World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i21.2626

World J Gastroenterol 2010 June 7; 16(21): 2626-2632
ISSN 1007-9327 (print)

TOPIC HIGHLIGHT

Peter L Lakatos, MD, PhD, Assistant Professor, *Series Editor*

Role of endoscopy in predicting the disease course in inflammatory bowel disease

Matthieu Allez, Marc Lémann

Matthieu Allez, Marc Lémann, Department of Gastroenterology and Equipe AVENIR INSERM, Saint-Louis Hospital, APHP, Université Denis Diderot Paris 7, 75010 Paris, France
Author contributions: Allez M wrote the manuscript; Lémann M critically reviewed the manuscript.
Correspondence to: Matthieu Allez, MD, PhD, Department of Gastroenterology, Saint-Louis Hospital, APHP, Université Denis Diderot Paris 7, 75010 Paris, France. matthieu.allez@sls.aphp.fr
Telephone: +33-1-42499575 Fax: +33-1-42499168
Received: January 25, 2010 Revised: April 22, 2010
Accepted: April 29, 2010
Published online: June 7, 2010

Abstract

Endoscopy provides a direct evaluation of mucosal lesions in inflammatory bowel disease (IBD), permitting the description of elementary lesions, their surface extent and severity. The severity of mucosal lesions directly reflects disease activity and may help to identify an aggressive behavior of the disease. Several studies have recently pointed out the potential role of endoscopy in the prediction of IBD outcome. Indeed, severe endoscopic lesions in Crohn's disease (CD) patients, defined by deep and extensive ulcerations on at least one part of the colon, are associated with an increased risk of penetrating complication and surgery. Severe endoscopic lesions during severe attacks of ulcerative colitis (UC) are associated with an increased risk of colectomy in the short and long term. Severity of postoperative recurrence in CD may help to predict the risk of clinical relapse and need for further surgery. Achievement of mucosal healing, which can be obtained by administration of several types of drugs, is associated with a better outcome, less surgery and hospitalization. This review focuses on the assessment of endoscopic severity in CD and UC and on the impact of endoscopic severity on disease outcome. More specifically, we discuss how endoscopy can be used at different stages of IBD to predict the disease course and/or to adapt treatment strategies.

Key words: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease; Colonoscopy; Natural history; Outcome; Medical therapy; Surgery

Peer reviewer: Antonello Trecca, MD, Usi Group Digestive Endoscopy and Gastroenterology, Via Machiavelli, 22, 00185 Rome, Italy

Allez M, Lémann M. Role of endoscopy in predicting the disease course in inflammatory bowel disease. *World J Gastroenterol* 2010; 16(21): 2626-2632 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i21/2626.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i21.2626

INTRODUCTION

The management of inflammatory bowel diseases (IBD) has dramatically changed over the last decade. Progress has been supported by the increasing size of the therapeutic arsenal, the introduction of biologics providing more alternative options in patients with severe diseases, and new concepts as to how and when treatments should be used. Immunosuppressants and biologics are classically used following a step-up approach in patients with refractory disease, who are unresponsive to conventional therapies or are steroid-dependent. Beyond their high efficacy in induction and maintenance of remission, it has been demonstrated that anti-tumor necrosis factor (TNF) therapies can close fistulae and heal mucosal lesions, and reduce rates of hospitalization and surgery[1]. Several recent studies suggest that early intervention with combination therapy may modify the long-term course of Crohn's disease (CD)[2-4]. However, these strategies should

not be used in all patients, but only in selected patients with severe diseases and/or with features predicting a poor prognosis[1]. Good predictors of IBD outcome are still lacking in our daily practice. Studies performed with regard to prediction have mainly focused on clinical and biological parameters. Endoscopy has been rarely investigated as a predictor of the clinical course of IBD. However, there is now growing evidence that morphological examination, including endoscopy, may help to identify among IBD patients those who should be treated with more intensive treatments. Furthermore, as demonstrated in a recent study assessing early intervention with combination of infliximab and azathioprine in CD, endoscopy may help to select patients who will obtain the best results with early intervention[2].

Endoscopy allows the examination of mucosal lesions in IBD[5,6]. The severity of mucosal lesions directly reflects the activity of the disease and may thus be considered as an indication of an aggressive behavior of the disease. In this article, we review aspects of assessment of endoscopic severity in CD and ulcerative colitis (UC) and discuss their role in predicting the course of these diseases and their impact on decisions regarding medical strategies.

ASSESSMENT OF ENDOSCOPIC SEVERITY IN CD

Endoscopic scores of severity in CD

A number of mucosal characteristics may be observed at endoscopy in CD, such as erythema, swelling, nodularity, strictures, aphtoid ulcerations and ulcers of variable size and depth. The severity of ileocolonic lesions can be quantified by validated endoscopic indices of disease activity. The CD endoscopic index of severity (CDEIS) is based on the recognition of elementary lesions (non-ulcerated lesions, superficial and deep ulcerations), associated with the appreciation of their surface in five segments (ileum, right colon, transverse, left colon and sigmoid, and rectum)[7,8]. A simplified index, the simple endoscopic score for CD (SES-CD), has been proposed and correlates well with the CDEIS[9]. The CDEIS is considered as the gold standard for quantifying endoscopic severity, but is often regarded as not easy to use. It requires a specific training for the estimation of ulcerated or diseased mucosal surfaces.

These scores can be used to assess endoscopic severity during active phases of the disease, and they may also be used to assess changes induced by medical treatments. Several studies on mucosal healing have been performed in CD. However, there is no validated definition of mucosal healing in CD[10]. The ideal definition is absence of ulcerated lesions. However, this definition may be excessively strict. For example, a patient who had deep and extensive ulcerations at index colonoscopy and who healed almost all lesions but still had one aphtous ulcer would not be considered as achieving complete mucosal healing. For this reason, we think that mucosal healing should be evaluated through validated scores on endoscopic severity.

Severe endoscopic lesions in CD

It is widely accepted that severity of colonic lesions in CD relies on the extent in depth and in surface of the mucosal damage. Recognition of these lesions by an endoscopist may be seen as subjective. However, it appears that diagnosis of severe endoscopic lesions may not be difficult. A previous interobserver variation study targeted on evaluation of ileocolonoscopic lesions in CD[11] has shown that deep ulcerations and estimation of ulcerated surface were among the most reproducible endoscopic items. Such lesions were also selected by multivariate analysis for the construction of the CDEIS[7].

Nahon *et al*[12] demonstrated that colonoscopy accurately predicts the anatomical severity of colonic CD attacks. In this retrospective study of 78 patients operated for colonic CD resistant to medical treatment, criteria of severity in colectomy specimens were defined as either deep ulcerations eroding the muscle layer, or mucosal detachments, or ulcerations limited to the submucosa but extending to more than one third of one defined colonic segment (right, transverse, left colon). Three endoscopic criteria of severity were defined: (1) deep ulcerations eroding the muscle layer; (2) deep ulcerations not eroding the muscle layer but involving more than one third of the mucosal area; and (3) mucosal detachment at the edge of ulcerations. Evaluation of endoscopic severity correlated well with findings on colectomy specimens. At least one of these criteria was found in 95% of patients with severe anatomic lesions on colectomy specimens. The extent of ulcerations at colonoscopy was correlated to the results of colectomy specimen examination ($P < 0.001$). Of note, usual clinical and biological severity criteria were not different in patients with severe colonic lesions or without. This study further demonstrates that colonoscopy can accurately assess anatomical severity of colonic CD.

THE ROLE OF ENDOSCOPY IN PREDICTING THE COURSE IN CD

Severe endoscopic lesions predict a more aggressive outcome with increased rates of complications and surgery in CD

Early studies by the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID) have shown that endoscopic pattern severity (assessed by the CDEIS) correlated poorly with clinical (assessed by the CDAI) and biological activity (assessed by C-reactive protein measurement)[8]. Furthermore, clinical improvement is not always associated with healing of mucosal lesions in CD. Indeed, clinical remission obtained with steroids is associated with mucosal healing in only one third of CD patients[11]. Moreover, the degree of endoscopic improvement in patients with prednisolone-induced clinical remission did not predict

the subsequent clinical course in terms of steroid weaning, or occurrence of relapse[13].

However, endoscopic severity may still have an impact on the long term course of the disease. We have shown in a retrospective study that patients with CD exhibiting deep and extensive ulcerations at colonoscopy have a more aggressive clinical course with an increased rate of penetrating complications and surgery[14]. Among the 102 patients included, 53 had severe endoscopic lesions at index colonoscopy, defined as extensive and deep ulcerations covering more than 10% of the mucosal area of at least one segment of the colon. During the follow-up (median 52 mo), 37 patients underwent colonic resection. Patients with severe endoscopic lesions needed significantly more colonic resections than patients without severe lesions (relative risk 5.43, 95% CI: 2.64-11.18)[14]. Six patients had penetrating complications during the follow-up. All had severe endoscopic lesions at index colonoscopy, performed in most of them several years before. These data suggest that a subset of CD patients have a more aggressive disease, characterized by severe endoscopic lesions in the ileocolon during symptomatic phases, and a higher risk of surgery and penetrating complications[14].

Mucosal healing and long term outcome in CD

In clinical trials, the efficacy of therapies in CD is usually assessed by improvement in clinical activity (defined by a decrease of the CDAI). Assessment of endoscopic improvement was not usually performed until recently in clinical trials assessing the efficacy of drugs in CD. The main reason for this was that steroid-induced clinical remission is not associated with mucosal healing in two-thirds of CD patients. Furthermore, endoscopic remission obtained with steroids does not correlate with the risk of relapse after steroid withdrawal. However, there is growing evidence that mucosal healing during therapy is a sign of a good efficacy of a drug[10,15]. Data from the IBSEN cohort strongly suggests that mucosal healing predicts a generally favorable outcome of disease based on all types of treatment strategies (except corticosteroids) and is related to treatment efficacy, reduced frequency of surgery and hospitalizations[16].

Moreover, it is now clearly demonstrated that mucosal healing can be achieved with azathioprine and anti-TNF[17-21]. Rates of mucosal healing under azathioprine vary among studies, probably due to differences in the timing of endoscopy and the population analyzed. In a randomized controlled trial performed in steroid-dependent CD patients, Mantzaris *et al*[22] have recently shown that azathioprine was superior to budesonide in inducing mucosal healing at 1 year; complete or near complete healing was achieved in 83% of azathioprine-treated patients compared with only 24% of budesonide-treated patients ($P < 0.0001$). In a GETAID study, long lasting remission ($\geq$ 42 mo) maintained with azathioprine was associated with a complete mucosal healing (CDEIS = 0) in only 36% of CD patients[23]. In the SONIC study, which concerned CD patients naïve to immunosuppressants and biologics, only 15.6% of patients treated with azathioprine achieved mucosal healing at week 26[2].

In the endoscopic substudy of the ACCENT I study, patients treated with scheduled maintenance therapy with infliximab had superior rates of mucosal healing, and those who maintained complete mucosal healing over 1 year had a lower rate (but the difference was not significant) of hospitalizations and surgeries[24,25]. A study of mucosal healing in a cohort of CD patients under long-term treatment with infliximab was recently reported[26]. In this study from the Leuven group, 214 patients had a colonoscopy before and a second one within months after starting infliximab. Mucosal healing (complete or partial) was observed in 68% of the 183 initial responders. Mucosal healing was associated with a significantly lower need for major abdominal surgery during long-term follow-up (14.1% major surgeries in patients with mucosal healing *vs* 38.4% in patients without mucosal healing, $P < 0.0001$). Interestingly, partial mucosal healing had the same favorable impact as complete mucosal healing.

Several studies suggest that immunosuppressants and anti-TNF therapy may be more effective when given early in the course of the disease. Two studies have been recently performed in CD patients naïve to immunosuppressants and biologics, including "top-down strategy" which refers to early introduction of immunosuppressive or biologic therapies. In the SONIC study, infliximab therapy was superior to azathioprine in inducing mucosal healing at week 26 (30.1% *vs* 15.6%), but inferior to infliximab plus azathioprine combination therapy[2]. D'Haens *et al*[3] compared a top-down strategy to a more classical step-up strategy. Top-down strategy, which consisted of early induction with infliximab and maintenance with azathioprine, resulted in mucosal healing in 19/26 of patients (73%) at week 104. In the other arm (step-up strategy), mucosal healing was significantly less frequent (7/23 patients, 30%). This difference may have an impact in the long term. Indeed, when mucosal healing was achieved at 2 years (SES-CD score at 0), 70% of the patients (17/24) were in stable clinical remission during the following 2 years as compared to only 6 of the 22 (27%) who had mucosal lesions (SES-CD score above 0)[4]. Fifteen of the 17 patients with mucosal healing at year 2 maintained in remission without further infliximab infusions during the following 2 years. Mucosal healing obtained with immunosuppressants or anti-TNF agents was also associated with a decreased risk of surgery in the long term. Altogether these data would suggest checking endoscopic response in patients treated with immunosuppressants or anti-TNF. However, this attitude would make sense only if we are ready to optimize or switch to another treatment those patients who have no mucosal healing. Another question which is raised by recent studies is whether partial mucosal healing is sufficient to modify the disease outcome with decreased risk of hospitalizations, surgery and complications.

A further question is whether mucosal healing under a therapy is associated with a decreased risk of relapse after

discontinuation of this therapy. In a placebo-controlled study of the GETAID, presence of ulcerations at ileocolonoscopy before withdrawal of azathioprine was not predictive of the risk of relapse[23]. A recent study from the GETAID assessed the risk of relapse after infliximab discontinuation in patients in remission on combined maintenance therapy, who continued the immunosuppressant (azathioprine or methotrexate). Mucosal healing was among the factors strongly associated with a decreased risk of relapse[27].

Endoscopy in predicting relapses of CD after surgery

CD patients who have "curative" ileal resection and ileocolonic anastomosis are exposed to a high risk of postoperative recurrence[28]. Rutgeerts *et al*[29] demonstrated in 1990 that ileocolonoscopy performed within 1 year of surgery may predict the risk of clinical recurrence. Eighty-nine patients treated by ileal resection for CD were included in this prospective cohort follow-up to study the natural course of early postoperative lesions. Within 1 year of surgery, ileocolonoscopy detected recurrent lesions in the neo-terminal ileum in 73% of the patients, although only 20% had a clinical relapse. The rate of clinical relapse was 34% at 3 years. A score was devised to assess the severity of recurrent endoscopic lesions. The course of the disease was best predicted by the severity of the early postoperative lesions, as observed at ileocolonoscopy, on the anastomosis and/or on the neo-terminal ileum. Indeed, patients with less severe endoscopic lesions according to Rutgeerts' score (less than 5 aphtoid ulcers at anastomosis site), have a lower risk of clinical recurrence risk at 9% compared with 100% risk at 4 years for patients with more severe endoscopic recurrence (Rutgeerts' score i2 or greater). This score is widely used in clinical practice, and ECCO guidelines state that ileocolonoscopy should be the gold standard in the diagnosis of postoperative recurrence by defining the presence and severity of morphologic recurrence and predicting the clinical course. Ileocolonoscopy is recommended within the first year after surgery where decisions of postoperative treatment may be affected[30].

ASSESSMENT OF ENDOSCOPIC SEVERITY IN UC

Endoscopic scores of severity in UC

Nine different scores have been proposed to measure endoscopic severity in UC. Some of these scores focus on the severity of bleeding, but most of them rely on the recognition of elementary lesions such as abnormal vascular pattern, granularity, friability, bleeding and ulcers[10].

Endoscopic severity in severe attacks of UC

Carbonnel *et al*[31] demonstrated that total colonoscopy is feasible in 86% of cases in severe UC (73/85). In this study, endoscopy accurately identified severe endoscopic lesions (extensive deep ulcerations). Eighty-five consecutive patients with attacks of UC were reviewed. Extensive deep colonic ulcerations were diagnosed in 46 of them. No complication related to colonoscopy occurred except for one colonic dilatation. Forty-three of the 46 patients with severe endoscopic colitis underwent surgery. Extensive ulcerations reaching at least the circular muscle layer were found on pathological examination and were confirmed in 42/43[31]. Because of potential risks of complications, some rules have to be applied when performing colonoscopy in patients presenting severe attacks of UC, including pre-radiological examination to exclude megacolon, minimal insufflations, and when severe lesions are detected, the examination can be stopped as further examination has no additional prognostic value.

THE ROLE OF ENDOSCOPY IN PREDICTING THE COURSE OF UC

Patients with severe endoscopic lesions during severe attacks of UC have an increased risk of colectomy

Among patients hospitalized for a severe attack of UC, the presence of extensive and deep ulcerations at colonoscopy is associated with an increased risk of colectomy on that admission[31]. In their study performed in the prebiologic era, Carbonnel *et al*[31] showed that colectomy was performed in 43 of the 46 patients who presented severe endoscopic lesions (93%) as compared to 10/39 (26%) of those without such lesions (OR 41). In another study performed in severe UC patients, severe endoscopic lesions at colonoscopy were significantly more frequent in non-responders to medical treatment (91%) compared with responders (34%) (OR > 20)[32].

The colonoscopies performed during severe attacks of UC have also an impact on the long term outcome, with an increased rate of surgery in the long term in patients who exhibit extensive and deep ulcerations at index colonoscopy[33].

Mucosal healing and outcome in UC

Mucosal healing is classically assessed in patients treated for UC. However, there is no consensus on the definition of mucosal healing in UC[10]. The International Organization of IBD proposed the following definition: absence of friability, blood, erosions and ulcers in all visualized segments of the gut mucosa. According to this definition, disappearance of the normal vascular pattern is compatible with mucosal healing.

Mucosal healing may be obtained with several types of drugs[10,34]. It has been shown that it can be obtained with 5-aminosalicylates (5-ASA), steroids, azathioprine or methotrexate, and infliximab. Mucosal healing has been assessed in recent trials with different formulations of 5-ASA. In the ASCEND studies, evaluating different dosages of a delayed-released oral mesalazine in patients with mild or moderate UC, complete remission (including endoscopic remission) ranged between 18% and 25% at

week 6[35,36]. Truelove *et al*[37] demonstrated in 1954 that mucosal healing can be obtained with a high-dose of oral steroids in 30% of patients at week 6 compared with 10% in patients who received placebo ($P = 0.02$). In a recent review, it was considered that corticosteroids induce mucosal healing in 12%-41% of patients with UC, depending on the method of administration and the medication[10]. Some data suggest that mucosal healing may also be obtained with azathioprine or methotrexate[38,39]. Anti-TNF agents probably induce mucosal healing more rapidly. In ACT 1 and ACT 2, patients with refractory moderate-to-severe UC received placebo or infliximab intravenously[40]. Induction therapy with infliximab resulted in mucosal healing at week 8 in 61% of patients (148/242) compared with 32% (79/244) in the placebo groups ($P < 0.001$)[40]. At week 54 (ACT 1), scheduled maintenance therapy with infliximab resulted in mucosal healing in 45.5% (55/121) of patients compared with 18.2% (22/121) in the placebo group ($P < 0.001$).

Data from several studies suggest that mucosal healing may be associated with a better outcome in UC, more specifically a decreased risk of relapse. Reduced relapse rates have been demonstrated in UC patients who achieved mucosal healing with steroids. In a study published in 1966, Wright *et al*[41] found that 40% of patients who achieved mucosal healing with oral and rectal steroids did not relapse during 1 year of follow up as compared to 18% of those who still had lesions. In the ACT1 and 2 studies on infliximab maintenance in patients with moderately to severely active UC, 48.3% of the patients who achieved mucosal healing at week 8 were in remission at week 30 as compared to only 9.5% of those who did not achieve mucosal healing[39].

Mucosal healing may also be associated with reduced risk of surgery in UC. In the IBSEN population-based study, UC patients who achieved mucosal healing at 1 year (whatever the treatment) had a decreased risk of colectomy at 5 years (2% *vs* 7%, $P = 0.02$)[16]. A study performed in the Leuven cohort of UC patients treated with infliximab showed that colectomy was more frequent in patients who did not achieve mucosal healing at week 4 or 10 (Mayo endoscopic subscore greater than 1)[42]. In ACT1 and 2, it was shown that patients treated with infliximab were less likely to undergo colectomy through 54 wk than those receiving placebo[43]. However, data on the relationship between mucosal healing and risk of colectomy are not available in these studies.

Finally, there is a clear relationship between the grade and chronicity of inflammation in the colon and the risk of colorectal cancer. Better control of inflammation, as demonstrated with mucosal healing, may be associated with decreased risk of colorectal cancer.

PERSPECTIVES

There is growing evidence that morphological evaluation of lesions may provide help in the selection of IBD patients who should be treated more intensively. Endoscopy may help to select patients who will better respond to a therapy and those who should be treated because of exposure to an increased risk of complication and surgery. Assessment of mucosal healing should be increasingly performed in the future. However, it is not yet proven that patients not achieving mucosal healing should be treated more intensively. As endoscopy may be difficult to repeat in these patients, surrogate markers such as calprotectin or C-reactive protein levels, provided they are closely related to the presence of severe lesions, could be increasingly used.

Another limit of endoscopy relies on the fact that only mucosal aspects can be assessed by endoscopy. Radiological techniques, including ultrasonography, CT scan or MRI, can also describe the wall and identify penetrating and stricturing complications. Recent studies with MRI suggest that this technique could be proposed to assess severity of mucosal and parietal disease[44].

CONCLUSION

Endoscopy, which allows a direct assessment of severity and extent of mucosal lesions, may help in the management of IBD. In patients with active IBD, endoscopy may help to select patients who should receive early and active therapies and this is for two reasons. First, severe endoscopic lesions may predict a poor outcome with increased risk of colectomy and complications. Second, patients with no lesions gain no benefit in receiving active treatments with potential risks. In treated IBD patients, mucosal healing is associated with a better outcome, with decreased risks of relapse and major surgery. Assessment of mucosal healing may help to characterize the response to treatments and in decisions of optimal strategies.

REFERENCES

1 **Hanauer SB**. Positioning biologic agents in the treatment of Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 1570-1582
2 **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
3 **D'Haens G**, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, Vermeire S, Van de Mierop FJ, Coche JC, van der Woude J, Ochsenkühn T, van Bodegraven AA, Van Hootegem PP, Lambrecht GL, Mana F, Rutgeerts P, Feagan BG, Hommes D. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008; **371**: 660-667
4 **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 e10-e11
5 **Fefferman DS**, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. *Clin Gastroenterol Hepatol* 2005; **3**: 11-24
6 **Hommes DW**, van Deventer SJ. Endoscopy in inflammatory bowel diseases. *Gastroenterology* 2004; **126:** 1561-1573

7 **Mary JY**, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). *Gut* 1989; **30**: 983-989

8 **Cellier C**, Sahmoud T, Froguel E, Adenis A, Belaiche J, Bretagne JF, Florent C, Bouvry M, Mary JY, Modigliani R. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. *Gut* 1994; **35**: 231-235

9 **Daperno M**, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary JY, Colombel JF, Rutgeerts P. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004; **60**: 505-512

10 **Pineton de Chambrun G**, Peyrin-Biroulet L, Lémann M, Colombel JF. Clinical implications of mucosal healing for the management of IBD. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 15-29

11 **Modigliani R**, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, Rene E. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives. *Gastroenterology* 1990; **98**: 811-818

12 **Nahon S**, Bouhnik Y, Lavergne-Slove A, Bitoun A, Panis Y, Valleur P, Vahedi K, Messing B, Matuchansky C, Rambaud JC. Colonoscopy accurately predicts the anatomical severity of colonic Crohn's disease attacks: correlation with findings from colectomy specimens. *Am J Gastroenterol* 2002; **97**: 3102-3107

13 **Landi B**, Anh TN, Cortot A, Soule JC, Rene E, Gendre JP, Bories P, See A, Metman EH, Florent C. Endoscopic monitoring of Crohn's disease treatment: a prospective, randomized clinical trial. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gastroenterology* 1992; **102**: 1647-1653

14 **Allez M**, Lemann M, Bonnet J, Cattan P, Jian R, Modigliani R. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. *Am J Gastroenterol* 2002; **97**: 947-953

15 **Rutgeerts P**, Vermeire S, Van Assche G. What is the role of endoscopy in predicting Crohn's disease relapse or course? *Inflamm Bowel Dis* 2008; **14** Suppl 2: S183-S184

16 **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

17 **van Assche G**, Vermeire S, Rutgeerts P. Mucosal healing and anti TNFs in IBD. *Curr Drug Targets* 2010; **11**: 227-233

18 **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

19 **D'Haens G**, Geboes K, Ponette E, Penninckx F, Rutgeerts P. Healing of severe recurrent ileitis with azathioprine therapy in patients with Crohn's disease. *Gastroenterology* 1997; **112**: 1475-1481

20 **D'Haens G**, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. *Gastrointest Endosc* 1999; **50**: 667-671

21 **Baert FJ**, D'Haens GR, Peeters M, Hiele MI, Schaible TF, Shealy D, Geboes K, Rutgeerts PJ. Tumor necrosis factor alpha antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. *Gastroenterology* 1999; **116**: 22-28

22 **Mantzaris GJ**, Christidou A, Sfakianakis M, Roussos A, Koilakou S, Petraki K, Polyzou P. Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. *Inflamm Bowel Dis* 2009; **15**: 375-382

23 **Lémann M**, Mary JY, Colombel JF, Duclos B, Soule JC, Lerebours E, Modigliani R, Bouhnik Y. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005; **128**: 1812-1818

24 **Rutgeerts P**, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, Patel K, Wolf DC, Safdi M, Colombel JF, Lashner B, Hanauer SB. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006; **63**: 433-442; quiz 464

25 **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

26 **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

27 **Louis E**, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Dupas JL, Pillant H, Picon L, Veyrac M, Flamant M, Savoye G, Jian R, De Vos M, Paintaud G, Piver E, Colombel JF, Mary JY, Lemann M. 961 infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors: a prospective ongoing cohort study. *Gastroenterology* 2009; **5** Suppl 1; A-146

28 **Rutgeerts P**, Van Assche G. What is the role of endoscopy in the postoperative management of Crohn's disease? *Inflamm Bowel Dis* 2008; **14** Suppl 2: S179-S180

29 **Rutgeerts P**, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **99**: 956-963

30 **Caprilli R**, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, Hommes DW, Lochs H, Angelucci E, Cocco A, Vucelic B, Hildebrand H, Kolacek S, Riis L, Lukas M, de Franchis R, Hamilton M, Jantschek G, Michetti P, O'Morain C, Anwar MM, Freitas JL, Mouzas IA, Baert F, Mitchell R, Hawkey CJ. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. *Gut* 2006; **55** Suppl 1: i36-i58

31 **Carbonnel F**, Lavergne A, Lémann M, Bitoun A, Valleur P, Hautefeuille P, Galian A, Modigliani R, Rambaud JC. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. *Dig Dis Sci* 1994; **39**: 1550-1557

32 **Daperno M**, Sostegni R, Scaglione N, Ercole E, Rigazio C, Rocca R, Pera A. Outcome of a conservative approach in severe ulcerative colitis. *Dig Liver Dis* 2004; **36**: 21-28

33 **Carbonnel F**, Gargouri D, Lémann M, Beaugerie L, Cattan S, Cosnes J, Gendre JP. Predictive factors of outcome of intensive intravenous treatment for attacks of ulcerative colitis. *Aliment Pharmacol Ther* 2000; **14**: 273-279

34 **Lichtenstein GR**, Rutgeerts P. Importance of mucosal healing in ulcerative colitis. *Inflamm Bowel Dis* 2010; **16**: 338-346

35 **Hanauer SB**, Sandborn WJ, Dallaire C, Archambault A, Yacyshyn B, Yeh C, Smith-Hall N. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. *Can J Gastroenterol* 2007; **21**: 827-834

36 **Hanauer SB**, Sandborn WJ, Kornbluth A, Katz S, Safdi M, Woogen S, Regalli G, Yeh C, Smith-Hall N, Ajayi F. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol* 2005; **100**: 2478-2485

37 **Truelove SC**, Witts LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. *Br Med J* 1954; **2**: 375-378

38 **Paoluzi OA**, Pica R, Marcheggiano A, Crispino P, Iacopini F, Iannoni C, Rivera M, Paoluzi P. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-

resistant ulcerative colitis: results of an open-label study on efficacy and tolerability in inducing and maintaining remission. *Aliment Pharmacol Ther* 2002; **16**: 1751-1759

39 **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

40 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476

41 **Wright R**, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. *Am J Dig Dis* 1966; **11**: 847-857

42 **Ferrante M**, Vermeire S, Fidder H, Schnitzler F, Noman M, Van Assche G, De Hertogh G, Hoffman I, D'Hoore A, Van Steen K, Geboes K, Penninckx F, Rutgeerts P. Long-term outcome after infliximab for refractory ulcerative colitis. *J Crohns colitis* 2008; **2**: 219-225

43 **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

44 **Rimola J**, Rodriguez S, García-Bosch O, Ordás I, Ayala E, Aceituno M, Pellisé M, Ayuso C, Ricart E, Donoso L, Panés J. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. *Gut* 2009; **58**: 1113-1120

S- Editor Wang YR **L- Editor** Logan S **E- Editor** Zheng XM