Updated Management of Ulcerative Colitis

Muhamad Reza Prabowo, Achmad Fauzi***

*Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo General National Hospital, Jakarta

**Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo General National Hospital, Jakarta

Corresponding author:
Muhamad Reza Prabowo, Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo General National Hospital, Jakarta. Jl. Diponegoro No. 71, Central Jakarta, Indonesia. Email: muhammadrezaprabowo@gmail.com

ABSTRACT

Ulcerative Colitis (UC) is a chronic disorder of Inflammatory Bowel Disease (IBD) which showed pathological changes of mucosa (symmetrical, diffuse) that involving rectum and may be extended to proximal colon. In general, target of the treatment quite indistinguishable to Crohn's Disease (CD), such as improving quality of life, treating the acute condition, maintaining remission status, preventing complications, and achieving adequate nutritional status. Nowadays, there are so many therapeutic agents which were more effective than previous drugs. Another reason we should have left prior medicine is the safety of newer agents are promising. Today's technology advances make gastroenterologist easier to give more treatment choice to every spectrum of ulcerative colitis. This review aims to provide an updated overview of ulcerative colitis management.

Keywords: *Anti-integrin, biologic agent, management, small molecules, ulcerative colitis*

ABSTRAK

Kolitis ulseratif merupakan suatu kelompok penyakit usus inflamatorik kronik yang ditandai dengan perubahan patologis mukosa (simetris, difus) yang melibatkan rektum dan bahkan dapat meluas ke kolon proksimal. Secara umum, target pengobatan kolitis ulseratif kurang lebih sama dengan penyakit Crohn, yakni memperbaiki kualitas hidup, memperbaiki kondisi akut, mempertahankan status remisi, mencegah komplikasi, dan mencapai status gizi yang adekuat. Saat ini, banyak obat baru yang lebih efektif dibandingkan obat sebelumnya. Alasan lain tenaga medis meninggalkan obat-obat sebelumnya adalah keamanan dari obat baru yang menjanjikan. Kemajuan teknologi saat ini mempermudah ahli gastroeneterologi memberikan pilihan pengobatan lebih banyak pada berbagai spektrum kolitis ulseratif. Tinjauan ini bertujuan untuk memberikan gambaran terkini tentang penanganan kolitis ulseratif.

Kata kunci: *Anti-integrin, agen biologis, manajemen, molekul kecil, kolitis ulseratif*

INTRODUCTION

Ulcerative Colitis (UC) is one of the inflammatory bowel disease subgroups, characterized by symmetrical and diffuse inflamed mucosa that involves the rectum and may extend to the proximal colon. The yearly incidence of UC is 0.55 per 100,000 population. The peak incidence is at 20–29 years of age, while the female-to-male ratio is 0.51–1.58.[1]

In the last decade, 5-aminosalicylic acid (5-ASA) and steroids have been the main choices for UC treatment. A high number of relapses, systemic side effects, and difficulty in achieving remission have led physicians to search for new strategies, including trials of new agents such as biological agents, integrin inhibitors, and small molecules.[2]

Treatment modalities should be chosen wisely, since every new agent may have disadvantages. Successful treatment is determined not only by the efficacy of the therapy, but also by patient adherence, drug resistance, and comorbidities.[3] This review aims to provide an updated overview of ulcerative colitis management.

INVESTIGATION OF ULCERATIVE COLITIS

UC diagnosis should be considered to every patient with defecation urgency and hematochezia by ruling out the infection first. The investigation should involve laboratory examination, stool culture, colonoscopy, histopathology, fecal calprotectin, and occasionally radiology examination.[2,3]

Not all examination on **Table 1** needed to establish the diagnosis, the examination could be a replacement or complementary each other since there are limitations in every health facility.[4-6]

DEGREE AND EXTENT OF ULCERATIVE COLITIS

The extent of ulcerative colitis still uses the Montreal criteria (2006). The anatomical hallmark of the criteria are rectum and splenic flexure as shown on **Table 2**.[7,8]

The degree of ulcerative colitis could be judged by clinical condition, laboratory basis, and colonoscopy findings. For limited resources area, clinicians may use simple clinical colitis activity index (SCCAI) on **Table 2.** Total score two or less indicates remission of UC.[7,8]

Modified Truelove and Witts criteria uses clinical and laboratory parameter as we can see on **Table 2.** Mild condition stated if all mild criteria fulfilled. While severe denominated as one or more criteria included as severe (except bloody stool per day). If the patient could not meet both mild and severe criteria, they considered as moderate degree.[7,8]

Mayo score is the most common score used by physicians and it comprises clinical and endoscopy items, figured on **Table 2.** Total score 2 or less indicates (if each indicator <2) clinical remission. Score 3-5 as mild, 6-10 as moderate, and 11-12 as severe.[7,8]

Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is a tool to have a look at the degree of UC based on endoscopic view. It consists of vascular pattern, hemorrhage, and ulcer/erosion. Per endoscopic, score 0-1 belong to remission, 2-4 as mild, 5-6 as moderate, and 7-8 as severe.[2]

All criteria that explained above were used for the next treatment that should be considered by physician. Without those tools, the judgement could be lost in direction and irrational. So, this step is vital before attempting therapy to the patient.[2,7,8]

Table 1. Investigation of Ulcerative Colitis

Parameter	Investigation	Findings	Notes
Laboratory	Complete blood count (CBC), ureum, electrolyte, C-reactive protein (CRP), liver function	Anemia, thrombocytosis, high CRP	Primary sclerosing cholangitis (PSC) associated with UC has liver function abnormality
Stool culture	*Clostridium difficile toxin*	Should be negative, unless coinfection	History of antibiotic use
Fecal calprotectin	Neutrophil migration to the bowel lumen through mucosa	Level 50-100 µg/g has negative predictive value 98-99% in IBD	Can be used as therapy monitoring
Endoscopy	Colonoscopy	Rule out Crohn, finds erythema, edema, vascular pattern, blood, erosion/ulcer	Using Mayo scale and *Ulcerative Colitis Endoscopy Index of Severity* to assess severity
Histology	Biopsy from every segment of colon	Basal plasmacytosis, crypta atrophy or distortion, irregularity of crypta surface	Granuloma tends to be Crohn disease
Imaging	BNO CT scan/MRI	Thumbprinting, lead-piping, toxic megacolon, gut wall edema, inflammatory pseudo polyp	In difficult case, intestines imaging could differ UC to CD

Table 2. Classification of Ulcerative Colitis

Montreal Classification of Ulcerative Colitis Extension					
Extension	**Definition**			**Proportion**	
Proctitis	Limited to rectum			30%	
Left sided colitis	Rectum and left side colon (distal to splenic flexure)			40%	
Pancolitis	Rectum until proximal to splenic flexure			30%	
Simple Clinical Colitis Activity Index (SCCAI)					
Indicator	**0**	**1**	**2**	**3**	**4**
Stool frequency (day)	1-3	4-6	7-9	>9	
Stool frequency (night)	0	1-3	4-6		
Defecation urgency	None	Urge	Immediate	Incontinence	
Fecal blood	None	Streak	Few	Dominant	
General condition	Very well	Slightly decrease	Poor	Very poor	Worst
Extracolonic manifestation	None	Add 1 per symptoms (uveitis, pyoderma gangrenosum, erythema nodosum, arthropathy)			
Modified Truelove and Witts Criteria					
Parameter	**Mild**		**Moderate**	**Severe**	
Bloody stool/day	<4		4-6	>6	
Heart rate (x/minute)	£90		£90	>90	
Temperature (°C)	<37,5		37,5-37,8	>37,8	
Hemoglobin (g/dL)	>11,5		10,5-11,5	<10,5	
ESR (mm/h) (or CRP, mg/dL)	<20 (normal)		20-30 (<3)	>30 (>3)	
Mayo Score					
Parameter	**0**	**1**	**2**	**3**	
Stool frequency	Normal	1-2 more	3-4 more	>=5 more	
Rectal bleeding	None	Blood in less than half of stool	Blood almost covers feces	Blood only without feces	
Endoscopic findings	Normal/inactive	Mild	Moderate	Severe	
General condition	Normal	Mildly ill	Moderately ill	Severely ill	

TREATMENT IN GENERAL

As mentioned before, the treatment given should be based on the extent and degree of UC. They are also influenced by other factors such as steroid dependency or refractory, young age, and also hospitalization needs.[9-11]

PROCTITIS

5-ASA is the first choice to induce clinical, endoscopic, and histologic remission. Suppository preparation is more tolerable than enema. Dose 1 g/day is satisfying and showing no benefit if given in higher doses or more frequent.[12] Single topical therapy proven to be more effective than oral agent alone.[13]

Topical 5-ASA is also superior than topical steroid.[14] Topical steroid could be considered to those who intolerant or failed to 5-ASA. Topical steroid combined with 5-ASA have synergistic effect but much data still needed.[15]

Higher doses should be given in relapsing proctitis (3 g/weeks divided dose per topical or 2 g/day per oral). To those who resistant to 5-ASA should change the regimen to combination of steroid and both oral and topical 5-ASA. Refractory proctitis should be managed by giving intravenous steroid, cyclosporin, tacrolimus, or biologic agent. Surgery may be considered if patient having quality of life problem.[10]

MILD-MODERATE ULCERATIVE COLITIS

Standard dose (2-3 g/day) or higher dose (up to 4.8 g/day) 5-ASA is beneficial for moderate cases. 5-ASA is not superior to sulfasalazine, but more tolerable.[16] If musculoskeletal problem accompanying symptoms, sulfasalazine is better than 5-ASA.[17]

Meanwhile the remission is achieved, maintenance dose must be continued to prevent relapse (at least 2 g/day). Higher doses needed if the patient only achieve on that dose or multiple relapses before.[18]

If the response unmeet the remission criteria, topical corticosteroid could be added. Failed response to topical steroid should be continued to oral steroid and tapered off until remission is achieved.[3,19,20] The algorithm showed in **Figure 1.**

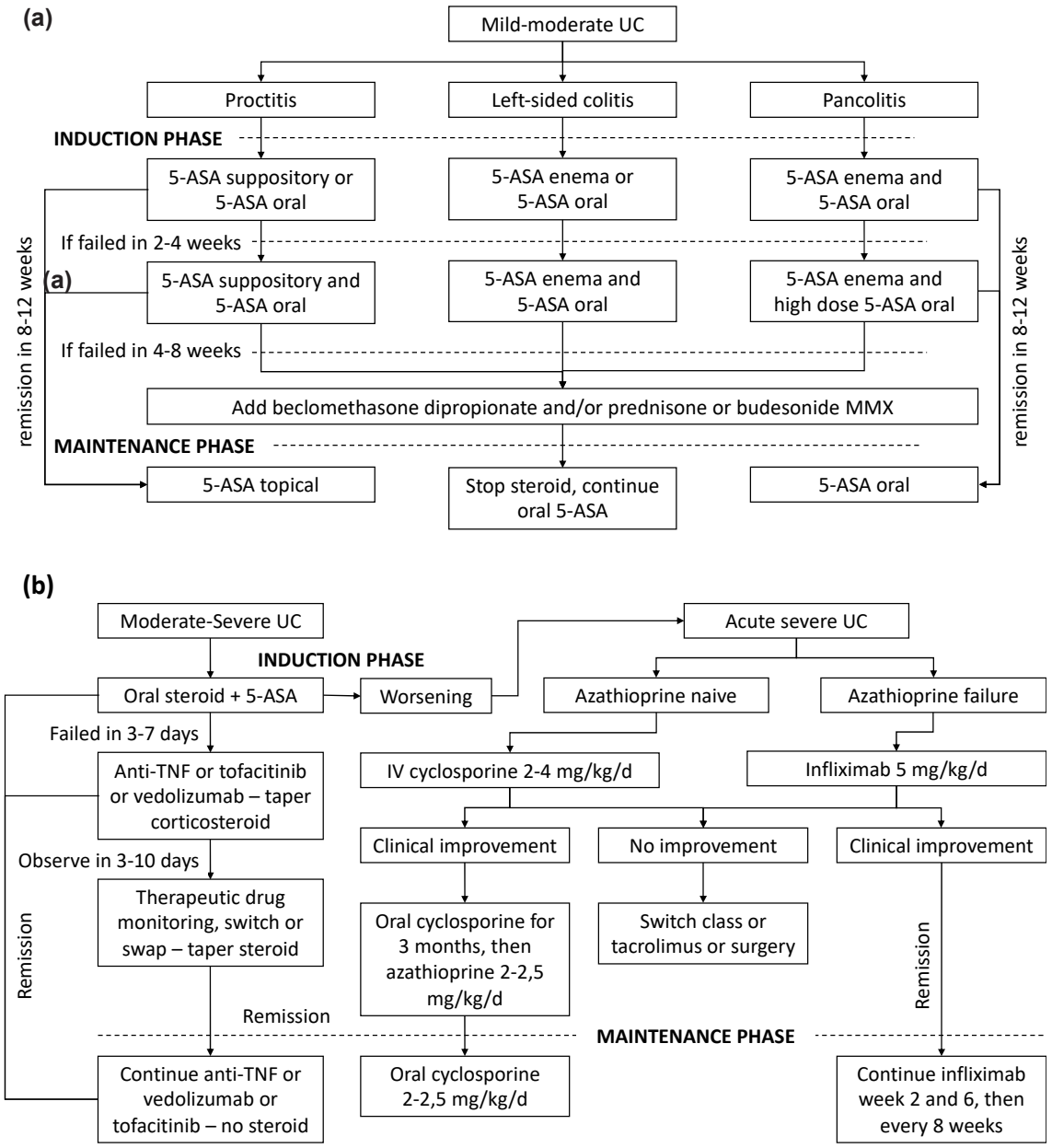

Figure 1. (a) Algorithm of Mild-Moderate Ulcerative Colitis Management[3,17,19,20]
(b) Algorithm of Moderate-Severe and Acute Severe Ulcerative Colitis Management[3,8,20]

MODERATE-SEVERE ULCERATIVE COLITIS

The prominent difference of this degree is systemic signs such as fever, hospitalization needs, and increased inflammatory markers (CRP, fecal calprotectin). In this case, systemic steroid is the drug of choice as shown in **Figure 2.**[10]

Thiopurines act slowly and could not be an agent to induce remission. Methotrexate is a sparing agent, like thiopurines. Anti-tumor necrosis factor (anti-TNF), such as infliximab, adalimumab, and golimumab are effective against moderate to severe UC. Vedolizumab and tofacitinib are other options since its promising efficacy.[21,22]

ACUTE SEVERE ULCERATIVE COLITIS

This condition can be established according to modified Truelove and Witts criteria as mentioned before. After ruling out infection, either 62.5 mg methylprednisolone or 4x100 mg hydrocortisone could be administered. Keeping the patient hydrated and electrolyte correction, antibiotic (if infection is present), thromboprophylaxis, are essential for the treatment.[3,10]

Patients who are not responded to intravenous steroid, should get salvage therapy, including IV cyclosporine 2 mg/kg BW or infliximab 5 mg/kg BW at week 0, 2, and 6. If the patients were induced by using cyclosporine, the maintenance should be

oral cyclosporine and azathioprine, vedolizumab, or tofacitinib. Those who received infliximab as induction, should use infliximab again as maintanance.[23,24,25]

Approximately one third patients experience cytomegalovirus (CMV) reactivation, especially who are steroid refractory. CMV must be excluded by biopsy and PCR examination. Ganciclovir is the first choice for CMV colitis.[3,9]

Persistently acute severe colitis needs colectomy. Absolute indications for surgery are toxic megacolon, perforation, uncontrolled bleeding, or multiple organ failure. Failure to medical therapy is the indication of surgery. The delay may cause malnutrition and postoperative complication since long term use of steroid. Laparoscopy is preferred because it has lower incidence of intraabdominal abscess, shorter length of stay, and less impact to female reproductive organ.[3,9]

STEROID-DEPENDENT ULCERATIVE COLITIS

Steroid dependent UC is a state which the patient cannot terminate or reduce the steroid dose in 12 weeks because of relapse, relapse in 16 weeks when tapering down, or two or more episodes of steroid use in a year. 5-ASA is the main choice, but adherence must be ensured and infection is excluded.[3]

Those who are intolerant to 5-ASA or sulfasalazine, azathioprine 2-3 mg/kg BW/day or 6-mercaptopurine 1-1.5 mg/kg BW/day is the maintenance agent in steroid dependency. Patients who are intolerant to azathioprine or 6-mercaptopurine, could choose other agents (anti-TNF, anti-integrin, or small molecules). The algorithm showed in **Figure 3.**[23,24,25]

STEROID-REFRACTORY ULCERATIVE COLITIS

Unrespond to 40-60 mg/day prednisone in 14 days should be named as steroid refractory. Steroid-refractory UC is treated by intravenous steroid (methylprednisolone 0,5-1 mg/kg BW/day or hydrocortisone 4x100 mg/day). Immunosuppressants act slowly so they cannot be the options. Biologic agent and small molecules are more effective than immunosuppressants.[3,25] **Figure 4** shows the path for those who are refractory to steroid.

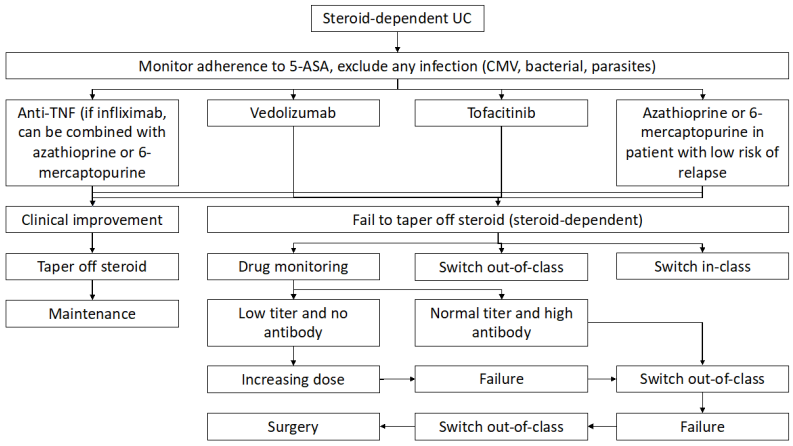

Figure 3. Algorithm of Steroid-Dependent Ulcerative Colitis Management[3,20,23]

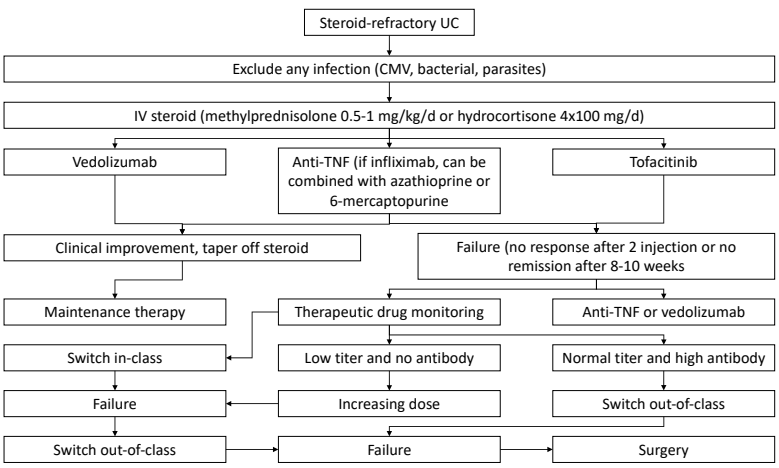

Figure 4. Algorithm of Steroid-Refractory Ulcerative Colitis Management[3,20,23,26]

DRUG SAFETY

5-ASA is safe for pregnant and lactating women. Interstitial nephritis is rare but kidney function should be observed. Other adverse events are pancreatitis, pericarditis, myocarditis, pneumonitis, and paradoxical diarrhea. Side effects of sulfasalazine are dyspepsia, headache, and skin reaction for almost half of patients and dose dependent.[9]

Long term steroid may impact worse condition. Cushing syndrome (acne, hyperglycemia, hypertension, moon face, buffalo hump) can be trademark of this condition. Infection is a serious complication of uncontrolled steroid use.[3]

Anti-TNF may fasten remission, mucosal healing, decrease length of stay, and improving quality of life. Subcutaneous or intravenous infliximab is superior to adalimumab and golimumab. Biosimilar infliximab is as same effective yet less expensive. Unwanted effect is opportunistic infection, such as herpes, tuberculosis, candida, CMV, and Epstein Barr. The incidence is higher if combined with steroid or immunosuppressant. Combination with thiopurines increases the likelihood of lymphoma.[27,28]

Vedolizumab is an integrin inhibitor. It also has promising effect in moderate-severe UC and shows superiority to adalimumab in mucosal healing and remission.[27] There is no opportunistic infection or malignancy reported from the use of vedolizumab. Headache, nausea, abdominal pain, fatigue, and pharyngitis are the most common side effects.[29]

Tofacitinib is nonselective Janus Kinase (JAK) inhibitor, a small molecule that has been used for rheumatoid arthritis treatment. Tofacitinib is not superior to other biologic agents. The most common side effect is herpes zoster reactivation (dose dependent).[30]

Tacrolimus is calcineurin inhibitor that act like cyclosporin but has fewer side effects. Tacrolimus is a part of immunosuppressants therefore infection is the most common side effect.[31]

TREATMENT FAILURE

Approximately 20% patients who receive anti-TNF are not responded in induction phase. Patients' compliance, inflammatory markers, and gastrointestinal infection should be monitored. Pharmacokinetic profile of the patient such as quicker drug clearance because of high degree of inflammation, protein loss, hypoalbuminemia, obesity, male gender, and neutralizing antibody should be considered.[3,32]

Therapeutic drug monitoring and antibody titer are important tools to control therapy. If the anti-TNF serum is low without any antibody, clinicians should increase the dose of the drug. If the anti-TNF serum is normal, but clinical is not improved, the physicians should change the medication in another class.[32,33]

Multidisciplinary approach is important since surgery may be the only option if medical therapy is failed. Digestive surgery must be informed early to have good timing for procedure without any delay, therefore lowering postoperative morbidity and mortality.[32]

OTHER TREATMENT MODALITIES

Probiotic formulation such as *Escherichia coli* Nissle 1917, *Bifidobacterium spp*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosum GG*, and Enterococcus have been tried but the efficacy is still questionable. *Escherichia coli* Nissle 1917 is superior in maintaining remission in 12 months if compared to 5-ASA. But the study is in limited samples.[3]

Beclomethasone dipropionate (BDP) and budesonide are examples of second-generation steroid. Those agents act locally, have high first pass metabolisms and minimal systemic effect. These can be induction agent but not for maintenance phase. Slow-release BDP is superior to 5-ASA in remission induction of mild-moderate UC. Combination of 5-ASA and budesonide MMX is more effective than 5-ASA alone.[34]

First-generation steroid is only used in case of inducing remission in moderate-severe UC. The steroid must be tapered off in 8-12 weeks. Systemic steroid could not be maintenance agent.[9] Each agent needed in UC is shown in **Table 3.**

Fecal transplantation is new modality to treat since gut dysbiosis is part of UC pathogenesis. Meta-analysis showed fecal transplant has significant therapeutical effect than placebo. Nevertheless, the heterogeneity is high because of different method, donor selection, fecal processing, modality, and transplantation frequency. American Gastroenterology Association recommend this modality in context of clinical trial.[35]

Table 3. Dose and Preparation of Ulcerative Colitis Agents

Groups	Substance(s)	Dose (preparation)
5-ASA	Mesalamine	2-4.8 g/d (oral) 1-2 g/d (rectal)
Sulfasalazine	Sulfasalazine	2-4.8 g/d (oral)
2nd gen steroid	Budesonide Budesonide MMX	0.2 mg/d (rectal) 9 mg/d (oral)
1st gen steroid	Prednisone Hydrocortisone Methylprednisolone	0.75-1 mg/kg/d (oral) 4x100 mg/d (IV) 62.5-125 mg/d (IV)
Immunosuppressants	Azathioprine 6-mercaptopurine Cyclosporine Tacrolimus	2-3 mg/kg/d (oral) 1-1,5 mg/kg/d (oral) 2-2.5 mg/kg/d (IV) 0,1 mg/kg/d (oral, serum level 10-15 ng/mL)
TNF-inhibitor	Adalimumab	Week 0: 160 mg (subcutaneously) Week 2: 80 mg Week 4: 40 mg Next every 2 weeks: 40 mg Dose intensification: 40 mg/week
	Golimumab	Week 0: 200 mg (subcutaneously) Week 2: 100 mg Week 4: 50 mg Next every 4 weeks: 50 mg (100 mg if BW >80 kg)
	Infliximab	Week 0, 2, 6: 5 mg/kg (subcutaneously or infusion in 30-90 minutes) Next every 8 weeks: 5 mg/kg Dose intensification: every 4 weeks 5-10 mg/kg
Anti-integrin	Vedolizumab	Week 0, 2, 6: 300 mg (infusion in 30 minutes) Next every 8 weeks: 300 mg Dose intensification: every 4 weeks 300 mg
Small molecules JAK inhibitor	Tofacitinib	First 8 weeks: 2x10 mg/d (tablet 5 or 10 mg) Second 8 weeks (if partial response): 2x10 mg/d, continue with 2x5 mg/d

THE DEVELOPMENT OF NEW AGENTS

Ustekinumab now is a promising agent. It is anti-p40 subunit that act to interleukin-12 and interleukin-23 (IL-12 and IL-23).[36] This agent can achieve remission in week 8 and 16. Other agents that still in development include selective p19/IL23 inhibitor (Mirikizumab, Risankizumab), anti-adhesive agents (etrolizumab, SHP647, and AJM300), newer JAK inhibitors (Upadacitinib, Filgotinib, dan TD-1473), and other new pathway, such as sphingosin-1-phosphate receptor (Ozanimod), antiCD3 (rituximab), matrixmetallopeptidase-9 (GS-5745), anti-CD20 (Visilizumab), anti-toll like receptor 3 (PRV-300), dan phosphatidylcholine.[3]

PROGNOSIS

Poor prognosis can be identified if we found some criteria, age less than 40 at diagnosis, pancolitis extension, Mayo score 3 or UCEIS 7-8, hospitalized as having colitis, high CRP, and hypoalbuminemia. The more prognostic factors one has, the worse the prognosis, and the greater the need for colectomy.[2]

CONCLUSION

By understanding clinical status, laboratory examination, and endoscopic view, the physician might prescribe proper treatment to the patients with UC. Limited resource and cost are big challenge because the drug of choice getting narrowed. Adequate monitoring could be strategy to decrease the incidence of morbidity and mortality caused by UC itself. Technology advances make gastroenterologist easier to treat, but different settings limit the choices.

REFERENCES

1. Makmun D, Fauzi A, Maulahela H, Pribadi RR. Konsensus Nasional Penatalaksanaan Inflammatory Bowel Disease (IBD) di Indonesia (Revisi 2019). Jakarta: PIPInterna; 2019.
2. Rubin DT, Ananthakrisnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019;114:384-413.
3. Annese V. An update on treatment of ulcerative colitis. Exp Opin on Orphan Drugs. 2019;7:295-304.
4. Segal JP, LeBlanc JF, Hart AL. Ulcerative colitis: an update. Clin Med. 2021;21;135-9.
5. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi, JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68:1–106.
6. Shah SC, Itzkowitz SH. Reappraising risk factors for inflammatory bowel disease-associated neoplasia: implications

for colonoscopic surveillance in IBD. J Crohns Colitis 2020;14:1172–7.
7. Teixeira FV, Hosne RS, Sobrado CW. Management of ulcerative colitis: a clinical update. J Coloproctol. 2015;35:230-7.
8. Feuerstein JD, Isaacs KL, Schneider Y, Siddique SM, Falck-Ytter Y, Singh S. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020;158:1450-61.
9. Magro F, Gionchetti P, Eliakim R, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis. 2017;11:649–67.
10. Harbord M, Eliakim R, Bettenworth D, Karmiris K, Kopylov U, Kucharzik T, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. J Crohns Colitis. 2017;11:769–84.
11. Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, et al. Clinical practice guidelines for the medical management of non-hospitalized ulcerative colitis: the Toronto consensus. Gastroenterology. 2015;148:1035–58.
12. Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012;11:CD004118.
13. Gionchetti P, Rizzello F, Venturi A, Ferretti M, Brignola C, Miglioli M, et al. Comparison of oral with rectal mesalazine in the treatment of ulcerative proctitis. Dis Colon Rectum. 1998;41:93–7.
14. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut. 1997;40:775–81.
15. Mulder CJ, Fockens P, Meijer JW, van der Heide H, Witlink EH, Tytgat GN. Beclomethasone dipropio- nate (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;8:549–553.
16. Ford AC, Khan KJ, Achkar JP, Moayyedi P. Efficacy of oral vs. topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol. 2012;107:167–76.
17. Ko CW, Singh S, Feuerstein JD, Falck-Ytter C, Falck-Ytter Y, Cross RK. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. Gastroenterology. 2019;156:748–76.
18. Feagan BG, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012;10:CD000544.
19. Eder P, Lodyga M, Gawron-Kiszka M, Dobrowolska A, Gonciarz M, Hartleb M, et al. Guidelines for the management of ulcerative colitis: recommendations of the polish society of gastroenterology and the polish national consultant in gastroenterology. Gastroenterology Rev. 2023;18:1-42.
20. Raine T, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, et al. ECCO guidelines on therapeutics in ulcerative Colitis: medical treatment. J Crohns Colitis. 2022;16:2-17.
21. Khan KJ, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011;106:630–42.
22. Carbonnel F, Colombel JF, Filippi J, Katsanos KH, Peyrin-Biroulet L, Allez M. Methotrexate is not superior to placebo for inducing steroid-free remission, but induces steroid-free clinical remission in a larger proportion of patients with ulcerative colitis. Gastroenterology. 2016;150:380–8.
23. Kucharzik T, Koletzko S, Kannengiesser K, Dignass A. Ulcerative colitis - diagnostic and therapeutic algorithms. Dtsch Arztebl Int. 2020;117:564–74.
24. Laharie D, Bourreille A, Branche J, Allez M, Bouhnik Y, Filippi J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet. 2012;380:1909–15.
25. Timmer A, Patton PH, Chande N, McDonald JWD, MacDonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2016; 2016:CD000478.
26. Burri E, Maillard MH, Schoepfer AM, Seibold F, Assche GV, Riviere P, et al. Treatment Algorithm for Mild and Moderate-to-Severe Ulcerative Colitis: An Update. Digestion. 2020;101:2-5.
27. Danese S, Fiorino G, Peyrin-Biroulet L, Lucenteforte E, Virgili G, Moja L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med. 2014;160:704–11.
28. Panaccione R, Ghosh S, Middleton S, Marquez JR, Scott BB, Flint L, van Hoogstraten JF, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;146:392–400.
29. Feagan BG, Rubin DT, Danese S, Vermeire S, Abhyankar B, Sankoh S, et al. Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. Clin Gastroenterol Hepatol. 2017;15:229–239.
30. Sandborn WJ, Su C, Sands BE. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376:1723– 36.
31. Lawrance IC, Baird A, Lightower D, Radford-Smith G, Andrews JM, Connor S. Efficacy of rectal tacrolimus for induction therapy in patients with resistant ulcerative proctitis. Clin Gastroenterol Hepatol. 2017;15:1248–55.
32. Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, de Acosta MB, et al. Third european evidence-based consensus on diagnosis and management of ulcerative colitis. part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis. 2017;11:649-70.
33. NV Casteele, Herfarth H, Katz J, Falck-ytter Y, Singh S. American gastroenterological association institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. Gastroenterology. 2017;153:835-57.
34. Sherlock ME, MacDonald JK, Griffiths AM, Steinhart AH, Seow CH. Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2015;2015:CD007698.
35. Singh S, Feuerstein JD, Binion DG, Tremaine WJ. AGA technical review on the management of mild-to-moderate ulcerative colitis. Gastroenterology. 2019;156:769–808.
36. Danese S, Sands BE, Abreu MT. O'Brien CD, Bravata I, Nazar M, et al. Early Symptomatic Improvement After Ustekinumab Therapy in Patients With Ulcerative Colitis: 16-Week Data From the UNIFI Trial. Clin Gastroenterol Hepatol. 2022;20:2858-67.