomes of Patients With Ulcerative Colitis: A Systematic Review and Meta-analysis. *Clinical Gastroenterol Hepatol* 2016; 14:1245–1255.
27. Sandborn WJ, Kamm MA, Lichtenstein GR, et al. MMX Multi Matrix System mesalazine for the induction of remission in patients with mild-to-moderate active ulcerative colitis: a combined analysis of two randomized, double-blind, placebo-controlled trials. *Aliment Pharmacol Ther* 2007; 26:205–215.
28. Kamm MA, Lichtenstein GR, Sandborn WJ, et al. Effect of extended MMX mesalamine therapy for acute, mild-tomoderate ulcerative colitis. *Inflamm Bowel Dis* 2009; 15:1–8.
29. Lichtenstein GR, Ramsey D, Rubin DT. Randomised controlled trial: delayed-release oral mesalazine 4.8 g/day vs. 2.4 g/day in endoscopic mucosal healing—ASCEND I and II combined analysis. *Aliment Pharmacol Ther* 2011; 33:672–678.
30. Ardizzone S, Maconi G, Russo A, et al. Randomised

controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; 55:47–53.

31. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; 353:2462-76.
32. Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011; 60:780-7.
33. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; 142:257-265.e13.
34. Velayos FS, Sandborn WJ. Positioning biologic therapy for Crohn's disease and ulcerative colitis. *Curr Gastroenterol Rep* 2007; 9:521-7.