JAMA Clinical Guidelines Synopsis

Ulcerative Colitis in Adults

Laura R. Glick, MD; Adam S. Cifu, MD; Lauren Feld, MD

GUIDELINE TITLE ACG Clinical Guideline: Ulcerative Colitis in Adults

DEVELOPER American College of Gastroenterology (ACG)

RELEASE DATE February 2019

PRIOR VERSION March 2010

TARGET POPULATION Adult patients with ulcerative colitis

MAJOR RECOMMENDATIONS

- In patients with moderately to severely active ulcerative colitis of any extent, oral systemic corticosteroids are recommended for induction of remission but not for maintenance of remission (strong recommendation; moderate-quality evidence).
- For induction of remission in patients with moderately to severely active ulcerative colitis, anti–tumor necrosis factor (TNF) therapy (adalimumab, golimumab, or infliximab) (strong recommendation; high-quality evidence) or novel treatment options (vedolizumab and tofacitinib) (strong recommendation; moderate-quality evidence) are recommended.
- Patients with ulcerative colitis of any extent beyond the rectum should have colonoscopy and surveillance to identify neoplasia every 1 to 3 years based on risk factors (such as degree of inflammation and disease duration) and previous findings (conditional recommendation; very low-quality evidence).
- Fecal calprotectin (FC) can be considered in patients with ulcerative colitis as a noninvasive marker of disease activity and to assess response to therapy and relapse (key concept statement; no level of recommendation or strength of evidence).

Summary of the Clinical Problem

Ulcerative colitis is a chronic, immune-mediated inflammatory disease that affects the large intestine. Disease severity is determined by patient-reported outcomes, inflammatory burden as measured by endoscopic assessment and markers of inflammation, disease course, and how the disease affects patients. Management of ulcerative colitis is increasingly complex with new treatments available and improved understanding of the disease's pathophysiology.

Characteristics of the Guideline Source

This guideline was developed by the ACG. The writing committee included board-certified gastroenterologists with expertise in diagnosis and management of ulcerative colitis. The guideline lists potential conflicts of interest but does not state how the disclosed conflicts were managed (**Table**).[1] The literature searches used were limited to primary clinical trials, meta-analyses, systemic reviews, and prior guidelines. Quality of evidence was assessed using GRADE. A final review was conducted with the board of trustees, the practice parameters committee, and the *American Journal of Gastroenterology* prior to publication.

Evidence Base

This guideline has 49 graded recommendations based on clinical trial data and 54 key concept statements (provided when clinical data were not available). The recommendations covered herein were chosen for their broad clinical relevance. The guideline recommends oral corticosteroids to induce remission in patients with moderately to severely active ulcerative colitis of any extent. A meta-analysis demonstrated that oral corticosteroids were more effective in inducing ulcerative colitis remission vs placebo (relative risk, 0.65; 95% CI, 0.45-0.93).[2] Clinical improvement should be observed within 5 to 7 days of beginning treatment. The course of corticosteroids should be as short as possible. The guidelines recommend against corticosteroids for maintenance of ulcerative colitis remission. Patients who do not respond to corticosteroids should be evaluated for rescue therapy, including infliximab or cyclosporine, and surgical intervention should be considered.

Anti-TNF therapies are recommended for induction of remission in patients with moderately to severely active ulcerative colitis. This is a strong recommendation based on randomized trials showing that each of these therapies is more effective than placebo in inducing remission. In a representative trial comparing adalimumab with placebo, overall rates of clinical remission were 16.5% with adalimumab and 9.3% with placebo at 8 weeks (P = .02) and 17.3% and 8.5%, respectively, at 52 weeks (P = .02).[3]

Audio

The anti-integrin drug vedolizumab is recommended for induction of remission in patients with moderately to severely active ulcerative colitis (strong recommendation; moderate-quality evidence). This recommendation is based on, among others, the GEMINI 1 trial (n = 374 randomized), which showed clinical response rates at 6 weeks in 47.1% of the vedolizumab group vs 25.5% of the placebo group (difference, 21.7%; 95% CI, 11.6%-31.7%; P < .001).[4]

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the guideline development group	Fair
Guideline development group composition	Good
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Good
Updating	Good
Implementation issues	Good

Tofacitinib, an oral small-molecule Janus kinase enzyme inhibitor, is also recommended for induction of remission in patients with moderately to severely active ulcerative colitis (strong recommendation; moderate-quality evidence). Tofacitinib is currently approved for use only after anti-TNF therapy fails. The OCTAVE 1 (n = 598) and OCTAVE 2 (n = 541) trials assessed the efficacy of tofacitinib vs placebo in inducing remission in patients with moderately to severely active ulcerative colitis in whom conventional therapies, including anti-TNF agents, had failed.[5] The primary end point of the trials was clinical remission at 8 weeks. This was reached in 18.5% of patients in the tofacitinib group vs 8.2% of patients in the placebo group (difference, 10.3%; 95% CI, 4.3%-6.3%; *P* = .007) in the OCTAVE 1 trial and in 16.6% vs 3.6% (difference, 13.0%; 95% CI, 8.1%-17.9%; *P* < .001) in the OCTAVE 2 trial.

The guideline recommends use of previously more common immunomodulators, including thiopurines, in combination with anti-TNF therapies (with the most data supporting combination therapy of infliximab and thiopurines). Methotrexate is not recommended either for induction or maintenance of ulcerative colitis.

The guideline recommends colonoscopic surveillance to identify neoplasia in patients with ulcerative colitis beyond the rectum beginning 8 years after diagnosis. Also recommended are surveillance colonoscopies at 1- to 3-year intervals, which are stratified and individualized based on a patient's risk factors (such as degree of inflammation and disease duration) and previous colonoscopy findings. This is a conditional recommendation based on a lack of evidence supporting its benefit.

Elevations in FC can help differentiate inflammatory bowel disease or infectious diarrhea from irritable bowel syndrome. Fecal calprotectin levels correlate with degrees of endoscopic and histologic inflammation in ulcerative colitis and can therefore also be used as a treatment target and marker of inflammation when endoscopy is not possible to assess mucosal healing. Sensitivity and specificity of FC are 0.88 (95% CI, 0.84-0.90) and 0.73 (95% CI, 0.66-0.79), respectively.[6] These test characteristics are better than those of serum inflammatory markers.

Benefits and Harms

The recommendation for using anti-TNF, anti-integrin, and Janus kinase enzyme inhibitor therapies has the potential to promote clinical and endoscopic remission without steroids. This recommendation involves some risks of harm. These medications have been associated with both rare (lymphoma, progressive multifocal leukoencephalopathy, and opportunistic infections) and more common (upper respiratory tract infections, urinary tract infections, and infusion reactions) adverse events. These medications also are very expensive.

Discussion

This guideline emphasizes new tests, including serum drug levels and FC, and novel therapies approved by the US Food and Drug Administration. The guideline does not specify which of the newer therapies should be used first. In general, the guidelines recommend organ-selective therapies over systemic therapies. Data from a clinical trial of 769 patients published after completion of the guideline demonstrates that vedolizumab is more effective than adalimumab for achievement of clinical remission and endoscopic improvement but not corticosteroid-free clinical remission.[7]

This guideline also highlights a shift from tailoring therapy based exclusively on symptom control to incorporating objective measures of inflammation and mucosal healing.

Areas in Need of Future Study or Ongoing Research

Although the novel therapies are promising, further research is needed to help physicians choose the appropriate therapy at the appropriate time. Ideally, physicians should be able to determine the therapy with the highest efficacy and highest safety margin for each patient prior to initiating treatment. Determining the appropriate interval for colorectal cancer screening in ulcerative colitis is difficult, and data supporting use of colonoscopy for prevention of colorectal cancer remain limited. While there is evidence that cancers are detected at an earlier stage with increased surveillance, there are no data showing that patients have improved outcomes or survival.

Related guideline

2019 American Gastroenterological Association clinical practice guidelines on management of mild to moderate ulcerative colitis

2017 American College of Gastroenterology clinical guideline on preventive care in inflammatory bowel disease

ARTICLE INFORMATION

Author Affiliations: Yale University, New Haven, Connecticut (Glick); University of Chicago, Chicago, Illinois (Cifu); University of Washington, Seattle (Feld).

Corresponding Author: Adam S. Cifu, MD, University of Chicago, 5841 S Maryland Ave, MC 3051, Chicago, IL 60637 (adamcifu@uchicago.edu).

Section Editor: Edward H. Livingston, MD, Deputy Editor, *JAMA*.

Published Online: August 27, 2020. doi:10.1001/jama.2020.11583

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413. doi:10.14309/ajg.0000000000000152

2. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease. *Am J Gastroenterol*. 2011;106(4):590-599. doi:10.1038/ajg.2011.70

3. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142(2):257-265. doi:10.1053/j.gastro.2011.10.032

4. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369(8):699-710. doi:10.1056/NEJMoa1215734

5. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376(18):1723-1736. doi:10.1056/NEJMoa1606910

6. Mosli MH, Zou G, Garg SK, et al. C-reactive protein, fecal calprotectin, and stool lactoferrin for detection of endoscopic activity in symptomatic inflammatory bowel disease patients. *Am J Gastroenterol*. 2015;110(6):802-819. doi:10.1038/ajg.2015.120

7. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019;381(13):1215-1226. doi:10.1056/NEJMoa1905725