Initial medical management of severe acute ulcerative colitis

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Abstract

Severe colitis is life-threatening complication of ulcerative colitis. Early recognition of the severity of the colitis, intensive medical therapy and prompt surgery when necessary have all contributed to improved outcome. Initial medical treatment should be instituted as soon as the diagnosis is made with an intravenous corticosteroid associated with supportive treatment. If the patient fails to response to this intensive treatment after 5-7 days, cyclosporin should be initiated. If cyclosporin is not used then colectomy should be performed immediately. Moreover, significant deterioration at any point during medical therapy is an indication for colectomy. The gravity of the patient's condition require close interaction between physician an surgeon. (Acta gastroenterol. belg., **2000**, 63, **275-278**).

Key words : severe acute colitis, steroids, toxic megacolon, colectomy.

Severe colitis is a potentially life-threatening complication of ulcerative colitis. In early series the mortality ranged from 25 to 35%. More recent data show that in specialized centers with experienced gastroenterologists and surgeons working together, the mortality rate has fallen to approximately 1% (1). Between 5 and 15% of patients will develop severe acute colitis, and it is important to stress that in onethird of cases it presents during the first attack. This article will focus only on the initial medical treatment for severe ulcerativre colitis. Cyclosporin therapy which is not a first line accepted treatment will not be discussed in this paper.

Definition of severe attack

There is no universally accepted definition of severe attack of ulcerative colitis. It is defined in classical terms by clinico-biological and morphological criteria to which has to be added resistance to oral corticosteroid therapy. These criteria are however far from being always present in one individual, particularly in patients who are already receving steroids.

The most widely definition used in clinical practice is based on the classical Truelove and Witts criteria (2) includied six or more grossly bloody stools daily, a mean evening temperature of more than 37°,5 C or temperature of 37°,8 on at least 2 of 4 days, tachycardia with pulse rate of 90 /min or greater, haemoglobin of 9g/dl or less, and an erythrocyte sedimentation rate greater than 30 mm/h. To this simple assessment, others have added serum albumin, weight loss, abdominal pain and tenderness as well as radiographic or endoscopic features. It must be noted, however, that these criteria and clinical findings can be altered by corticosteroids and/or antibiotics (3). A simplified clinical index has been recently proposed, but has not been extensively validated (4).

Another predictor factor of severe ulcerative colitis may be the depth of the mucosal ulcers. Deep ulcers involving the muscularis propria predicts complications, namely dilatation and, also perforation. Depth of ulcers can be assessed in several ways. It is usually recognizable on a plain abdominal film and is responsible for the "mucosal island" sign wich was found to be a risk factor for colectomy (5). The presence of three or more distended small bowel loops and a dilated colon (> 6 cm in diameter) were also associated with severe disease.

Colonoscopy and more rarely these days barium enema can also be used to assess deep ulceration. Traditionally, colonoscopy has been considered to be contra-indicated in severe attacks of colitis (6). However this procedure is safe if it is performed very carefully and by expert hands (7,8). For major referral centers receiving patients who are not responding to standard therapy from other hospitals, there may be a place for colonoscopy. However, colonoscopy, does not have to be systematic especially if the plain abdominal film gives enough informations . If an endoscopic assessment is to be made, a colonoscopy limited to the left colon is usually sufficient as the deepest ulcerations tend to occur in the left colon. Perhaps the major role for colonoscopy is in the assessment of patients who have incomplete response to treatment and for whom colectomy is considered (9).

General medical management

Hospitalization is mandatory for these patients. Management should be through a team approach and a surgeon should be consulted at the time of diagnosis. Diagnostic procedures should include a complete blood count with differential, biochemical profile included erythrocyte sedimentation rate, C-reactive protein and albumin. Stools should be sent for culture, ova, parasites and Cl. difficile. A plain abdominal film is requested to determin the extent of the colitis and to exclude a toxic

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megacolon or a perforation. Physical examination should be carried out daily by both medical and surgical teams to evaluate for abdominal tenderness, rebound tenderness, percussion for distension and possible loss of hepatic dullness. Regular observation of temperature and blood pressure are recorded and a stool chart should be kept noting stool frequency, consistency and presence of blood. Intravenous fluids should be administered and electrolyte abnormalities should be corrected. Patients should be transfused if anaemia is significant. Patients should not be given oral fluids and food for the first 24-48 hours after admission to the hospital. There is no evidence to suggest that bowel rest and total parenteral nutrition are effective and controlled trials have failed to demonstrate any benefit (6). Total parenteral nutrition should be reserved for severely ill patients who are cachectic and present with hypoalbuminemia. Prophylactic doses of heparin, such as low weight heparin (5000 units subcutaneously once daily) should be indicated, since patients with active ulcerative colitis are at risk of thromboembolisation and pulmonary embolism. Drugs that may tend to induce toxic megacolon, such as antidiarrhoeals and anticholinergics should be avoided.

Complications of severe ulcerative colitis

Free perforation may occur at any time during the course of medical therapy for severe ulcerative colitis and requires emergency colectomy.

Massive haemorrhage is uncommon and more often requires a subtotal colectomy.

For toxic megacolon, timing of surgery will depend on the circumstance. If the megacolon develops during medical therapy, colectomy should be performed without delay. If the megacolon is present on the initial plain radiograph, then it is worth starting medical treatment with intravenous steroids since about 50% will settle. Some teams add to medical treatment, therapeutic modalities to decompress the dilated colon (10).

Medications for acute severe ulcerative colitis

Steroids

Corticosteroids have been shown to be effective in acute severe ulcerative colitis (11). However the regimen of treatment is not "evidence- based". No trial of intravenous *versus* oral steroids has been made but high doses intravenously appear to produce a more rapid response than high doses orally. No controlled studies have been performed demonstrating greater efficacy of one steroid over another. Moreover in the absence of dose-response studies, the choice of dosage remains empirical and controversial. The dose commonly used in France is 1 mg/kg/24 hours of prednisolone. Other intravenous corticosteroids used are hydrocortisone (100 mg 6 hourly) or methylprednisolone (6-15 mg 6 hourly). Intravenous ACTH can also be used in a dose of 40 units every 8 hours. One trial suggested that intravenous ACTH was more effective than intravenous hydrocortisone in patients who had not received oral prednisolone prior to admission with severe attack (12). For patients who had received prior steroids, hydrocortisone was more effective than ACTH.

Systemic corticosteroids are often combined with rectal administration of hydrocortisone enema 100 mg or budesonide enema 2 mg once or twice daily to reduce tenesmus and urgency. In patients that cannot retain the medication streroids foam can be administred.

The precise duration of intensive treatment is not well defined. It was advised that if the patients did not respond within 5-7 days to intravenous steroids they should udergo surgery (13). In patients who were deteriorating during this time or were not thought to be in remission at the end of this period, further management decision must be made immediately.

Antibiotics

The use of antibiotics remains controversial. Several trials have no shown that antibiotics (metronidazole, vancomycin, tobramycin) given routinely to patients with severe attacks, in addition to steroids, provide no beneft (14-16). However some authors advocate the use of broad-spectrum antibiotics such metronidazole plus ampicillin or a third-generation cephalosporin. The rationale for antibiotic includes presumption of transmural extension of the disease, risk of microperforation, systemic bacteremia, and a potential perioperative prophylaxis for patients with a high risk of emergency colectomy. A recent study have shown a benefit effect of ciprofloxacine in addition to steroids (17).

Sulfasalazine, 5-aminosalicylic acid (5-ASA)

Although 5-ASA has been shown to be a better treatment than placebo in mild to moderate ulcerative colitis, it has not been used for severe attacks. The relatively slow response to 5-ASA makes it an inappropriate form of treatment for critically sick patients.In clinical practice, there has been no indication that combination of 5 ASA and steroids is better than steroids alone.

Immunosuppressives

Both azathioprine and 6-mercaptopurine have shown efficacy in controlled and uncontrolled trials in the treament of ulcerative colitis (18). However, they have no role in the initial treatment of severe acute ulcerative colitis, since the mean response time is thought to be slightly over 3 months.

Methotrexate, which has also shown efficacy in uncontrolled trials in ulcerative colitis (19), takes several weeks to induce any response and is therefore not indicated in the management of acute severe ulcerative colitis.

Intravenous cyclosporin monotherapy without steroid has been proposed by some but remain criticable (20, 21). It issue should not be down out of controlled trials.

Heparin

Acute ulcerative colitis is associated with thrombophilic state. A series of openlabeled trial suggest a benefict of heparin for treatment of severe ulcerative colitis (22). Heparin has wide range of interesting anti-inflammatory effects and the results of ongoing controlled trials are awaited (23).

Predicting response to initial medical therapy

About 20-30% of patients with a severe attack fail to respond to intravenous steroids (13). Some of these will respond to the addition of cyclosporin (24), but others will require surgery. If these patients could be identified early on, the management decisions such as the need to start cyclosporin or the need for colectomy could be made during the first days of treatment. Various clinical, laboratory or morphological features are now proposed to predict outcome. In patients with acute colitis treated with intravenous steroids, factors that have been advocated as predictive of poor outcome include advanced age, anorexia, longer disease duration, first episodes and severe, extensive disease (11,25). A prospective study has identified two factors which were highly predictive of the need for surgery : stool frequency and CRP. Patients with more than 8 stools daily or 3-8 stools daily with a CRP > 45 mg/l required surgery with 85% accuracy on day 3 of intravenous steroids (26). This "3 days rule" has been validated by a subsequent retrospective study (27). In another retrospective study,the presence of perinuclear antineutrophil cytoplasmic antibodies was associated with relative resistance to medical therapy (28). A recent study suggest that T lymphocyte steroid resistance is an important factor in determining response to steroid treatment in patients with severe ulcerative colitis and may be a better predictor of outcome than disease severity (29).

Beside clinical data, morphological feature also allow to predict the response to medical treatment. Deep ulcers are significantely associated with the need for surgery. These ulcers can be identified by abdominal plain film (26), possibely after air insuflation (30) or by colonoscopy (8). This last exploration is further usefull, as we have seen, when the response to therapy is difficult to interpret and when a decision for surgery has to be made (31).

Conclusions

Over 70% of patients with an acute attack of severe ulcerative colitis can be spared colectomy using intensive initial medical treatment. If a patient fails to response to intravenous streroid therapy after 5-7 days, cyclosporin should be initiated. If cyclosporin is not used then colectomy should be performed immediately. Moreover, significant deterioration at any point during medical therapy is an indication for colectomy. The gravity of the patient's condition requires close interaction between physician and surgeon.

References

1. JEWELL D., CAPRILLI R., MORTENSEN N., NICHOLLS R.J., WRIGHT J.P. Indication and timing of surgery for severe ulcerative colitis. *Gastroenterol. Intern.*, 1991, **4** : 161-164.
2. TRUELOVE S.C., WITTS L.J. Cortisone in ulcerative colitis. Final report on a therapeutic trial. *Br. Med. J.* 1955, **2** : 1041-1048.
3. MARION J.F., PRESENT D.H. The modern medical management of acute, severe ulcerative colitis. *Eur. J. Gastroenterol. Hepatol.*, 1997, **9** : 831-835.
4. WALMSLEY R.S., AYRES R.C.S., POUNDER R.E., ALLAN R.N. A simple clinical colitis activity index. *Gut*, 1998, **43** : 29-32.
5. PRANTERA C., LORENZETTI R., CERRO P., DAVOLI M., BRANCATO G., FANUCCI A. The plain abdominal film accurately estimates extent of active ulcerative colitis. *J. Clin. Gastroenterol.*, 1991, **13** : 231-234.
6. PRESENT D. Management of acute severe colitis. *In* : ALLAN R.N., RHODES J.M., HANAUER S.B., KEIGHLEY M.R.B., ALEXANDER-WILLIAMS J., FAZIO V.W. (eds). Inflammatory bowel diseases. New York : Churchill Livingstone, 1997 : 565-570.
7. ALEMAYEHU G., JARNEROT G. Colonoscopy during an attack of severe ulcerative colitis is a safe procedure and of great value in clinical decision making. *Am. J. Gastroenterol.*, 1991, **86** : 187-190.
8. CARBONNEL F., LAVERGNE A., LEMANN M., BITOUN A., VALLEUR P., HAUTEFEUILLE P., GALIAN A., MODIGLIANI R., RAMBAUD J.C. Colonoscopy of acute colitis. A safe and reliable tool for the assessment of severity. *Dig. Dis. Sci.*, 1994, **39** : 1550-1557.
9. HYDE G.M., JEWELL D. Review article : the management of severe ulcerative colitis. *Aliment Pharmacol. Ther.*, 1997, **11** : 419-424.
10. PRESENT D.H., WOLFSON D., GELERNT I.M., RUBBIN P.H., BAUER J., CHAPMAN M.L. Medical decompression of toxic megacolon by "rolling". A new technique of decompression with favorable long terme follow-up. *J. Clin. Gastroenterol.*, 1988, **10** : 485-490.
11. KORNBLUTH M., MARION J.F., SALOMON P., JANOWITZ H.D. How effective is current medical therapy for severe ulcerative and Crohn's colitis ? An analytic review of selected trials. *J. Clin. Gastroenterol.*, 1995, **20** : 280-284.
12. MEYERS S., SACHAR D.B., GOLDBERG J.D., JANOWITZ H.O. Corticotrophin versus hydrocortisone in the intravenous treatment of ulcerative colitis. *Gastroenterology*, 1983, **85** : 351-357.
13. JEWELL D.P. The management of severe ulcerative colitis. In Mignon M, Colombel JF eds. Recent advances in the pathophysiology and management of inflammatory bowel diseases and digestive endocrine tumors. John Libbey Eurotext Paris, 1999 : 128-35.
14. CHAPMAN R.W., SELBY W.S., JEWELL D.P. Controlled trial of intravenous metronidazole as an adjunct to corticosteroids in severe ulcerative colitis. *Gut*, 1986, **27** : 1210-1212.
15. DICKNSON R.J., O'CONNER H.J., PINDER I., HAMILTON I., JOHNSTON D., AXON A.T. Doubleblind controlled trial of oral vancomycin as adjunction therapy in acute exarcebation of ulcerative colitis. *Gut*, 1985, **26** : 1380-1384.
16. MANTZARIS G.J., HATZIS A., KONTOGIANNIS P., TRIADAPHYLLOU G. Intravenous tobramycine and metronidazole as an adjunct to corticosteroids in acute, severe ulcerative colitis. *Am. J. Gastroenterol.*, 1994, **89** : 43-46.
17. TURUNEN U.M., FARKKILA M.A., HAKALA K., SINOVEN A., OGREN M., VUORISTO M., VALTONEN W., MEITTINEN T.A. Long-term treatment of ulcerative colitis with ciprofloxacine : a prospective double-blind, placebo-controlled study. *Gastroenterology*, 1998, **115** : 1072-1078.
18. GEORGE J., PRESENT D.H., POU R., BODIAN C., RUBIN P.H. The long-term outcome of ulcerative colitis treated with 6-mercaptopurine. *Am. J. Gastroenterol.*, 1996, **91** : 1711-1714.
19. KOZAREC R.A. Review article : Immunosuppressive therapy for inflammatory bowel disease. *Alim. Pharmacol. Ther.*, 1993, **7** : 117-123.
20. D'HAENS G., LEMMENS L., HIELE M., VANDEPUTTE L., NEVENS F., PEETERS M., VERMEIRE S., BAERT F., GOBOES K., RUTGEERTS P.

Intravenous cyclosporine A (CyA) monotherapy versus intravenous methyprednisolone (MP) monotherapy in severe ulcerative colitis : a double blind controlled trial. *Gastroenterology*, 1998, **114** : G3948.

21. SVANONI F., BONASSI U., BAGNOLO F., CAPORUSCIO S. Effectiveness of cyclosporine A in the treatment of active refractory ulcerative colitis. *Gastroenterology*, 1998, **114** : G4484.
22. EVANS R.C., CLARCKE L., HEATH P., STEPHENS S., MORRIS A.L., RHODES J.M. Treatment of corticosteroid resistant ulcerative colitis with heparin-a report of 16 cases. *Aliment Pharmacol. Ther.*, 1997, **11** : 1037-1040.
23. KORZENIK J.R., ROBERT M.E., BITTON A., ROBINSON M., SCHERL E.J., FISHER R.L., BINDER H.J. A multi-canter randomiezed, controlled trial of heparin for the treatment of ulcerative colitis. *Gastroenterology*, 1999, **116** : G3264.
24. LICHTIGER S., PRESENT D.H., KORNBLUTH A., GELERNT I., BAUEUR G., GALLER G., MICHELASSI F., HANAUEUR S. Cyclosporin in severe ulcerative colitis refractory to steroid therapy. *N. Engl. J. Med.*, 1994, **330** : 1841-1845.
25. MEYERS S., LERER P.K., FEUER E.J., JOHNSON J.W., JANOWITZ H.D. Predicting the outcome of corticoid therapy for acute ulcerative colitis. Results of a prospective randomized double-blind trial. *J. Clin. Gastroenterol.*, 1987, **9** : 50-54.
26. TRAVIS S.P.L., FARRANT J.M., RICKETTS C., NOLAN D.J., MORTENSEN N.M., KETTLEWELL M.G.W., JEWELL D.P. Predicting outcome in severe ulcerative colitis. *Gut*, 1996, **38** : 905-910.
27. LINDGREN S.C., FLOOD L.M., KILANDER A.F., LOFBERG R., PERSSON T.B., SJODAHL R.I. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. *Eur. J. Gastroenterol. Hepatol.*, 1998, **10** : 831-835.
28. SANDBORN W.J., LANDERS C.J., TREMAINE W.J., TARGANT S.R. Association of antineutrophil cytoplasmic antibodies with resistance to treatment of left-sided ulcerative colitis : results of a pilot study. *Mayo Clin. Proc.*, 1996, **71** : 431-436.
29. HEARING S.D., NORMAN M., PROBERT C.S.J., HASLAM N., DAYAN C.M. Predicting therapeutic outcome in severe ulcerative colitis by measuring in vitro steroid sensitivity of proliferating perpheral blood lymphocytes. *Gut*, 1999, **45** : 382-388.
30. ALMER S., BODEMAR G., FRANZEN L., LINDSTROM E., NYSTROM P., STROM M. Use of air enema radiography to assess depth of ulceration during acute attacks of ulcerative colitis. *Lancet*, 1996, **347** : 1731-1735.
31. LÉMANN M., MODIGLIANI R. traitement des MICI : vue d'ensemble. *In* : LÉMAN M, MODIGLIANI R. (eds). Maladies inflammatoires de l'intestin. Paris : Doin, 1998 : 225-271.