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TOPIC HIGHLIGHT

Giovanni Latella, MD, *Series Editor*

Impact of medical therapies on inflammatory bowel disease complication rate

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Abstract

Crohn's disease and ulcerative colitis are progressive diseases associated with a high risk of complications over time including strictures, fistulae, perianal complications, surgery, and colorectal cancer. Changing the natural history and avoiding evolution to a disabling disease should be the main goal of treatment. In recent studies, mucosal healing has been associated with longer-term remission and fewer complications. Conventional therapies with immunosuppressive drugs are able to induce mucosal healing in a minority of cases but their impact on disease progression appears modest. Higher rates of mucosal healing can be achieved with anti-tumor necrosis factor therapies that reduce the risk of relapse, surgery and hospitalization, and are associated with perianal fistulae closure. These drugs might be able to change the natural history of the disease mainly when introduced early in the course of the disease. Treatment strategy in inflammatory bowel diseases should thus be tailored according to the risk that each patient could develop disabling disease.

Key words: Crohn's disease; Ulcerative colitis; Inflammatory bowel diseases; Therapy; Surgery; Complications

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INTRODUCTION

The natural history of Crohn's disease (CD) is the progression to chronic complications including strictures, penetrating fistulae[1,2] or complex perianal disease[3], leading to the need for surgery and hospitalization[4]. This leads to the concept of cumulative tissue damage for which a quantitative score is currently under development[5]. Coloproctectomy due to chronic refractory disease or acute severe colitis is a major complication of ulcerative colitis (UC) and develops in 20%-25% of patients after 25 years. An increased risk of colorectal cancer (CRC) in long-standing colitis is a second major complication in UC[6], but also in Crohn's colitis, with a relative risk of 2.5 compared to the general population. The aim of medical therapies was the improvement of inflammatory bowel disease (IBD) symptoms 20 years ago, however, the current objective is to achieve deep remission, including cessation of corticosteroids, and mucosal healing. Therefore, treatments should modify the course of the disease by avoiding disabling disease and irreversible tissue damage. This review focuses on the impact of treatment on the natural history of IBD.

MUCOSAL HEALING

Mucosal healing (MH) has become a major goal of treatment of IBD because it has been correlated with fewer complications[7,8], fewer relapses after surgery[9], and drug

withdrawal[10]. There is no validated definition of MH in IBD. Mucosal healing is usually assessed by endoscopy in CD and UC and defined as the absence of ulcers[10]. Although poorly studied, MH is achievable with thiopurine analogs in active CD. In earlier uncontrolled studies, among azathioprine (AZA) clinical responders, 74% achieved MH after a mean of 2 years[11,12]. However, in a more recent controlled trial (SONIC) studying infliximab (IFX), AZA, or combination therapy for immunosuppressive-naive CD patients[13], only 16% of CD patients in the AZA arm achieved mucosal healing at week 26. Few data are available about the efficacy of methotrexate (MTX) in inducing MH. A preliminary study[14] of 11 CD patients treated with MTX 25 mg weekly intramuscular injection showed MH and histological healing in five and four patients, respectively, after 12 wk. No MH was observed in UC, although 5/7 patients had a clinical response with histological improvement. A recent prospective study showed MH in only 11% of CD patients in clinical remission on MTX, compared to 50% on AZA and 60% on IFX[15]. A possible bias in this study may have been the small size of the groups, the more refractory disease, and the shorter treatment duration in the MTX group. Anti-tumor necrosis factor (TNF) treatments have changed the management of IBD since the late 1990s. A subanalysis of a Crohn's disease clinical study evaluating infliximab in a new long-term treatment regimen (ACCENT1) trial demonstrated that MH on IFX was associated with fewer relapses[16]. A retrospective single center study has shown that, among IFX responders, 68% had MH (45% complete MH) and MH was associated with fewer relapses (64% *vs* 40%)[17]. In the step-up top-down study, 71% of patients with MH at 2 years were still in remission 2 years later, compared to patients who had endoscopic signs of activity[18]. At week 26 of the SONIC trial, IFX was more effective to induce MH than AZA, (16.5%), either in mono- (30.1%) or combination therapy with AZA (39.5%). In the prospective ACT1/ACT2 trials studying IFX for induction and maintenance therapy in UC, IFX efficacy in inducing MH was also demonstrated with 62%/60% of MH at week 8 compared to 32%/30% in the placebo group. Adalimumab (ADA) was also more effective than placebo in inducing and maintaining clinical remission in patients with moderate-to-severe UC[19], and MH was achieved more frequently in the ADA arm compared to placebo (25% *vs* 15% at week 52).

In CD, mucosal healing has also been consistently described as more frequently achieved when an anti-TNF was started earlier in the disease course[20].

SURGERY AND HOSPITALIZATION

CD is a chronic condition that leads to tissue damage and complications requiring surgery in 70%-80% of patients at 20 years[4,8]. In UC, the cumulative probability of colectomy after 25 years varies from 20% to 30%[21,22]. In 2005, Cosnes *et al*[23] demonstrated that immunosuppressive drugs (AZA and MTX) were introduced more frequently and earlier in the course of the CD over the past 25 years but the percentage of patients requiring intestinal surgery each year remained stable. These results should be interpreted with caution because < 10% of the patients included in this study received AZA before surgery. Recent contradictory data have demonstrated that increased immunosuppressant prescriptions, from 11% to 45% over 25 years, have decreased the rate of intestinal resection from 59% to 25% 5 years after diagnosis[24]. Early introduction of thiopurine was a protective factor. French results recently have demonstrated that AZA is associated with less surgery in patients newly diagnosed with CD but the benefit was modest compared to IFX[25]. In UC, Ardizzone *et al*[26] have demonstrated higher rates of clinical response in patients treated with AZA compared to 5-aminosalicylic acid, but the colectomy rate was similar in both groups (8%). The ACCENT 1 and 2 trials have reported a decreased risk of surgery in patients on IFX scheduled therapy at week 54 (3% *vs* 7% with IFX episodic therapy)[27,28]. Schnitzler *et al*[17] have demonstrated less intra-abdominal surgery (14%) and hospitalization (42%) for active CD in patients achieving MH on scheduled IFX compared to those who had endoscopically active disease (38% and 59% respectively). Lower colectomy rates in IBD were also associated with MH in a retrospective Norwegian population-based study[29]. Recently, IFX given for at least 16 mo was reported as a protective factor against surgery in active CD[25]. Jones *et al*[30] have reported a stable rate of surgery in CD from 1993 to 2004, but these data should be interpreted with caution because they concern a period when IFX was mainly prescribed as episodic therapy, which is clearly a suboptimal strategy and does not represent the current practice. In the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) trial, CD patients treated with scheduled ADA had less hospitalization at 3 mo (1.6%) and 12 mo (5.9%) compared to placebo (7.3% and 13.9% respectively)[31]. Surgery at 1 year also decreased from 3.8% in the placebo group to 0.6% in the ADA groups. These results were confirmed at 2 years follow-up[32]. A sub-analysis of the ACT1 and ACT2 trials demonstrated a 10% cumulative incidence of colectomy in UC through 54 wk in the IFX group compared to 17% in the placebo group. Less UC-related hospitalization was reported in the IFX group[33]. Moreover, the degree of MH after 8 wk IFX was correlated with less colectomy[34].

PERIANAL COMPLICATIONS OF CD

Perianal fistulae occur in 21%-26% of CD patients after 20 years[3]. Anti-TNF antibodies have dramatically improved the ability to heal fistula with medical therapy. After 54 wk of scheduled IFX treatment for active CD fistulae, partial response was observed in 46% of patients *vs* 23% in the placebo group and 36% had a complete response compared to 19% with placebo[28]. After primary drainage, high rates of clinical response (85%)

and remission (74%) at week 14 were also reported in patients with severe active perianal CD treated with three infusions of IFX followed by MTX as maintenance therapy (25 mg weekly intramuscular or subcutaneous). Fifty percent of patients were still in remission from their perianal disease at 1 year, but this strategy failed to achieve a prolonged remission of luminal disease in the majority of patients[35]. No other prospective studies have investigated the efficacy of MTX in perianal CD. In the CHARM trial that studied the long-term efficacy of ADA in CD, 33% of active fistulae achieved complete healing on ADA after 56 wk compared to 13% in the placebo group[31]. This effect was globally maintained over 3 years follow-up[32]. Fistula healing in a substantial proportion of patients under ADA was also confirmed in a large European open label trial mimicking routine practice[36]. In this trial, full fistula closure was achieved in 26% of patients after 20 wk. The impact of thiopurine on fistula closure was poorly studied. A meta-analysis showed a complete closure or an improvement of the fistulae in 54% of the patients compared to 21% in the placebo group. However, these results should be interpreted with caution because fistula closure was not the primary endpoint of this study[37].

CANCER

Chronic colitis predisposes to CRC over time, with cumulative estimated incidence rates of 2%, 8% and 18% at 10, 20 and 30 years of evolution, respectively[6]. This risk was however reported as lower in more recent cohorts[38], with a relative risk around 2.0 over disease course. The risk of CRC in CD has also been reported[39]. Risk factors for CRC in chronic colitis are extensive location, long duration of the disease, familial history of CRC, and associated primary sclerosing cholangitis[40]. Few studies have addressed the severity of colonic inflammation over time as an independent risk factor for progression to neoplasia. Rutter *et al*[41,42] have demonstrated a highly significant correlation between colonic inflammation scores and the risk of CRC in UC. Only association with histological inflammation was significant in the multivariable analysis [odds ratio (OR): 4.7]. In the case of normal colonoscopy, the 5-year risk of CRC was the same as that of the matched general population (OR: 0.38). Gupta *et al*[43] also have demonstrated that the severity of microscopic inflammation is an independent risk factor for dysplasia in patients with longstanding UC. Such data are not yet available in CD. Due to the ability of medical treatment to maintain tissue healing in IBD, we can speculate on the potential impact of these treatments on the risk of cancer. Mesalazine is effective at maintaining clinical remission in UC and remains the main drug in this disease. In retrospective studies and meta-analyses, a significant decrease in CRC in UC has been described with mesalazine. More intriguingly, this has also been suggested for ileal cancer in CD[44]. More recently, in the Cesame cohort, a potential decrease in CRC was also suggested in extensive longstanding UC treated with purine analogs[45]. No data are available yet with anti-TNF agents.

CONCLUSION

In conclusion, anti-TNFs and to a lesser extent immunosuppressants, can induce MH, which is associated with long-term clinical remission, closure of perianal fistulae, less hospitalization and surgery, suggesting an impact of these medications on the natural history of the disease. The benefit might be higher if MH is achieved earlier in the course of the disease. Histological remission is also associated with a reduced risk of CRC in UC. Although immunosuppressive treatments with thiopurine or MTX are able to induce MH, their benefit on the complications of IBD appears more modest. Many questions remain open, including the degree of MH achievement (complete *vs* partial) required to improve the prognosis, when and how often in the course of the disease should this healing be assessed, and how to adapt the treatment according to MH. Prospective randomized clinical trials are ongoing to answer these questions. Furthermore, the validation and the further use of a tissue damage score in CD (Lemann score) will be an important step to assess adequately the ability of treatment strategies to change natural history.

REFERENCES

1 **Louis E**, Collard A, Oger AF, Degroote E, Aboul Nasr El Yafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001; **49**: 777-782

2 **Cosnes J**, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, Gendre JP. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 244-250

3 **Hellers G**, Bergstrand O, Ewerth S, Holmström B. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. *Gut* 1980; **21**: 525-527

4 **Mekhjian HS**, Switz DM, Melnyk CS, Rankin GB, Brooks RK. Clinical features and natural history of Crohn's disease. *Gastroenterology* 1979; **77**: 898-906

5 **Pariente B**, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG, Chowers Y, D'Haens G, Feagan BG, Hibi T, Hommes DW, Irvine EJ, Kamm MA, Loftus EV, Louis E, Michetti P, Munkholm P, Oresland T, Panés J, Peyrin-Biroulet L, Reinisch W, Sands BE, Schoelmerich J, Schreiber S, Tilg H, Travis S, van Assche G, Vecchi M, Mary JY, Colombel JF, Lémann M. Development of the Crohn's disease digestive damage score, the Lémann score. *Inflamm Bowel Dis* 2011; **17**: 1415-1422

6 **Eaden JA**, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001; **48**: 526-535

7 **Sandborn WJ**. Current directions in IBD therapy: what goals are feasible with biological modifiers? *Gastroenterology* 2008; **135**: 1442-1447

8 **Munkholm P**, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol* 1995; **30**: 699-706

9 **Rutgeerts P**, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent Crohn'

s disease at the ileocolonic anastomosis after curative surgery. *Gut* 1984; **25**: 665-672
10 **Louis E**, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Dupas JL, Pillant H, Picon L, Veyrac M, Flamant M, Savoye G, Jian R, Devos M, Porcher R, Paintaud G, Piver E, Colombel JF, Lemann M. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012; **142**: 63-70.e5; quiz e31
11 **Sandborn WJ**, Van O EC, Zins BJ, Tremaine WJ, Mays DC, Lipsky JJ. An intravenous loading dose of azathioprine decreases the time to response in patients with Crohn's disease. *Gastroenterology* 1995; **109**: 1808-1817
12 **D'Haens G**, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. *Gastrointest Endosc* 1999; **50**: 667-671
13 **Colombel JF**, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362**: 1383-1395
14 **Kozarek RA**, Patterson DJ, Gelfand MD, Botoman VA, Ball TJ, Wilske KR. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. *Ann Intern Med* 1989; **110**: 353-356
15 **Laharie D**, Reffet A, Belleannée G, Chabrun E, Subtil C, Razaire S, Capdepont M, de Lédinghen V. Mucosal healing with methotrexate in Crohn's disease: a prospective comparative study with azathioprine and infliximab. *Aliment Pharmacol Ther* 2011; **33**: 714-721
16 **D'haens G**, Van Deventer S, Van Hogezand R, Chalmers D, Kothe C, Baert F, Braakman T, Schaible T, Geboes K, Rutgeerts P. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. *Gastroenterology* 1999; **116**: 1029-1034
17 **Schnitzler F**, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 1295-1301
18 **Baert F**, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, D'Haens G. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010; **138**: 463-468; quiz 10-11
19 **Sandborn WJ**, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; **142**: 257-265.e1-3
20 **Hanauer SB**. Top-down versus step-up approaches to chronic inflammatory bowel disease: presumed innocent or presumed guilty. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 493
21 **Langholz E**, Munkholm P, Davidsen M, Nielsen OH, Binder V. Changes in extent of ulcerative colitis: a study on the course and prognostic factors. *Scand J Gastroenterol* 1996; **31**: 260-266
22 **Hoie O**, Wolters FL, Riis L, Bernklev T, Aamodt G, Clofent J, Tsianos E, Beltrami M, Odes S, Munkholm P, Vatn M, Stockbrügger RW, Moum B. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. *Gastroenterology* 2007; **132**: 507-515
23 **Cosnes J**, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 2005; **54**: 237-241
24 **Ramadas AV**, Gunesh S, Thomas GA, Williams GT, Hawthorne AB. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986-2003): a study of changes in medical treatment and surgical resection rates. *Gut* 2010; **59**: 1200-1206
25 **Peyrin-Biroulet L**, Oussalah A, Williet N, Pillot C, Bresler L, Bigard MA. Impact of azathioprine and tumour necrosis factor antagonists on the need for surgery in newly diagnosed Crohn's disease. *Gut* 2011; **60**: 930-936
26 **Ardizzone S**, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; **55**: 47-53
27 **Hanauer SB**, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549
28 **Sands BE**, Blank MA, Patel K, van Deventer SJ. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. *Clin Gastroenterol Hepatol* 2004; **2**: 912-920
29 **Frøslie KF**, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. *Gastroenterology* 2007; **133**: 412-422
30 **Jones DW**, Finlayson SR. Trends in surgery for Crohn's disease in the era of infliximab. *Ann Surg* 2010; **252**: 307-312
31 **Feagan BG**, Panaccione R, Sandborn WJ, D'Haens GR, Schreiber S, Rutgeerts PJ, Loftus EV, Lomax KG, Yu AP, Wu EQ, Chao J, Mulani P. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology* 2008; **135**: 1493-1499
32 **Panaccione R**, Colombel JF, Sandborn WJ, Rutgeerts P, D'Haens GR, Robinson AM, Chao J, Mulani PM, Pollack PF. Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. *Aliment Pharmacol Ther* 2010; **31**: 1296-1309
33 **Sandborn WJ**, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, Lu J, Horgan K, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* 2009; **137**: 1250-1260; quiz 1520
34 **Colombel JF**, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, Hanauer SB, Lichtenstein GR, Present D, Sands BE, Sandborn WJ. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; **141**: 1194-1201
35 **Roumeguère P**, Bouchard D, Pigot F, Castinel A, Juguet F, Gaye D, Capdepont M, Zerbib F, Laharie D. Combined approach with infliximab, surgery, and methotrexate in severe fistulizing anoperineal Crohn's disease: results from a prospective study. *Inflamm Bowel Dis* 2011; **17**: 69-76
36 **Löfberg R**, Louis EV, Reinisch W, Robinson AM, Kron M, Camez A, Pollack PF. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: results from CARE. *Inflamm Bowel Dis* 2012; **18**: 1-9
37 **Pearson DC**, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. *Ann Intern Med* 1995; **123**: 132-142
38 **Rubio CA**, Kapraali M, Befrits R. Further studies on the frequency of colorectal cancer in Crohn's colitis: an 11-year survey in the Northwest Stockholm County. *Anticancer Res* 2009; **29**: 4291-4295
39 **Ekbom A**, Helmick C, Zack M, Adami HO. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. *Lancet* 1990; **336**: 357-359
40 **Bergeron V**, Vienne A, Sokol H, Seksik P, Nion-Larmurier I, Ruskone-Fourmestraux A, Svrcek M, Beaugerie L, Cosnes J.

Risk factors for neoplasia in inflammatory bowel disease patients with pancolitis. *Am J Gastroenterol* 2010; **105**: 2405-2411

41 **Rutter M**, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, Williams C, Price A, Talbot I, Forbes A. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004; **126**: 451-459

42 **Rutter MD**, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. *Gut* 2004; **53**: 256-260

43 **Gupta RB**, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, Bodian C, Ullman T. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology* 2007; **133**: 1099-1105; quiz 1340-1341

44 **Piton G**, Cosnes J, Monnet E, Beaugerie L, Seksik P, Savoye G, Cadiot G, Flourie B, Capelle P, Marteau P, Lemann M, Colombel JF, Khouri E, Bonaz B, Carbonnel F. Risk factors associated with small bowel adenocarcinoma in Crohn's disease: a case-control study. *Am J Gastroenterol* 2008; **103**: 1730-1736

45 **Vienne A**, Simon T, Cosnes J, Baudry C, Bouhnik Y, Soulé JC, Chaussade S, Marteau P, Jian R, Delchier JC, Coffin B, Admane H, Carrat F, Drouet E, Beaugerie L. Low prevalence of colonoscopic surveillance of inflammatory bowel disease patients with longstanding extensive colitis: a clinical practice survey nested in the CESAME cohort. *Aliment Pharmacol Ther* 2011; **34**: 188-195

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