Principles of Medical Management of Ulcerative Colitis

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Keywords

Chronic disease management • Ulcerative colitis • Medical therapies • Long-term remission • Inflammatory bowel disease • Disease classification • Activity indices • Corticosteroids • Cyclosporine • Immunomodulators • Monoclonal antibodies against tumor necrosis factor-α • Clinical remission • Quality of life • Prevention of complications • Management of complications • Mucosal healing

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease with a relapsing-remitting course. It affects patients in young adulthood, with a mean age of 34.5 years at diagnosis [1], a point in life when the afflicted individuals are completing their higher education, establishing their careers, and starting their families. As patients with UC have a normal lifespan [2], the relapsing course of the disease portends decades of morbidity. The choice of therapy must take into account the long-term issues of compliance and adverse events. In addition, UC is a pervasive disease that can impinge on every aspect of a person's life, from their current functional and mental state to their future reproductive health and risk of malignancy. Optimal management of this chronic condition must therefore be comprehensive in addressing every facet of the disease. This chapter discusses the principles of management of UC patients, with a focus on evidence-based, patient-centered, systematic, and comprehensive therapy. We provide an overview of the therapeutic options and goals of treatment and provide recommendations for individualizing treatment.

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Ulcerative Colitis as a Model of Chronic Disease Management

The concept of chronic disease management grew out of the realization that the standard, ambulatory care model of acute illness does not meet the needs of patients with chronic illnesses [3, 4]. Models of chronic disease management thus evolved, aiming at improving short- and long-term care, optimizing quality of life, and preventing disease progression and complications. There are several key aspects to the management of UC. These include a coordinated treatment plan for inducing and maintaining remission, a focus on patient function and quality of life, monitoring for and preventing disease and treatment complications, evidence-based care, and behaviorally sophisticated support for the patient in his/her role as self-manager. Coordinating care between multiple providers and/or settings is paramount and is facilitated by regular clinic follow-up and by information systems. Hence, conceptually, patients with UC should benefit from the framework of a structured disease approach.

Central to the chronic disease management model is patient empowerment and involvement. Physicians must establish strong, long-term relationships with their UC patients and provide them with education, support, and open lines of communication. Patients can thus become active

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partners in their own health management and achieve better outcomes. In this regard, recent data suggest that patient trust in the physician is associated with improved adherence to IBD therapy [5], which is a surrogate for long-term remission.

Patients with UC need to be well informed regarding their condition and their physician can be instrumental in their education. Education and discussions on the natural course of disease, treatment goals, and patient preferences and expectations allow for individualized management and cultivate effective patient-physician interactions. For example, a patient's wish to avoid surgery may lead them to pursue a more aggressive medical strategy, such as entering a clinical trial. Educational resources and online websites (such as the website of the Crohn's and Colitis Foundation of America; www.ccfa.org) may supplement office discussions and answer questions and concerns not raised in clinic [6]. More knowledgeable patients may take greater personal responsibility for their health and may eventually become comfortable with self-managing certain aspects of their condition. For example, patients may learn to increase doses or start medications when they first develop symptoms of a flare, so that their disease can be controlled at an early stage. Physicians and patients may together devise an action plan to help guide patient self-management. The advantages of this approach were demonstrated in a randomized controlled trial (RCT) that compared guided self-management and patient-directed follow-up to traditional outpatient management [7]. Subjects in the intervention arm had their relapses treated significantly faster and made significantly fewer doctor and hospital visits. Flexible lines of communication may allow patients to update their gastroenterologist on their current clinical status and have simple questions answered. Telecommunication options have expanded so that electronic mail may be used to aid in caring for patients living at a distance or patients more comfortable with this mode of communication. The feasibility and benefits of these approaches were shown in a recent RCT in Danish and Irish patients with mild and moderate ulcerative colitis on 5-aminosalicylate acid treatment [8]. Subjects were randomized to a web group that received disease-specific education and self-treatment or a control group that continued the usual care for 12 months. The web-based group demonstrated significantly better adherence and shorter duration of relapses. The web-based group also had fewer acute and routine visits to the outpatient clinic, leading to cost savings. Among the Danish subjects, general IBD knowledge and disease-specific quality of life was higher in the web-based group, without associated increases in depression and anxiety.

Management of a chronic disease such as UC requires establishment of a high-quality, coordinated health system [9]. Effective care is enhanced through involvement of the primary care physicians who follow patients for health maintenance issues. These include updating vaccinations (influenza annually, pneumococcus, tetanus, meningococcus, hepatitis B, and human papilloma virus in young females), monitoring bone health (including bone densitometry and vitamin D levels), and screening for cancer [10]. Thiopurines increase the risk of nonmelanoma skin cancer, whereas anti-TNF biologics increase the risk of melanoma [11]. Women with IBD receiving corticosteroids and immunosuppressants may have a higher risk of cervical abnormalities [12]. Highlighting the central role of the primary physician, a recent study from Kaiser Permanente, an integrated care organization, showed a significant shift in the outpatient care of UC patients [13]. Between 1998 and 2005, the annual rate of visits to a gastroenterologist for treatment of gastrointestinal disease decreased by 25 % per patient ($P<0.0001$), whereas the rate of visits to primary care providers increased by 350 % ($P<0.0001$) (similar significant trends were seen for Crohn's disease).

An emerging trend in the care of UC patients involves the increased use of mid-level providers. Given the rising demands on physicians, as well as the emphasis on health promotion and disease prevention, specialist nurses, nurse practitioners, and physician assistants will inevitably assume greater roles in the management of patients and may even direct care in some domains. The members of these "IBD-dedicated teams" can address straightforward patient concerns without need for an office appointment. They can also answer questions regarding insurance and cost issues and refer patients to social workers or pharmaceutical assistance programs. Studies are beginning to examine the effects of care by IBD-specialist nurses on outcomes. A recent study from Norway found that, in comparison to conventional follow-up, the utilization of a systematic, nurse-led follow-up produced similar outcomes in terms of hospitalizations, surgery, sick leave, performance of endoscopic procedures, and number of additional telephone consultations [14]. Moreover, nurse-led follow-up was associated with a significantly faster treatment upon relapse.

The management of extraintestinal manifestations (EIM) associated with UC frequently requires referral to other specialists, including ophthalmologists, rheumatologists, dermatologists, and hematologists. Concomitant primary sclerosing cholangitis may require management by an advanced endoscopist, general hepatologist, or transplant hepatologist. Stress, depression, and anxiety are also comorbid conditions associated with UC and other chronic diseases. In inflammatory bowel disease, psychiatric comorbidity is associated with poorer clinical outcomes and greater healthcare costs [15–17]. Treatment of these disorders by the primary care physician or the psychiatrist improves disease control and enhances general and emotional well-being [18, 19] and may improve disease outcome [20].

Good communication between the patient and the members of the health care team is critical to the development of an informed, individualized management plan, as well as to the prevention and early detection of complications.

There is surprising variability in the patterns and quality of IBD care, likely reflecting the heterogeneity of the disease but also poor adherence to guidelines [13, 21–23]. This variability mandates efforts to identify specific areas for quality improvement. The American Gastroenterological Association (AGA) has recognized the need to distinguish physicians and practices that deliver high-quality and resource-efficient care for patients with digestive disorders. Using the Physician Consortium for Performance Improvement® (PCPI™) model, the AGA has developed a set of clinical performance measures designed for the purpose of improving IBD quality of care [24]. The performance measures enable the physician to track his/her performance in individual patient care. In the future, reimbursement by insurers may require meeting quality-based targets and outcomes. Ultimately, applying the chronic disease management model in UC should be expected to yield higher-quality health care.

Classification of Disease

UC is classified by disease extent and severity. This classification is important as disease presentation, outcomes, and therapy depend on these disease characteristics. Disease extent is determined endoscopically. Approximately 40 % of patients have disease limited to the rectum (ulcerative proctitis), and 30–40 % of patients have disease limited to the rectosigmoid (ulcerative proctosigmoiditis) or the left colon (left-sided UC) [25]. 20–30 % of patients have involvement of mucosa proximal to the splenic flexure (extensive colitis) or encompassing the entire colon (pancolitis). Disease extent should be described accurately at the time of the index colonoscopy, as medical therapy (particularly topical therapy) may lead to patchy healing. Topical therapy may explain an atypical finding of rectal sparing in subsequent colonoscopies. A periappendiceal "red patch" and backwash ileitis may also be seen in UC and should not be confused for Crohn's disease.

Patients with distal UC (ulcerative proctitis and proctosigmoiditis) frequently present with the typical symptoms of tenesmus, urgency, and passage of fresh blood. Patients may also complain of constipation, a symptom probably resulting from slower transit in the more proximal colon. More extensive involvement of UC leads to bloody diarrhea, abdominal cramping, and systemic symptoms including, anorexia, weight loss, dehydration, fevers (typically low-grade), and extraintestinal manifestations of UC.

UC is also classified according to disease activity [26]. The American College of Gastroenterology has developed operational definitions. Patients in remission are asymptomatic, with ≤3 stools daily and without rectal bleeding or systemic symptoms. Mild disease is defined as ≤4 stools daily, rare passage of blood or mucus, and no systemic symptoms. Moderate disease is defined as >4 stools daily with daily passage of blood or mucus and minimal systemic symptoms. Severe disease is defined as >6 bloody stools daily with evidence of toxicity including fever, tachycardia, anemia, or elevated erythrocyte sedimentation rate (ESR). Fulminant colitis is characterized by bloody diarrhea with >10 movements daily, continuous bleeding, abdominal pain, and systemic toxicity [27]. Toxic megacolon is defined as systemic toxicity (fever and tachycardia) and colonic dilatation ≥6 cm, which is associated with abdominal distention, hypoactive bowel sounds, and constipation or obstipation [28].

Activity Indices

Several measures of disease activity have been developed based on clinical symptoms, biochemical data, and endoscopic findings. Most of these indices were developed for the purposes of drug trials and research studies [29]. Nonetheless, the simpler indices may be used in clinical practice. The Truelove and Witts' Severity Index [30] incorporates six variables (number of stools, bleeding, temperature, pulse, hemoglobin, and ESR) to classify patients into three groups (mild, moderate, and severe). Though useful in the general classification of patients, the use of this index has been limited by its qualitative nature. The Powell-Tuck Index [31] uses ten variables (general health, abdominal pain/tenderness, bowel frequency, stool consistency, bleeding, anorexia, nausea/vomiting, temperature, and presence of EIM) to determine a score ranging from 0 to 20. In addition, sigmoidoscopy findings may be added with scores from 0 to 2. The Activity Index (AI) or Seo Index [32] was developed to predict disease severity as classified by the Truelove and Witts' classification. Five quantitative variables (number of stools, number of bloody stools, ESR, hemoglobin, and albumin) were selected after multiple stepwise regressions. The equation ($AI = 60 \times \text{bloody stools} + 13 \times \text{number of stools} + 0.5 \times \text{ESR} - 4 \times \text{hemoglobin} - 15 \times \text{albumin} + 200$) results in a score from 50 to 250. Mild disease is defined as a score <150, moderate as 150–200, and severe as >200. The AI has been shown to predict clinical remission, endoscopic findings, response to infliximab, and need for colectomy [33–36].

Two indices that are frequently used and incorporate endoscopic findings into their determination are the Mayo Clinic Score [37] and the Sutherland Index/UC Disease Activity Index (UC DAI) [38]. The Mayo Score is calculated

using four variables (stool frequency, rectal bleeding, flexible sigmoidoscopy findings scored 0–3, and physician global assessment) to determine a score of 0–12. The Mayo Score has been used in multiple studies and has been shown to correlate with quality of life measures. The UC DAI also incorporates four variables (stool frequency, rectal bleeding, endoscopic mucosal appearance, and physician's rating of disease activity) to determine a score ranging from 0 to 12. The UC DAI has been shown to correlate with patient-defined remission [39].

Medical Therapies

The choice of medical therapy must take into account both disease location and disease activity. Targeted delivery of mesalamine to the inflamed colonic segments leads to optimal effectiveness and minimizes systemic side effects. Systemic therapies are necessary in patients with moderate or severe disease. Therapeutic decisions should also take into consideration the patient's history of response to different therapies, compliance, and comorbidities. Frequent reassessment of the treatment regimen is required given the relapsing-remitting course of the disease and the possibility of worsening activity or proximal progression (Table 4.1).

Aminosalicylates

The aminosalicylates, sulfasalazine (SASP), and mesalamine (or 5-aminosalicylic acid or 5-ASA) constitute first-line treatment for both the induction of remission and the maintenance of remission in patients with mild to moderate UC. The mechanism of action involves several pathways, including inhibition of activation of transcription factor NF-κB [40], inhibition of prostaglandin synthesis [41], and scavenging of free radicals [42]. SASP (4–6 g/day), the prototype aminosalicylate formulation, contains a sulfapyridine moiety linked by an azo bond to the 5-ASA moiety. Sulfapyridine accounts for most of the adverse effects, whereas 5-ASA accounts for most of the therapeutic benefits. SASP is minimally absorbed by the small intestine and remains intact until reaching the colon, where bacteria cleave the azo bond to release free sulfapyridine and 5-ASA. 5-ASA is poorly absorbed by the colon (and therefore has minimal systemic effects) and has topical (mucosal) anti-inflammatory activity. In effect, sulfapyridine functions as a carrier, delivering the active 5-ASA moiety to the colon. Dose-dependent efficacy and toxicity are observed, mediated by the mesalamine and sulfapyridine moieties, respectively. Up to 40 % of patients may experience dose-related side effects, such as nausea, dyspepsia, headaches, and sperm abnormalities. Idiosyncratic

Table 4.1 Overview of medical therapies

	Induction therapy [1, 2]	Maintenance therapy
Mild	• Oral 5-ASA • Topical 5-ASA • Topical steroid	• Oral 5-ASA, with or without topical 5-ASA
Moderate	• Oral 5-ASA • Topical 5-ASA • Topical steroid • Prednisone in patients with more severe disease or in patients with milder disease who failed oral 5-ASA, topical 5-ASA, and topical steroid • IFX in patients with steroid-refractory disease or intolerance to 5-ASA and thiopurines • ADA in patients with steroid-refractory disease or intolerance to 5-ASA and thiopurines • GOL in patients with steroid-refractory disease or intolerance to 5-ASA and thiopurines	• Oral 5-ASA, with or without topical 5-ASA (in patients who achieved remission on oral 5-ASA, topical 5-ASA or topical steroid • Thiopurines in patients with steroid-dependent disease or patients with frequent flares despite maximal 5-ASA therapy • IFX or IFX-thiopurine combination therapy in patients who achieved remission on IFX and in patients with steroid-dependent disease • ADA or ADA-thiopurine combination therapy in patients who achieved remission on ADA and in patients with steroid-dependent disease • GOL or GOL-thiopurine combination therapy in patients who achieved remission on ADA and in patients with steroid-dependent disease
Severe	• IV corticosteroid (first line) • IV Cyclosporine (first line or after failure of IV steroids) • IFX (first line or after failure of IV steroids)	• Thiopurines in patients who achieved remission on IV corticosteroids or IV cyclosporine • IFX or IFX-thiopurine combination therapy in patients who achieved remission on IFX

Notes: (1) Patients with active distal disease are treated with any combination of topical 5-ASA, oral 5-ASA, and/or topical corticosteroids. (2) Topical therapies are critical in patients with active distal disease. However, they also reduce symptoms of distal disease in patients with extensive UC or pancolitis independent of disease severity

side effects are also observed, including bone marrow suppression and hepatotoxicity. SASP inhibits absorption of folate. Advantages of SASP include lower cost than mesalamine and effectiveness against peripheral arthritis. The starting dose is typically 500 mg 2–3 times daily with meals. The dose is gradually increased as tolerated to a maximal dose of 4–6 g/day, taken three times daily with meals. As SASP inhibits folate absorption, folate supplementation is advised.

Oral, sulfa-free aminosalicylates were developed in order to circumvent the side effects of sulfapyridine and now constitute the most commonly prescribed oral therapies. These formulations target 5-ASA release to the site of inflammation along the gastrointestinal tract, differing in the mode of release and site of 5-ASA delivery. Preparations that are available in the USA, the sites of targeted 5-ASA release, and the usual dosages for the treatment of UC are listed below:

- Delzicol® (400 mg) and Asacol HD® (800 mg) (Warner Chilcott, Rockaway, NJ, USA) are mesalamine coated with an acrylic-based resin that dissolves at pH of 7 or greater, releasing the drug in a delayed, pH-dependent manner in the terminal ileum and colon. The usual dose is 2.4–4.8 g/day. In the USA, Delzicol® is approved for the treatment of mildly to moderately active UC and for the maintenance of remission. Asacol HD® is approved for the treatment of moderately active UC.
- Pentasa® (250 and 500 mg; Shire Pharmaceuticals, Wayne, PA, USA) is mesalamine formulated within semipermeable ethyl cellulose microgranules that release the drug in a time-dependent manner throughout the small bowel and colon. The usual dose is 2–4 g/day. In the USA, Pentasa® is approved for the induction of remission and for the treatment of patients with mildly to moderately active UC.
- Lialda® (1,200 mg; Shire Pharmaceuticals, Wayne, PA, USA) is mesalamine coated with a gastro-resistant pH-dependent polymer film, which dissolves at or above pH 7, releasing mesalamine from the tablet core in the terminal ileum and colon. The tablet core contains mesalamine in a multimatrix (MMX) of hydrophilic and lipophilic excipients. The usual dose is 2.4–4.8 g/day. In the USA, Lialda® is approved for the induction of remission in adults with active, mild to moderate UC, and for the maintenance of remission.
- Balsalazide (Colazal® 750 mg; Salix Pharmaceuticals, Raleigh, NC, USA; and generic) consists of 5-ASA in an azo bond with an inert carrier. Colonic bacteria cleave the azo bond to release 5-ASA throughout the colon. The usual dose is 6.75 g/day. Colazal® is approved for the treatment of mildly to moderately active UC.
- Olsalazine (Dipentum®, 250 mg; Pfizer, New York, NY, USA) is a 5-ASA dimer. Colonic bacteria cleave the azo bond to release 5-ASA throughout the colon. The usual dose is 2 g/day. Dipentum® is approved for the maintenance of remission only.
- Apriso® (0.375 g; Salix Pharmaceuticals, Raleigh, NC, USA) is mesalamine with delayed and extended release as granules that dissolve at pH of 6 or greater for delivery throughout the colon. Apriso is approved for the maintenance of remission only. The usual dose is 1.5 g/day.

A recent systematic review included 11 RCTs with 2,086 patients comparing 5-ASA or SASP versus placebo as inductive therapy in active UC [43]. The majority of studies enrolled patients with mild to moderately active UC. There was a strong effect in favor of 5-ASA therapy, with a number needed to treat (NNT) of 6 (95 % confidence interval (CI) 5–8). 40 % of patients achieved remission in the active treatment group, compared with 20 % in the placebo group. The quality of evidence was graded as moderate. There was no difference in efficacy among the different 5-ASA preparations. The systematic review found similar remission rates at low (2.0–2.5 mg/day) versus high doses (>2.5 mg/day). Nonetheless, RCTs and clinical experience are consistent with a dose-response curve with specific oral 5-ASA agents (Asacol®, Pentasa®, Lialda®), with a maximal effect at 4.0–4.8 g/day [44]. In clinical practice, the choice of preparation is usually based on cost and convenience, rather than on claims of superiority of a particular formulation.

The same systematic review also assessed 11 RCTs with 1,502 participants that compared 5-ASA versus placebo in patients with quiescent UC. There was a strong effect in favor of 5-ASA, with a NNT of 4 (95 % CI 3–7). 40 % of patients on 5-ASA relapsed compared with 63 % of patients taking placebo over 6–12 months. The quality of evidence was graded as high. As with active UC, there was no evidence that efficacy varied between different preparations. The optimal maintenance 5-ASA dose appeared to be 2.0–2.4 g/day. Among the seven trials that compared a daily dose of <2 g of 5-ASA with a dose of ≥2 g/day, there was a statistically significant effect in favor of the higher dose (NNT = 10; 95 % CI 5–33). The single trial comparing high versus standard dose (>2.5 g/day vs. 2.0–2.5 g/day; $n = 113$) found no difference between the two doses. The authors stated that current evidence supports using 2.4 g/day, but conceded that further research is needed to address a possible dose response of 5-ASA in preventing relapse. Again, clinical experience suggests that higher doses (3.6–4.8 g/day) are more effective than lower doses (2.4 g/day) in maintaining remission. In clinical practice, the maintenance dose is frequently the same as the inductive dose.

Only 40 % of patients are compliant with oral 5-ASA therapy [45] and noncompliance is associated with a higher risk of relapse [46]. A study of once daily dosing found lower relapse rates [47]. 5-ASA nephrotoxicity is seen rarely so that renal function should be monitored periodically [48].

Topical forms, either as monotherapy or in conjunction with oral therapies, should be used in patients with distal

UC, as well as patients with more extensive disease but prominent distal symptoms. Topical mesalamine formulations that are available in the USA include:

- Suppositories (Canasa®, Aptalis Pharma, Birmingham, AL, USA), 1,000 mg QD. Suppositories deliver the drug to the distal 10–15 cm of the rectum. Canasa® is approved for the treatment of mild to moderately active ulcerative proctitis.
- Enemas (generic and Rowasa®, Meda Pharmaceuticals, Somerset, NJ, USA) 60 ml daily. Enemas deliver the drug up to the splenic flexure. Rowasa® is approved for the treatment of mild to moderately active distal ulcerative colitis, proctosigmoiditis, or proctitis.

Response is usually seen within 3–4 weeks. Remission rates in distal UC using topical formulations are 50–75 %, superior to those observed with oral 5-ASA monotherapy and with topical steroids [49]. However, the combination of topical and oral 5-ASA is more effective than either agent alone [50, 51]. In addition, the combination of oral 5-ASA and enemas twice a week has been shown to be superior to oral 5-ASA alone in maintaining remission in patients with disease extent greater than proctitis and a history of multiple relapses [52]. Patients on topical therapies may complain of leakage, problems with retention, anal irritation, cramps, and bloating but these symptoms improve over time. Common treatment errors included not maximizing topical therapies in the induction of remission and not utilizing them for maintenance.

Corticosteroids

Corticosteroids are used for the induction of remission in patients with moderate disease (oral steroids) or severe disease (intravenous steroids). The patient is then transitioned to appropriate maintenance therapy, such 5-ASA (oral and/or topical), thiopurines, or infliximab, depending on the clinical assessment. A subset of patients develops steroid-dependent disease, defined as inability to taper off steroids without experiencing a flare. In these patients, the multitude of steroid toxicities mandates the initiation of steroid-sparing, maintenance therapies. In one population study, approximately one-third of 185 patients with newly diagnosed UC required corticosteroid treatment [53]. Half of these patients went into remission with prolonged response at 1 year. However, 14 (22 %) patients became steroid-dependent and 18 (29 %) required surgery.

Corticosteroids were first shown to be effective in UC in 1955 [54]. Patients with chronic, active UC severe enough to require at least 6 weeks of hospital stay were randomized to cortisone (100 mg orally once daily, $n=109$) versus placebo ($n=101$). In the cortisone group, 58.7 % failed to achieve remission, compared with 84.2 % in the placebo group. The absolute risk reduction was 25.4 % (13.8 % vs. 37.1 %), and the NNT was 4. A recent meta-analysis of RCTs found that 54 % of patients receiving oral steroids failed to achieve remission compared with 79.0 % of patients randomized to placebo. The likelihood of failure to achieve remission was significantly reduced with steroid therapy (relative risk (RR) = 0.65; 95 % CI 0.45–0.93) [55].

Patients with severe UC require hospitalization and intravenous corticosteroids. In a study from Oxford, 49 patients with severe UC were treated with a 5-day course of IV prednisolone (60 mg/day) and rectal hydrocortisone (100 mg twice daily) during the period between 1969 and 1973. Thirty-six patients (74 %) were in complete remission at the end of the 5-day course, 4 (8 %) showed clinical improvement but no remission and required surgery within the next 6 weeks, and 9 (18 %) required emergent surgery after 5 days of treatment [56]. The same group reported their results in an additional 100 courses of the same regimen in 87 patients with severe UC, treated during the period between 1974 and 1978. 60 % of the attacks responded swiftly to the regimen; in 15 %, there was improvement; and in 25 %, failure to respond resulted in emergency colectomy [57]. More recent studies have reported remission rates of 50–61 % [58–60].

A French retrospective study assessed factors predictive of failure of intravenous corticosteroid therapy, defined as colectomy before day 30, intravenous cyclosporine, or death. On multivariate analysis, severe endoscopic lesions (defined as extensive deep ulcerations, mucosal detachment on the edge of these ulcerations, well-like ulcerations, and/or large mucosal abrasions) were associated with an increased risk of failure ($P=0.007$). The presence of Truelove and Witts' criteria for severe disease ($P=0.018$) and an attack that had lasted more than 6 weeks ($P=0.001$) were also independent predictors of failure. Patients with severe endoscopic lesions and Truelove and Witts' criteria for severe disease had a failure rate of 86 %, whereas those with severe endoscopic lesions and moderate disease by the Truelove and Witts' criteria had a failure rate of 50 % [61]. An English prospective study evaluated clinical parameters predictive of surgery in 51 consecutive episodes of severe colitis by the Truelove and Witts' criteria. All patients were treated with intravenous and rectal hydrocortisone. In addition, 14 of 51 patients were treated with intravenous cyclosporine. There was complete response in 21 episodes (<or = 3 stools on day 7, without visible blood), incomplete response in 15 (>3 stools or visible blood on day 7, but no colectomy), and colectomy on that admission in 15. Patients with more than eight stools on day 3, or a stool frequency between three and eight together with a CRP >45 mg/l, had an 85 % risk of colectomy during the hospitalization [62].

Corticosteroids are available in oral, intravenous, and topical formulations. Oral corticosteroids are indicated in

mild to moderate UC when a patient is flaring despite maximal 5-ASA use [63]. Recommended dosing is prednisone 40–60 mg (or its equivalent) until clinical remission (*not* response) is achieved, usually in 7–14 days [64]. The rapidity of the taper is dictated by how quickly the patient responds. Common errors are starting the prednisone taper as soon as the patient begins to improve, rather than waiting for the patient to achieve clinical remission tapering too quickly in a patient who responded slowly, and tapering too slowly in a patient who promptly entered remission. Generally, prednisone is tapered by 5–10 mg each week until 20 mg, then by 2.5–5 mg each week. However, the importance of individualizing the taper cannot be overemphasized. Patients should not be treated with a "standard" taper and should be instructed to contact their physician periodically regarding the dose changes. On the basis of two RCTs, extended-release budesonide (Uceris® 9 mg; Santarus, San Diego, CA, USA) was recently approved in the USA for the induction of remission in patients with active, mild to moderate UC [65, 66]. The formulation (budesonide in a multimatrix (MMX) of hydrophilic and lipophilic excipients) was designed to deliver the agent to the colon and thus minimize systemic absorption.

Accepted intravenous steroid therapies include methylprednisolone 20 mg every 8 h, hydrocortisone 100 mg every 8 h, or prednisolone 30 mg every 12 h. There is no difference between intravenous bolus delivery and 24-h continuous infusions [67]. Intravenous corticosteroids are administered until clinical remission is achieved—only then should the patient be switched to an oral form. During their hospitalization, patients with severe UC should be monitored for dehydration, electrolyte abnormalities, anemia, and signs of toxicity and megacolon. If no improvement is seen after 5–7 days, then surgical consultation is sought, and the patient is offered the options of cyclosporine, infliximab, or surgery. Common management errors in the hospitalized patient include prematurely switching to oral steroids, not employing topical 5-ASA and steroid therapies, omitting measures to prevent venous thromboembolism, not feeding the patient, underestimating the severity of the disease, and therefore delaying surgical consultation.

Topical corticosteroids are available as foam (hydrocortisone acetate 10 %); each application delivers approximately 900 mg of foam containing 80 mg of hydrocortisone (90 mg of hydrocortisone acetate) and enema (one 60 mL enema delivers 100 mg hydrocortisone) preparations. Topical budesonide formulations are also available in other countries. These options are useful in treating flares in patients with distal or left-sided UC or in those with prominent distal symptoms. The combination of topical 5-ASA and corticosteroids has been shown to be superior to either therapy alone in distal UC [68].

Cyclosporine

Cyclosporine is a calcineurin inhibitor used as a salvage therapy in patients with severe UC failing intravenous corticosteroids after 5–7 days. In the seminal study by Lichtiger et al. 82 % of patients with severe, steroid-refractory UC treated with intravenous (IV) cyclosporine avoided colectomy in the short term [69]. Based on pooled data from controlled and uncontrolled trials, approximately 80 % of patients respond to IV cyclosporine and avoid colectomy in the short term [70]. However, 88 % of responders will require colectomy at 7 years [71]. Cyclosporine is also effective as first-line therapy in patients with severe UC (in lieu of IV corticosteroids). In a Belgian, double-blind RCT, IV cyclosporine was as effective as IV methylprednisolone in patients with severe UC (response rates of 64 % and 53 %, respectively) [72]. Cyclosporine is administered at a dose of 2 mg/kg/day by continuous IV infusion. The dose is adjusted targeting serum concentrations of 350–500 ng/ml [73]. Dose-dependent toxicities include nephrotoxicity, infection, hypertrichosis, gingival hyperplasia, paresthesias, tremor, and seizures [74]. The risk of seizures is increased in the setting of hypomagnesemia and hypocholesterolemia. Shortly after successful induction with cyclosporine, immunomodulators are started. Steroids are tapered off first, followed by cyclosporine, so that by 4–6 months the patient is in remission on immunomodulators alone. In a study from the University of Chicago, this approach improved long-term success of avoiding colectomy (59 % with vs. 39 % without immunomodulators) [75]. Prophylaxis against *Pneumocystis jiroveci* (*carinii*) with trimethoprim-sulfamethoxazole or dapsone should be administered in cyclosporine-treated patients.

Small, open-label studies of tacrolimus, a calcineurin inhibitor-like cyclosporine, showed effectiveness in preventing colectomy in the short term in two-thirds of patients with refractory UC [76, 77]. In a recent randomized, placebo-controlled trial of oral tacrolimus in hospitalized patients with steroid-refractory UC, tacrolimus therapy improved clinical response at week 2 (50 % vs. 13 %; $P=0.003$) and mucosal healing (44 % vs. 13 %; $P=0.012$) [78].

Immunomodulators

The thiopurines, 6-mercaptopurine (6-MP) and its pro-drug azathioprine (AZA), modulate immune response through several mechanisms, including inhibition of DNA and RNA synthesis and apoptosis of activated T-cells [79]. 6-MP and AZA are metabolized into the active 6-thioguanine nucleotide (6-TGN) metabolites as well as the inactive metabolites,

6-methylmercaptopurine nucleotides (6-MMPN) and 6-thiouric acid [80]. High 6TGN concentrations lead to leukopenia, where as high 6MMPN concentrations lead to hepatotoxicity. Conversion to the 6-MMPN metabolites is mediated by the enzyme thiopurine methyltransferase (TPMT). The activity of TPMT is largely determined genetically. Alleles conferring high ($TPMT^{H}$) and low enzyme activity ($TPMT^{L}$) are inherited in autosomal, codominant fashion. Approximately 89 % of Caucasians carry only $TPMT^{H}$ alleles ($TPMT^{H}/TPMT^{H}$) and have normal TPMT activity, 11 % are heterozygous ($TPMT^{H}/TPMT^{L}$) and have intermediate activity, and 0.3 % are homozygous for the same $TPMT^{L}$ allele ($TPMT^{L}/TPMT^{L}$) or are heterozygous with two different low activity alleles ($TPMT^{L}/TPMT^{L'}$; compound heterozygotes) and have low or undetectable activity. Measurement of TPMT activity is recommended to determine initial optimal dosage and avoid toxicity. Individuals with low or undetectable activity are generally not treated with the thiopurines, as they invariable develop very high 6-TGN concentrations resulting in neutropenia. Individuals with normal activity are treated with standard doses (6-MP 1–1.5 mg/kg/day or AZA 2.0–3.0 mg/kg/day), whereas those with intermediate activity are given half the standard doses (6-MP 0.5 mg/kg/day or AZA 1.0 mg/kg/day) [81].

RCTs [82–84] and observational studies [85–87] have found the thiopurines effective in maintaining steroid-free remission in patients with steroid-dependent UC. The thiopurines are also useful in patients experiencing frequent flares despite maximal 5-ASA therapy. Long-term therapy is required since 87 % of patients with refractory UC relapse once treatment is discontinued [75]. Due to their slow onset of action, the thiopurines are not used as inductive therapies. A recent meta-analysis reported a nonsignificant trend for benefit from thiopurine induction therapy in patients with active UC (RR = 0.85; 95 % CI = 0.71–1.01) [88].

Leukopenia (frequently, but not always, associated with high 6-TGN concentrations) and transaminitis (frequently, but not always, associated with high 6-MMPN concentrations) are reversible with dose adjustments. Pancreatitis occurs in 1–2 % of patients, usually in the first 6–8 weeks of treatment. Other adverse effects include nausea, emesis, malaise, rash, arthralgias, and myalgias [89]. These may not recur on switching to the alternate thiopurine. Only pancreatitis and fever are absolute contraindications to future use of the alternate thiopurine. Other risks associated with thiopurines include infections (especially in combination with corticosteroids and/or anti-TNF agents) [90] and lymphoma [91].

Oral methotrexate was not effective in a double-blind, randomized, Israeli trial in patients with active, steroid-requiring UC [92]. Mycophenolate mofetil inhibits lymphocyte proliferation by blocking guanine synthesis. Mycophenolate was less effective than AZA in a small, open-label trial in patients with active UC [93].

Monoclonal Antibodies Against Tumor Necrosis Factor-α

Infliximab (IFX) is a chimeric monoclonal antibody that targets tumor necrosis factor (TNF)-α, an inflammatory cytokine central to IBD pathogenesis. IFX is approved for the induction and maintenance of clinical remission in adults and children with moderately to severely active UC who have had an inadequate response to conventional therapy. IFX is therefore used in patients with (a) steroid-dependent disease failing thiopurines, (b) steroid-refractory disease, (c) intolerance to 5-ASA and thiopurines, and (d) severe UC requiring hospitalization. IFX is administered as an intravenous infusion at a dose of 5 mg/kg at weeks 0, 2, and 6 for induction, and then every 8 weeks for maintenance.

In two large, phase III trials, IFX led to 61–69 % response and 31–47 % remission rates at 8 weeks [94]. This benefit was maintained through 54 weeks with 44–45 % response and 34–35 % remission rates in IFX-treated patients compared to 20 % and 16 % of placebo-treated patients, respectively. Combination IFX and AZA therapy has been shown to result in higher rates of clinical remission in moderate to severe UC compared to monotherapy (40 % vs. 22–24 %) [95]. Similar results were reported with combination therapy in active Crohn's disease [96], likely reflecting the reduced formation of antibodies against IFX in patients also receiving AZA.

IFX has proven effective as salvage therapy in severe, steroid-refractory UC. Treatment with IFX decreased the need for colectomy among hospitalized patients with severe fulminant UC and failing intravenous steroids [97, 98]. Nonetheless half of patients eventually required colectomy at 5 years [99]. In a recent study that compared IFX to cyclosporine in patients with severe, steroid-refractory UC, IFX demonstrated comparable rates of clinical response at 1 week (86 % vs. 84 %) and need for colectomy (23 % vs. 18 %) [100]. IFX may also be used in hospitalized patients as first-line therapy (in lieu of IV corticosteroids) [101].

An important question concerns the possibility of third-line therapy in patients who have failed cyclosporine or IFX. A French retrospective study examined patients treated between 2000 and 2008 with cyclosporine followed by IFX ($n = 65$) and with IFX followed by cyclosporine ($n = 21$) [102]. The median (±standard error) follow-up time was 23 (7) months. During the study period, 49 patients failed to respond to the second-line rescue therapy and underwent a colectomy. The probability of colectomy-free survival (61 ± 5 % at 3 months and 41 ± 6 % at 12 months) was similar in the two groups. Eight serious infections occurred during first-line therapy in seven patients, including two bacterial central-line infections, two cases of *Clostridium difficile* infection, two cases of cytomegalovirus viremia, one viral pericarditis, and one esophageal candidiasis.

All infections had resolved by the time rescue therapy was started. During rescue therapy, nine serious infections occurred in nine patients (cyclosporine → IFX, $n=7$; and IFX → cyclosporine, $n=2$), and there was one fatal pulmonary embolism. In our opinion, the risk-benefit ratio favors colectomy over second-line rescue therapy in patients who have failed cyclosporine or infliximab after also having failed intravenous steroids. Patients who elect second-line therapy should be advised that they have a 60 % chance of colectomy at 1 year and a significant risk of infection.

After successful induction, IFX is continued as scheduled, maintenance therapy. Infusion reactions occur in approximately 10 % of patients and are mitigated by concomitant immunomodulatory therapy or IV hydrocortisone before the infusions [103]. The most important risk concerns infections, particularly opportunistic infections with intracellular pathogens, including *M. tuberculosis*, histoplasmosis, coccidiomycosis, listeriosis, and others. Testing for latent tuberculosis is mandatory before initiation of therapy. Reactivation of the hepatitis B virus may also occur; hence serologies should be evaluated prior to treatment. Other side effects include hepatotoxicity, worsening of heart failure, drug-induced lupus, and demyelinating disorders, such as multiple sclerosis and optic neuritis. The risk of lymphoma does not appear to be increased [104]. Contraindications to treatment include active infection, untreated latent tuberculosis, preexisting demyelinating disorder, moderate to severe heart failure, and current or recent malignancy.

Adalimumab (ADA) is a humanized monoclonal antibody against TNF-α, which was approved after IFX. ADA is administered by subcutaneous injections of 160 mg at week 0 and 80 mg at week 2 for induction, followed by 40 mg every other week for maintenance.

Two small, open-label studies demonstrated that ADA was well tolerated and beneficial for patients with UC including those who had lost response or had developed intolerance to IFX [105, 106]. More recently, two large RCTs evaluated the efficacy of ADA in moderate to severe UC. A multicenter RCT was conducted in North America and Europe in anti-TNF-naïve patients who received ADA 160/80 (160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6), ADA 80/40 (80 mg at week 0, 40 mg at weeks 2, 4, and 6), or placebo [107]. More patients were in remission at week 8 in the ADA 160/80 group compared to placebo (18.5 % vs. 9.2 %). There was no difference between the ADA 80/40 group compared to placebo (10.0 % vs. 9.2 %). The second RCT evaluated ADA for the induction and maintenance of clinical remission in 494 patients who had moderate to severe UC and an inadequate response to corticosteroids and/or immunosuppressants [108]. Remission rates were higher in the ADA group than in the placebo group at week 8 (16.5 % vs. 9.3 %) and week 52 (17.3 % vs. 8.5 %). Remission rates were lower in patients who had previously received an anti-TNF agent versus those who were anti-TNF naïve. Rates of serious adverse events were similar between ADA and placebo groups in both studies.

ADA is an option in patients who have experienced loss of response to IFX due to the development of antibodies against IFX. ADA may be preferred over IFX by some patients due to its subcutaneous administration. Recent regulatory approval of golimumab offers another treatment option for patients with ulcerative colitis.

Golimumab is a newer, fully human, subcutaneously administered anti-TNF antibody. A randomized placebo-controlled trial evaluated induction therapy with golimumab in anti-TNF-α-naïve patients with moderate to severe ulcerative colitis [144]. Patients had a Mayo Score of 6–12 points (with an endoscopic subscore≥2 points) and had failed conventional medical therapy with oral mesalamine, oral corticosteroids, and AZA/6-mercaptopurine, or had been unable to taper corticosteroids without recurrence of disease activity. Golimumab was more efficacious than placebo in inducing clinical response, clinical remission and mucosal healing at week 6, and in improvising quality of life [144]. Responders from this trial were eligible for the subsequent, 52-week-long maintenance trial [145]. Golimumab was more efficacious than placebo in maintaining clinical response and remission and in achieving mucosal healing and corticosteroid-free clinical remission [145].

Other Medical Therapies

Controlled trials of antibiotics have demonstrated no therapeutic benefit when added to intravenous steroids [109, 110]. However, protocols outlining treatment regimens for severe colitis generally include broad-spectrum antibiotics for patients with signs of toxicity or with worsening symptoms despite maximal medical therapy [111]. Nicotine transdermal patches are effective in active UC, though less so than 5-ASA [112–114]. There is no evidence for its use as maintenance therapy. Side effects include lightheadedness, dermatitis, and nausea.

Two RCTs found the probiotic preparation VSL#3 (a combination of eight live, freeze-dried bacterial strains, including four strains of *Lactobacilli*, three strains of *Bifidobacterium*, and *Streptococcus thermophilus*) effective in inducing remission in UC patients failing oral 5-ASA [115, 116]. The evidence on other probiotics is more limited. Antidiarrheal agents are useful in decreasing diarrhea but are contraindicated in severe disease given the risk of toxic megacolon. Dietary arachidonic acid may play a role in the development of UC [117]. However, at the present time,

there is no recommended diet specific for UC patients. Physicians may suggest that their patients identify foods that aggravate their disease and eliminate them from their diet. Controlled studies of total parenteral nutrition (TPN) for patients with severe colitis have shown no benefit, so that TPN is limited to patients who are unable to eat or have significant malnutrition [118, 119].

Goals of Therapy

Clinical Remission

Traditionally, the treatment goal in UC has been the induction and maintenance of steroid-free clinical remission with complete resolution of symptoms. Partial clinical response and reduction in the need for corticosteroids have also been used as endpoints. Symptom-based indices of activity may be used to monitor patients' response to treatment but are influenced by symptoms that are subjective and scoring which may be nonuniform [120].

Quality of Life

Improved quality of life is an additional goal of UC therapy. In addition to bowel symptoms, UC produces constitutional and extraintestinal symptoms and affects multiple dimensions of patients' lives, including interpersonal relationships, emotional state, work productivity, sexual health, and reproduction decisions. Patient perception of the disease is often incongruent with the physician's perspective, possibly due to variability in symptoms, the waxing and waning nature of UC, and incomplete disclosure of symptoms to the physician. The most common quality of life measure is the McMaster Inflammatory Bowel Disease Questionnaire (IBDQ), which is available in long form and short form [121, 122]. The long form is a 32-item questionnaire used in many study trials. The short form consists of ten questions regarding social, emotional, bowel, and systemic measures of health and is more ideal for clinical use to monitor patients' quality of life.

Prevention and Management of Complications

An important goal of UC therapy is the prevention and management of disease and drug-related complications. These include anemia, venous thromboembolism, CRC, and the toxicity of steroids and other agents. Anemia is a common but surprisingly undertreated complication [123–125]. Successful treatment of iron-deficiency anemia correlates with improved quality of life [126, 127]. Multiple large studies have demonstrated that IBD patients have a 1.5- to 3.5-fold higher risk of venous thromboembolism when compared with non-IBD patients [128]. The Adult IBD Physician Performance Measures Set developed by the AGA includes a measure on prophylaxis for venous thromboembolism in IBD inpatients [24]. Although the incidence of CRC is increased in the UC population, emerging data suggest that risk may be declining, possibly as a result of surveillance and more effective therapies [129, 130]. Medication toxicity is minimized by patient education and appropriate clinical and laboratory monitoring.

Mucosal Healing

Demonstration of endoscopic remission was historically not necessary if a patient was asymptomatic. As demonstration of mucosal healing is proof of concept that a drug is effective in UC, assessment of healing has been a secondary endpoint in recent phase II and phase III RCTs. However, there is ongoing debate as to whether mucosal healing should also constitute an endpoint in clinical practice.

Endoscopic healing has been associated with improved long-term outcomes, such as lower rates of relapse and colectomy, decreased steroid use, and improved quality of life [131–136]. Besides endoscopic assessment, mucosal healing can also be assessed histologically. Increased histologic inflammation has been associated with higher rates of relapse, hospitalization, and colectomy [137, 138]. However, at the present time, management driven by endoscopic and/or histologic disease assessment cannot be recommended over management based on simple clinical assessment: There is a good correlation between clinical and endoscopic disease assessment [131, 139]; endoscopy with biopsies is expensive; and there is no evidence that, in patients in clinical remission but with persistent endoscopic or histologic inflammation, escalation of therapy improves outcomes in a cost-effective manner.

Endoscopic and histologic assessment may have a role in stratifying the risk of colorectal (CRC) cancer. The risk of CRC in UC is increased in patients with endoscopic and histologic evidence of active inflammation or evidence of chronic injury (such as colonic strictures, or a foreshortened or tubular colon) [140–142]. Incorporating these findings, the British Society of Gastroenterology has recommended surveillance at 5-year intervals in low-risk patients, including those without endoscopic/histological active inflammation on the previous colonoscopy [143].

Conclusions

Ulcerative colitis is a life-long disease portending decades of potential morbidity. Effective management requires education and empowerment of patients and a coordinated healthcare system involving primary care physicians,

dedicated IBD teams, and other subspecialists. The selection of medical therapy must take into account the severity and extent of the patient's disease but also suit the patient's lifestyle and treatment goals.

5-ASA is first-line therapy in patients with UC and dosing should be maximized with incorporation of topical formulations whenever tolerated. Corticosteroids are only indicated for induction therapy and should be tapered as soon as clinical remission is established. Maintenance therapy with immunomodulators should be considered in steroid-dependent UC as well as in patients with frequent flares, but may require up to 4 months to reach full effectiveness. Tumor necrosis factor antagonists are used (with or without concomitant immunomodulators) in steroid-dependent or refractory UC. These agents, as well as cyclosporine, are options for patients failing intravenous steroids and wishing to avoid colectomy in the short term.

Besides the induction and maintenance of clinical remission, the goals of treatment include improved quality of life and prevention of complications. It is premature to regard mucosal healing as a therapeutic goal in daily clinical practice. The medical therapy of UC patients requires a multifaceted, patient-centered approach that takes into account individual patient preferences.

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