Medical management of ulcerative colitis

Rogler, G


Posted at the Zurich Open Repository and Archive, University of Zurich. http://www.zora.uzh.ch

Medical management of ulcerative colitis

Abstract

Ulcerative colitis (UC) is a chronic and relapsing inflammation limited to the colonic mucosa and always involving the rectum with variable extension towards the cecum. The aim of medical treatment is to induce and maintain clinical remission. In contrast to Crohn's disease for which a 'top-down' or 'early aggressive' therapy is discussed, in UC the concept of a step-up treatment is still valid. This step-up approach includes local or systemic administration of 5-aminosalicylic acid as first-line therapy followed by topical or systemic steroid administration as well as azathioprine, 6-mercaptopurine, cyclosporine, and more recently anti-tumor necrosis factor monoclonal antibodies as options in refractory or chronic active disease. Colectomy may be necessary if medical treatments are unsuccessful or if complications develop. The decision about the individual therapy of UC is dependent on both disease activity and on disease location. Different therapy strategies are applied in ulcerative proctitis, left-sided colitis, pancolitis and fulminant colitis as well as in chronic active disease and maintenance of remission. This overview presents important concepts in the treatment of UC based on the published guidelines.
Medical management of ulcerative colitis

Gerhard Rogler

Address for correspondence:

Gerhard Rogler, MD, PhD, AGAF
Division of Gastroenterology and Hepatology
Department of Visceral Medicine
University Hospital Zürich
Rämistrasse 100
CH-8091 Zürich
Switzerland
Abstract

Ulcerative colitis (UC) is a chronic and relapsing inflammation of the limited to the colonic mucosa always involving the rectum with variable extension towards the cecum. The aim of medical treatment is to induce and maintain clinical remission. In contrast to Crohn’s disease for which a “top down” or “early aggressive” therapy is discussed in UC still the concept of a step up treatment is valid. This step up approach includes local or systemic administration of 5-aminosalicylic acid as first line therapy followed by topical or systemic steroid administration as well as azathioprine, 6-mercaptopurine, cyclosporine, and more recently anti-tumor necrosis factor (TNF) monoclonal antibodies as options in refractory or chronic active disease. Colectomy may be necessary if medical treatments are unsuccessful or if complications develop.

The decision about the individual therapy of ulcerative colitis is dependent on both disease activity and on disease location. Different therapy strategies are applied in ulcerative proctitis, left-sided colitis, pancolitis and fulminant colitis as well as in chronic active disease and maintenance of remission. This overview presents important concepts in the treatment of ulcerative colitis based on the published guidelines.

Key Words: ulcerative colitis; topical therapy; medical management; aminosalicylates; inflammatory bowel disease; systemic therapy
1. Introduction

Ulcerative colitis (UC) besides Crohn’s disease is the most important chronic inflammatory bowel disease (IBD). Its Incidence in Europe is estimated to be 5 to 25 new patients per 100,000 inhabitants per year \(^{1-5}\). The disease course and extend of the disease are very variable. Therefore an individualized diagnostic approach and therapy are mandatory.

Clearly the therapeutic management of UC is focussed on the induction and maintenance of remission. However, presently we face a discussion, whether clinical or endoscopical remission should be the final treatment goal. During relapses or flares of UC, pharmacological or surgical interventions are needed to re-establish remission. For the re-establishment of remission and achievement of long-term remission, strategies have to be employed that minimize steroid use and therapy-related side effects.

Treatment decisions are based on disease severity (mild, moderate or severe) on one hand. The degree of inflammation is a crucial factor for the choice of the therapeutic procedures. In addition the duration of the symptoms, the preceding therapy(ies), the “disease history” disease as well as the individual symptoms influence the therapy decision. The extent of the disease (pan-colitis, left sided colitis, recto-sigmoiditis or proctitis) will clearly be of impact on the decision for a specific therapy. Symptom indicating the severity of the disease flare such as vomiting, signs of bowel obstruction, number of bowel movements, presence of blood, weight loss, high fever and abdominal tenderness and pain during defecation
are useful practical criteria of severity in everyday medical practice. Frequently the efficacy of a topical the local therapy is underestimated, or is not addressed, because of the rectal application.

The valid guidelines represent the basis, on which for the individual patient the optimal therapy must be determined.

2. Medical management of acute flares of ulcerative colitis

An acute flare of ulcerative colitis usually is characterized by typical clinical complaints, such as frequent bowel movements, bloody diarrhoea and abdominal pain. It is frequently recommended to exclude an infectious colitis before starting any treatment. The impact and efficacy of such „routine diagnostics“, however, has never been really evaluated. A recent development is an increase in the incidence of Clostridium difficile colitis and CMV colitis among UC patients especially under immunosuppressive conditions. This has to be kept in mind in patients that seem to have steroid refractory UC.

The choice of therapy for acute flares or relapses of UC is based on the clinical presentation. The value of laboratory markers for the therapy decision is limited. As minimum requirement haemoglobin levels, leukocyte counts as well as general inflammation parameters such as thrombocyte counts, ESR or CRP should be determined 6. “Control colonoscopies” without therapeutic or prognostic consequences are not indicated and should not be performed during an acute flare
of UC. Changes in the extension of the disease can also be proven by ultrasound in the hands of an experienced doctor.

In general a step-up approach is recommended in all guidelines for the treatment of UC (Figure 1). An abundance of evidence exists that supports the use of aminosalicylates (5-ASA) in mild to moderate UC for the induction of remission. Corticosteroids are used in patients not responding to 5-ASA or in patients with more severe disease. Azathioprine (AZA) and 6-mercaptopurine have been shown to be useful in steroid refractory patients.

2.1. Left sided colitis, recto-sigmoiditis, proctitis

Distal or left-sided ulcerative colitis with mild to moderate activity should be initially treated topically. The rectal application of steroids (as enema or foam) is superior to placebo; however, 5-aminosalicylic acid (5-ASA) is superior to steroids in topical application.

Consecutively, treatment of first choice in mild to moderate left-sided colitis or recto-sigmoiditis are foams or enemas with 5-aminosalicylic acid (5-ASA, mesalamine). During an acute flare of a colitis application of enemas frequently in uncomfortable due to the sometimes large volume (up to 100 ml) which makes them less well tolerated by the patients. In patients with UC usually the rectum is the side of the most severe inflammation. It contains the highest number of sensory nerves in the bowel. Therefore, it is easily conceivable that such a large volume of fluid will cause complaints. Foams are better accepted by the patients in general.
(potentially also due to the smaller volume). In ulcerative proctitis 5-ASA suppositories should be used.

If the disease extends to the left colonic flexure it appears to be recommendable to combine topical therapy with an oral 5-ASA preparation.

The recommended duration of treatment is at least four weeks. The minimal, but sufficient topical dose for the achievement of a remission is 1 g 5-ASA per day. Higher doses up to 4 g/day have not been proven to be are not more effective.

After a topical therapy with 5-ASA over several weeks was ineffective, topical steroids should added for at least 4 weeks. If the topical therapy finally fails systemic steroids should be used. A severe flare of a distal colitis primarily should be treated orally with systemic steroids if possible in combination with topical use of 5-ASA.

In different studies initial steroid doses between 40 and 60 mg per day did not seem to exhibit remarkable differences in therapeutic efficacy.

### 2.2. Pan-colitis

A mild to moderate flare of a pan-colitis should initially be treated with oral 5-ASA (Figure 3). 4 g 5-ASA per day are superior to 2g. Usually it has been recommended that 5-ASA should be taken in three doses over the day. Newer studies from the last years indicate that the total daily dose can be taken at one time (e.g. in the morning) - or even should be taken at one time, as in some studies there was even increased efficacy under these conditions. The possibility to take the whole dose at one time is also likely to increase patient compliance and
adherence to therapy. From several studies we know that the main drawback of 5-ASA therapy (and probably the most important reason for therapy failure) is a reduced adherence due to the mode of intake and the number of tablets or capsules (up to 8 per day). With respect to this also the new formulations as "granules" or "sachets" may be of clear advantage.

During severe pancolitis or lack of response to a therapy with 5-aminosalicylic acid systemic glucocorticoids should be used orally or intravenously (initially 60 mg prednisone equivalent per day) \(^{27, 28}\) (Figure 4). In patients requiring steroid therapy, the immediate outcomes are favourable, but the long-term outcome at one year is somewhat disappointing. About half of the patients with UC initially treated with steroids will require additional therapy after one year. A population-based study has shown that a year after the initial course of corticosteroid treatment, a prolonged steroid response is seen in only 49% of patients with UC. However, sometimes a second course of steroid therapy will induce remission again. In addition, numbers may change with sufficient and well-adhered maintenance therapy. Steroid dependence has been reported to develop in 22% of UC patients, with surgery being required in 29% of those patients. In general, a state of steroid dependence should clearly be avoided. Therefore, it is questionable, whether this really can be a measure in clinical studies.

Whether the steroids for pan-colitis are given orally or intravenously should be decided with respect to the clinical presentation of the patient.

Usually steroids are combined with oral aminosalicylates, although the efficacy or advantage of such a combination has never been documented by appropriate clinical studies. The tapering of steroids has long been performed very schematically. Tapering regimes differing from country to country have been
established. In the meantime it is accepted that tapering of steroids should be 
planned individually according to the patient's clinical symptoms. If no response can 
be achieved by the oral administration of steroids, a change to one course of i.v. 
administration usually is recommended. This could be justified with the assumption 
that during severe colitis there is an increased peristaltic also of the small bowel and 
resorption of oral steroids could be reduced. Studies on the change of an oral 
Steroid administration to on an intravenous do not exist; to the experience of most 
clinicians for a number of patients this approach, however, clinically worked. An i.v. 
- therapy duration of 10 days is generally sufficient. If no improvement is observed 
within a period of 10 days, therapy has to be reconsidered and changed. Before the 
infliximab area primarily cyclosporine in a dose has been recommended if a dosage 
of 4 mg/kg kg/day i.v. \textsuperscript{28}. The Leuven group has shown that a dosage of 2 mg/kg 
kg/day i.v. cyclosporine is equivalent effective \textsuperscript{29}. Serum levels can be measured at 
any time during therapy, since by the continuous infusion steady state levels are 
reached early. The ACT I and ACT II studies among others showed that the anti-
TNF antibody infliximab (5mg/kg kg in weeks 0, 2 and 8 and then every 8 weeks) is 
effective in severe ulcerative colitis \textsuperscript{30-32}. The discussion, at which time point in the 
step up approach of severe UC treatment infliximab should be used is still ongoing 
\textsuperscript{33}. New data also exist for a successful therapy with Tacrolimus in this situation \textsuperscript{34}. 
\textsuperscript{35}. Tacrolimus can be used in individual cases as alternative to cyclosporine.

3. Medical management of severe acute colitis/toxic 
megacolon
A severe flare is characterized by the respective clinical symptoms which include systemic signs such as fever, tachycardia and anaemia as well as increased inflammation parameters. Crucial symptoms are frequent bloody diarrhoea, fever > 38.5°C and weight loss. An abdominal X-ray should be performed to search for a dilation of the colon (toxic megacolon) 36.

A megacolon is present if the diameter of the colon transversum is more than 5.5 cm. Ultrasound can be a useful diagnostic supplement in this situation 36. A sigmoidoscopy may be useful to exclude C. diff colitis and CMV colitis. Since a fulminant colitis or a toxic megacolon can also occur on the basis of an intestinal infection, investigations on Clostridium difficile toxin as well as an adequate CMV diagnostic (e.g. immunohistochemistry for pp65) should be performed 37-39. For the treatment of a fulminant flare of ulcerative colitis the patient should be hospitalized. An interdisciplinary approach between gastroenterologists and visceral surgeons is mandatory. A conservative therapy only should be performed if no contraindications exists 40.

Treatment can be started with a course of intravenous steroids, e.g. 4 x 100 mg hydrocortisone per day 41. In addition to fluid and electrolyte substitution parenteral nutrition may be indicated. If steroid therapy fails (no sufficient treatment response within 3-5 days) and a clear indication for surgery is not given a therapy with intravenous cyclosporine (cyclosporine: 2 mg/kg kg or 4 mg/kg kg per day as continuous infusion) may be applied 28, 42, 43.

As mentioned infliximab has been proven to be an alternative in this situation in several studies 31, 44-46.
If i.v. cyclosporine is successful after 7 - 10 days it is usually switched to oral therapy for maintenance of remission and combined with other immunosuppressants such as azathioprine (2.5mg/kg/KG per day) 43. Oral cyclosporine cannot be expected to maintain remission for longer periods. Approximately 60-80% of the patients benefit on a long-term basis and for 40% of the patients colectomy can be avoided 43. As an alternative to cyclosporine also tacrolimus successfully has been used 34, 47. This therapy should be reserved to centers with appropriate experience.

If the need for a rapid surgical intervention is possible, further corticosteroids should be avoided as steroids increase the risk of post-surgical (infectious) complications 48. For fluid and electrolyte substitution parenteral nutrition should applied. In controlled studies, however, this was not superior to enteral nutrition. Clearly enteral nutrition cannot be used under subileus/ileus conditions. Controlled studies do not show an advantage of an additional administration of antibiotics, therefore this should only be done if sings of infection/superinfection or peritonitis are present.

After achieving remission azathioprine (2 - 2.5 mg/kg) can be used for maintenance therapy 49, 50. A Pneumocystis carinei/jiroveci prophylaxis is recommended during the triple immunosuppression (cyclosporine, azathioprine and systemic steroids); The efficacy of such prophylaxis has not been proven so far 51. If therapy fails early colectomy should be performed. The clinical value of leukocyte apheresis is still a matter of discussion.

4. Medical management of chronic active ulcerative colitis
A chronic active disease is characterized by a persistence of clinical symptoms (diarrhoea, blood loss, pain) despite an adequate medical therapy. Also a disease course that shown some improvement upon therapy which is, however, not complete and permanent (<2 relapses per year) is termed to be chronic active disease. A colonoscopy with biopsies and subsequent histology may be helpful in individual cases e.g. for the exclusion of CMV colitis. In cases of the severe, chronically active ulcerative colitis the option of a colectomy should always be discussed with the patient.

If no colectomy is performed for the moment an immunosuppression with azathioprine/6-mercaptopurine may be useful. Newer studies indicate that also infliximab can be given, if a fast therapy response is desired or necessary.

In individual cases the discrimination of a chronically active colitis and irritable bowel syndrome can be difficult. Particularly in therapy refractory disease under immunosuppression an appropriate diagnostic procedure must be undertaken to exclude CMV colitis. Oral systemic steroids should not be used as continuous therapy due to their side effects. In chronically active distal colitis, however the long-term rectal administration of steroid enemas or foams may be acceptable due to their low systemic bio-availability.

A therapy failure on azathioprine therapy can earliest be diagnosed after 6 months of continuous administration. Maintenance therapy with azathioprine or 6-mercaptopurine should be applied for 3-5 years. The administration of azathioprine during pregnancy is regarded to be safe according to all available data. Upon administration of azathioprine/6-mercaptopurine the leukocyte count and the transaminases must be controlled regularly, if abdominal pain occurs additionally
serum lipase levels should be determined. After start of the immunosuppressive therapy leukocyte counts and GPT values should be controlled after 1, 2, 4, 8, 12 weeks, thereafter at least every 12 weeks. Upon azathioprine therapy bone marrow suppression may occur, which must be discovered in time. With leukocyte numbers < 2500 azathioprine therapy should be terminated. After normalization of the values a therapy may be restarted with lower doses (e.g. 50 mg/day) under close supervision. A pancreatitis may occur usually in the first weeks of the treatment and requires immediate termination the therapy. Minor increases in serum lipase or amylase without clinical symptoms are observed frequently in IBD patients; their relevance remains obscure, an observing attitude is acceptable. A subsequent rise of serum liver enzymes under therapy is also a reason for termination of azathioprine/6-MP therapy.

The use of infliximab represents an important therapy alternative \(^{32}\). It is regarded to be safe and well tolerated, however, a tuberculosis skin test or lymphocyte stimulation test (such as Quantiferon \(\text{R}^\text{\textregistered}\)) as well as a lung X-ray need to be performed prior to starting the therapy. It needs to be kept in mind that tuberculosis screening can be false negative due to immunosuppression. Only 22% of patients will be in remission without the need of additional steroids according to the ACT1 and ACT2 data. On the other hand, treatment success usually is rapid and an improvement of the patients can be observed sometimes already on the day after the administration.

The administration of methotrexate can be considered in individual cases in adult patients but also in children \(^{56}\). The initials dose is 20-25 mg parenterally (oral, i.m., s.c.) every week (children: 15mg/m\text{2} body surface). After achieving remission a dose reduction to 10-15mg/week usually is recommended. Regular blood cell
counts must also take place under a therapy with methotrexate. For the monitoring of the potential hepatotoxicity regular measurements of the liver enzymes should be performed. Pre-existing chronic liver disease or chronic lung disease represent contraindications for the therapy.

The oral administration of tacrolimus (0.1-0.2 mg/kg body weight) and the use of a leukocyte apheresis can be considered in individual cases.

5. Maintenance of remission in ulcerative colitis

The definition of remission is based on clinically features. Criteria for remission are absence of diarrhoea (> 3 bowel movements/day), no visible blood in stools as well as no UC associated intestinal or extra-intestinal complaints. For maintenance of remission in patients with UC the therapy of first choice are 5-aminosalicylates with oral or rectal administration\(^57-59\). The combination of oral and rectal/topical therapy is superior to the oral mono-therapy (Figure 2). In the case of distal UC evidence for the superiority of the rectal application exists\(^59\).

The compliance or adherence on maintenance therapy is crucial for its success\(^60\). If more than 2/3 of the recommended dose is taken, the risk of a flare or relapse in the first year is only approximately 10-20%\(^61\). With respect to this it is certainly favourable that newer studies point to the fact that the entire 5-ASA dosage can be taken at one time (e.g. in the morning or in the evening). The distribution into three doses is not necessary any longer.

For the following minimal dosages the effectiveness has been demonstrated in clinical studies:
- Oral administration: SASP 2g/day; 5-ASA 1.5g/day; Olsalazin 1.0 g/day;
- Rectal administration: Left sided colitis: 5-ASA-enemas either 1 g/day or 4 g each 3rd day or 4 g/day on the first 7 days of the month; Proctitis: 5-ASA-suppositories 2 x 500mg/day or 1g/day three times a week.

Since individual patients prefer mesalazine foams as compared to enemas this application form can be probably given at similar dosage, even if studies are not available for maintenance of remission with foam preparations. The maintenance therapy should be administrated for at least 2 years.

Upon incompatibility of 5-aminosalicylic acid also a preparation of a probiotic (a-pathogen Escherichia coli Nissle can be used successfully for the maintenance of remission with similar clinical efficacy \(^{62, 63}\).  

As alternatives for the complicated ulcerative colitis azathioprin/6-mercaptopurine \(^{53}\) and infliximab can be used for the maintenance of remission \(^{32}\). Systemic steroids should not be used for maintenance therapy. The increased efficacy of a combination of oral and rectal therapy with 5-ASA is well documented by clinical studies; however, most patients prefer mono-therapy.
Literature


18. Mulder CJ, Fockens P, Meijer JW, van der Heide H, Wiltink EH, Tytgat GN. Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2 g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. Eur J Gastroenterol Hepatol 1996;8:549-53.


44. Jarnerot G. Infliximab or cyclosporine for severe ulcerative colitis. Gastroenterology 2006;130:286; author reply 287.


Figure 1: Step up therapy approach in ulcerative colitis
Figure 2: Advantage of combination therapy of oral and rectal 5-ASA therapy over single therapy (according to Safdi, Am J Gastroenterol 1997)
Figure 3: Treatment algorithm for mild to moderate UC
Figure 4: Treatment algorithm for moderate to severe UC