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Review Article

Acute Severe Ulcerative Colitis: Optimal Strategies for Drug Therapy

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Acute severe ulcerative colitis (ASUC) is a life-threatening medical emergency with considerable morbidity (30% to 40%). Patients with ASUC require hospitalization for prompt medical treatment, and colectomy is considered if medical therapy fails. Corticosteroids remain the primary initial therapy, although one-third of patients do not respond to treatment. Clinical data have indicated that cyclosporine, tacrolimus, and infliximab can be used to treat patients with ASUC who do not respond to intravenous corticosteroids. The effectiveness and safety of sequential therapy have recently been reported; however, the data are not convincing. Importantly, timely decision-making with rescue therapy or surgical treatment is critical to manage ASUC without compromising the health or safety of the patients. In addition, risk stratification and the use of predictive clinical parameters have improved the clinical outcome.of ASUC. Multidisciplinary teams that include inflammatory bowel disease experts, colorectal surgeons, and other medical staff contribute to the better management of patients with ASUC. In this review, we introduce current evidence and present a clinical approach to manage ASUC. **(Gut Liver 2023;17:49-57)**

Key Words: Acute severe ulcerative colitis; Cyclosporine; Tacrolimus; Infliximab; Surgery

INTRODUCTION

Ulcerative colitis (UC) is a diffuse, nonspecific inflammation of unknown origin that continuously damages the colonic mucosa from the rectal side, often leading to erosions and ulcers.[1] The etiology of this condition remains unclear. However, a dysregulated immune response to intraluminal microbiota and environmental factors (diet and breast feeding) in a genetically susceptible host contributes to UC onset.[2] UC has two phases: the active phase, in which patients present symptoms, and the remission phase, in which the symptoms disappear. UC can be divided into three types according to the extent of the lesion: "proctitis," "left-sided colitis (up to the splenic flexure)," and "extensive colitis." The severity of UC is classified into "mild," "moderate," or "severe" based on clinical symptoms, signs, and blood test results.[3]

Overall, 20% to 25% of patients with UC experience severe exacerbations requiring hospitalization for prompt medical treatment, and colectomy is considered if medical treatments fail.[4] Several reports have shown that the morbidity related to patients with acute severe UC (ASUC) was considerable, with a 30% to 40% risk for colectomy after one or more severe exacerbations, and that 10% to 20% of these patients required colectomy at their first admission.[4-7] Meanwhile, from 1999 to 2005 Korean ASUC cohort indicated a better short- and long-term prognosis for ASUC in Koreans than in Caucasians.[8] A recent ASUC cohort study of an Italian group demonstrated that 1-, 3-, and 5-year colectomy-free survival were 93.5%, 81.5%, and 79.4%, respectively, and approximately 50% of patients with ASUC required additional treatment or hospitalization due to relapse. Thus, careful follow-up even after induction of remission of patients with ASUC is crucial.[9]

In the active stage, it is critical to diagnose the general condition of patients with ASUC accurately, determine the extent of the disease, and proceed with treatment based on the treatment recommendations by several guidelines.[3,10-12] Significantly, when physicians treat patients with ASUC, surgery should always be considered as a treatment option, and medical treatment should be carried out in close communication with the surgeon. This review discusses the

Table 1. Disease Activity in Ulcerative Colitis

Variable	Mild	Moderate in "between mild and severe"	Severe
Bloody stools, times/day	<4	4 or more if	≥6 and
Pulse, beats/min	<90	≤90	>90 or
Temperature, ℃	<37.5	≤37.8	>37.8 or
Hemoglobin, g/L	>115	≥105	<105 or
ESR, mm/hr	<20	≤30	>30
CRP, mg/L	Normal	≤30	>30

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
Adapted from Truelove SC *et al.* Br Med J 1955;2:1041-1048.[13]

Table 2. Summary of CMV Treatment for Refractory UC

· If patients have steroid-refractory UC, physicians should check tissue IHC and mucosal PCR for CMV.
· If patients respond to IFX, cyclosporin, or tacrolimus and CMV tests positive: No need for treatment, possibly, indicative of bystander reactivation or indicative of severe disease.
· If patients do not respond to immunosuppressive treatments and CMV tests positive, treat for CMV.
· Treatment recommendation: ganciclovir (5 mg/kg twice daily) for 3–5 days, then oral valganciclovir (900 mg twice daily).
· Stop immunosuppressive therapy if severe systemic CMV symptoms such as hepatitis, are present.

CMV, cytomegalovirus; UC, ulcerative colitis; IHC, immunohistochemistry; PCR, polymerase chain reaction; IFX, infliximab.

treatment strategy for patients with ASUC in clinical practice and the evolving evidence regarding the use of medical salvage therapies.

DEFINITION OF ASUC

Conventional diagnosis of ASUC is historically based on the Truelove and Witts' criteria (Table 1),[13] which consist of the presence of bloody stools ≥6 times a day and at least one of the following signs of systemic toxicity: pulse rate >90 beats/min, temperature >37.8°C, hemoglobin <10.5 g/dL, or erythrocyte sedimentation rate >30 mm/hr. These still remain the most sensitive criteria for defining ASUC, although they must always be applied and considered owing to individual circumstances and settings.[14] Other indices, such as the clinical partial Mayo score and the Montreal classification, are less frequently used in clinical practice; however, comparative studies for the diagnosis of ASUC are not available.[15,16]

REVIEW DAILY MANAGEMENT PLAN FOR ASUC

1. Clinical point on day 1

- Blood examination to be checked: cell blood count, urea, electrolytes including Mg, C-reactive protein (CRP), erythrocyte sedimentation rate, and lipid profile (total cholesterol).
- Abdominal radiography to rule out dilatation and abdominal computed tomography (CT).
- Stool studies: infectious pathogens, including *Clostridium difficile.*
- Sigmoidoscopy: biopsy to rule out cytomegalovirus (CMV) infection.

Generally, day 1 is the most critical time point for hospitalized patients. Physicians should check crucial components, including cell blood count and biomarkers, and in particular, the baseline CRP level. Additionally, physicians should obtain an X-ray to rule out any colonic dilatation and consider abdominal CT when patients have a high fever to evaluate the possibility of micro-perforation.[12] Patients with UC who have accompanying *C. difficile* infection have an increased risk of colectomy and mortality.[17-19] Therefore, hospitalized UC patients with *C. difficile* coinfection should be treated with vancomycin. Currently, we are in the coronavirus disease 2019 pandemic situation. Thus, in clinical practice, physicians must rule out concomitant severe acute respiratory syndrome coronavirus 2 in patients with ASUC.

The next step is to perform sigmoidoscopy to evaluate the patients' disease activity. Additionally, sigmoidoscopy is used to obtain the opportunity for potential biopsy to rule out CMV as a cause of disease flare.[20] Physicians should perform the endoscopic procedure with caution in patients with ASUC because endoscopic manipulation may worsen abdominal symptoms. In addition, if a deep ulcer is present, a deep insertion should not be furthered. Moreover, during the endoscopic examination, CO_2 insufflation would be better, if possible. Table 2 summarizes the proposed CMV treatment for ASUC based on the American Gastroenterological Association, European Crohn's and Colitis Organisation, and British Society of Gastroenterology gastro-guidelines.

The final phase of management of ASUC on day 1 is to test for tuberculosis by QuantiFERON/ tuberculin reaction and hepatitis B virus serology and investigate deep vein thrombosis. The consultation for surgery early in the hospitalization of ASUC is critical, and it is crucial to frame the consultation to the surgeon. Subsequently, intravenous (IV) administration of high-dose steroids for ASUC should be initiated. Moreover, physicians should acknowledge the following points regarding steroid therapy: (1) there have been no randomized controlled trial comparing steroid regimens; (2) no study has shown an incremental benefit to a total dose of methylprednisolone over 60 mg; and (3)

no studies have proven the benefits of continuous IV dosing versus daily dosing.

2. Management on days 2 and 3: clinical points on days 2 and 3

- Daily symptom evaluation should include the following: (1) frequency and urgency of stools; (2) rectal bleeding; and (3) increased pain or tenderness.
- Monitor inflammatory markers, such as CRP.
- Perform interval abdominal X-rays if indicated by symptoms: increased abdominal distension and marked decrease or cessation of bowel movements.

After hospitalization day 1, physicians should continue IV steroids on days 2 and 3 and evaluate daily symptoms such as frequency, urgency, bleeding, and stool formation.[12] In addition, it is clinically critical to ask patients whether they have severe abdominal pain, because abdominal pain in patients with ASUC is a marker of instability and X-ray should be checked if patients complained of sustained severe abdominal pain. Examining inflammatory markers, such as CRP, on a daily basis, is required to determine the response to steroid therapy.

3. Predictors of IV steroid failure after 3 days in patients with ASUC

Table 3 shows predictive indices for corticosteroid failure in ASUC and the need for "rescue therapy."[21-25] The most widely used risk stratification is the Travis' criteria, published in 1996.[21] On day 3 of corticosteroid therapy, patients who have a stool frequency of >8 times/day or a stool frequency of 3 times/day plus CRP >45 mg have an 85% likelihood of undergoing colectomy during the admission.

4. Management on day 4

On day 4, physicians must decide whether to continue medical therapy.[12] First, 3 to 4 days after the physician

Table 3. Predictive Indices of Corticosteroid Failure in Acute Severe Ulcerative Colitis Patients and the Need for "Rescue Therapy"

Index	Criteria	Predictive indices of corticosteroid failure in acute severe ulcerative colitis
Travis or Oxford criteria[21]	Stool frequency >8/day or stool frequency >3/day with CRP >45 mg/L on day 3 of IV corticosteroid	If any present on day 3 (85% probability of colectomy)
Ho or Scottish[22]	Colonic dilatation >5.5 cm (4 points) Albumin <3 g/dL on admission (1 point) Average daily number of stool over first 3 days: <4 (0 points), 4–6 (1 point), 6–9 (2 points), >9 (4 points)	≥4 Points on day 3 (85% probability of nonresponse)
Lindgren[23]	Serum CRP (mg/L)×0.14+stool frequency on day 3 of IV corticosteroid	>8 Points on day 3 (72% probability of nonresponse)
Seo[24]	The calculated score according to following variables; hematochezia, stool frequency, ESR, hemoglobin, and albumin	>180 Seo index on 2 weeks after corticosteroid probability of colectomy
Jain[25]	A UCEIS >6 at admission and FC >1,000 μg/g on day 3	Predictors of steroid failure and need for rescue therapy/ colectomy

CRP, C-reactive protein; IV, intravenous; ESR, erythrocyte sedimentation rate; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; FC, fecal calprotectin.

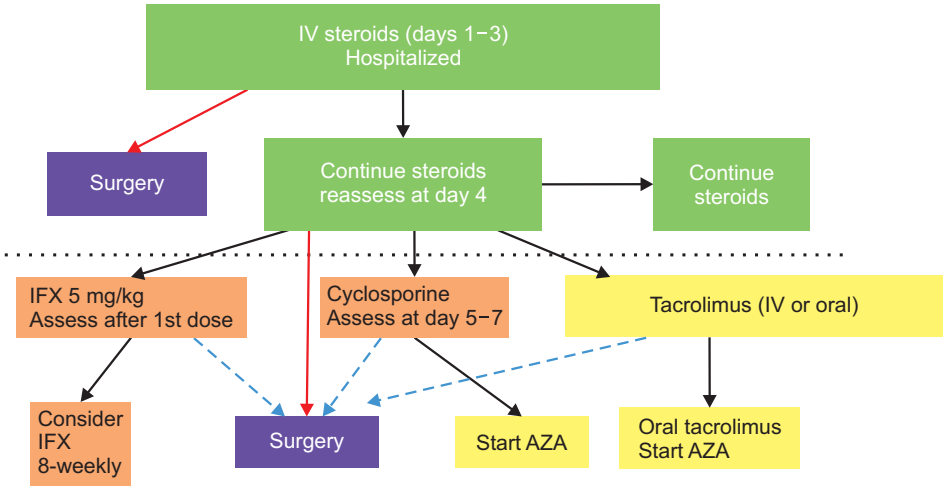

Fig. 1. Proposed treatment algorithm for acute severe ulcerative colitis.
IV, intravenous; IFX, infliximab; AZA, azathioprine.

Table 4. Indication for Surgery in Patients Who Do Not Respond to Rescue Therapy

· Toxic dilatation with impending perforation
· Intestinal perforation
· Massive hemorrhage
· Longstanding colitis with "intractability"

starts IV steroid therapy, they should decide whether steroids are effective or not for patients with ASUC (Fig. 1). Nationwide data by Kaplan *et al.*[26] demonstrated an association between the number of days of hospitalization due to UC and postoperative complications such as mortality.

Thus, before initiating medical rescue therapies, physicians should recognize that some patients with ASUC do not require rescue therapies, but must rather undergo surgery (Table 4).

Patients who are in the hospital for >11 days and require surgery have an increased risk of mortality. These data indicate the significance of making decisions regarding treatment strategies for patients with ASUC. Physicians should not wait for 1 to 2 weeks for a response to IV steroid before moving to the next step.

5. IV steroid responders

If patients respond to IV steroid therapy, physicians can continue IV steroids for 3 to 5 additional days and can consider switching to oral prednisolone 40 mg/day.[12] In addition, physicians should decide on a treatment plan to initiate a steroid-sparing strategy either during hospitalization or within 1 to 2 weeks of discharge.

6. IV steroid nonresponders

However, one-third of patients do not respond to IV steroids.[12] Physicians have three medical options for patients with ASUC (Fig. 1). Recently, biologics and other therapies have been used to treat refractory cases. However, there have been no established data regarding the effectiveness of adalimumab, golimumab, ustekinumab, vedolizumab, and tofacitinib (TOF) in patients with ASUC. Therefore, infliximab (IFX) and calcineurin inhibitors, such as cyclosporine (CsA) and tacrolimus (TAC), are the drugs of choice for severe cases.

1) Cyclosporine

In the past, CsA was the primary treatment for patients with ASUC. There are several key points for management of UC with CsA:

- Using 2 mg/kg/day CsA starting dose yields a similar response rate to as a starting dose of 4 mg/kg/day, but with less toxicity.
- The target CsA concentration is between 150 and 250 ng/mL.
- Serious infections have been reported in 5% of patients on CsA.
- The major side effects of CsA include nephrotoxicity, seizures, and anaphylaxis.

In 1994, the efficacy of calcineurin inhibitors in the treatment of UC was reported by Lichtiger *et al.*[27] in a randomized trial of continuous IV CsA versus placebo in steroid-refractory patients. In that study, 20 patients with steroid-refractory UC were randomly assigned to receive IV CsA (4 mg/kg) or a placebo. Seven days after treatment initiation, there was a significant difference in response rate to treatment between the IV CsA group (9/11, 82%) and the placebo group (0/9, 0%). Since then, several studies have reported good short-term response rates of approximately 70% to 80%.[28-31] In contrast, a study using survival table analysis revealed that 54.4% of patients required total colectomy at 11 years and 88% at 7 years.[30,31] Taken together, not only efficacy but also the need for total colectomy over time should be considered with caution.

2) Tacrolimus

- TAC is a calcineurin inhibitor with good bioavailability, even when administered orally.
- TAC was administered orally at an initial dose of 0.1 to 0.15 mg/kg/day or intravenously at an initial dose of 0.015 mg/kg/day.
- A blood trough level or concentration of 10 to 15 ng/mL at the time of remission induction should be maintained as far as possible until complete remission is achieved.
- The major side effects of TAC are similar to those of CsA.

A recent meta-analysis demonstrated significantly higher clinical response at 2 weeks with TAC than with placebo (relative risk, 4.61) and the colectomy-free rates at 1, 3, 6, and 12 months were 86%, 84%, 78%, and 69%, respectively.[32]

The first large-scale study of TAC was a double-blind comparative study of refractory UC conducted by Ogata *et al.* in 2006.[33] Two weeks after the start of TAC treatment, the response rate was 68.4% (13/19) in the high-trough group (trough level, 10 to 15 ng/mL), 38.1% (8/21) in the low-trough group (5 to 10 ng/mL), and 10% (2/20) in the placebo group, indicating that the therapeutic effect of TAC was dependent on the blood trough level. Since then, several studies have been conducted, though there have been variations in treatment outcomes due to differences in the initial doses and target trough levels among studies. Consequently, the short-term treatment efficacy of TAC in refractory UC cases is estimated to be about 70%.[34-37] In

addition, the long-term colectomy-free rate is estimated to be >50%, with an observation period of 1 to 2 years.[32,34,37] In addition to CsA, the efficacy of initial treatment with TAC has been demonstrated; however, the long-term prognosis of treatment has not been satisfactory.

3) Infliximab

While calcineurin inhibitors have been used in various centers for the treatment of ASUC, the use of tumor necrosis factor (TNF) inhibitors has become more common because of their side-effect profile and their availability as a maintenance therapy. A number of observational studies have reported a wide range of short-term response (0% to 100%) and long-term colectomy-free rates (41% to 81%) after rescue therapy with IFX for ASUC.[38] A significant shift in terms of using IFX over CsA came after the CYSIF study, in which a direct comparison of CsA and IFX in steroid-resistant severe UC was performed by GETAID, in France.[39] The primary outcome treatment failure for any reasons over a 3-month period. The study demonstrated no significant difference in the primary outcome between the CsA and IFX groups. The response rates in the CsA and IFX groups at day 7 were 85.4 % and 85.7%, respectively. Currently, several physicians in expert centers use IFX more than CsA because of the need to monitor CsA effects. In the short-term, approximately 20% of patients in both groups required surgery with no significant difference between groups according to the Kaplan-Meyer analysis. A report by Laharie *et al.*[40] has shown no difference in the colectomy-free survival rate at 5 years in patients with refractory UC receiving CsA (61.5%) or receiving IFX (65.1%). Thus, no significant differences were noted in the short- and medium- to long-term prognoses of patients treated initially with CsA and those treated initially with IFX. Moreover, there have been no randomized controlled trials comparing TAC to IFX in patients with ASUC. Minami *et al.*[41] have reported a retrospective data from Japan comparing the short-and long-term efficacy of TAC and of IFX in severe UC. They demonstrated no significant difference in clinical remission at 8 weeks and 5-year colectomy-free survival, according to a Kaplan-Meier curve, between the TAC and IFX groups. Based on these data, we consider TAC to be an option for ASUC. Komaki *et al.*[42] have conducted a network meta-analysis of eight randomized clinical trials in patients with steroid-resistant severe UC that were treated with IFX, CsA, or TAC and reported that IFX had a slightly greater therapeutic effect.

HOW SHOULD ASUC PATIENTS WHO DO NOT RESPOND TO IFX AS A RESCUE THERAPY BE MANAGED?

In the clinical setting, physicians encounter patients with ASUC who do not respond to IFX administration, which raises the question of whether the dose of IFX is optimal. It is unclear whether it is rational that ASUC patients with severe inflammatory burden are treated with the same dose of IFX as patients with moderate active UC, who receive 5 mg/kg at 0, 2, and 6 weeks. Several studies have indicated an increased clearance of IFX in patients with ASUC. Brandse *et al.*[43] measured fecal IFX levels a few days after the initial induction of IFX and found that the non-responder group had significantly increased fecal IFX level as compared to the complete responder group. Ungar *et al.*[44] obtained the trough level of IFX on the second induction at day 14 and showed that patients with ASUC had significantly lower trough levels than those with moderately severe UC. Based on previous reports, various factors have been implicated as causes of patients with ASUC in whom IFX failed. First, a high TNF burden is implicated in IFX failure. Second, proteolytic degradation of anti-TNF is associated with increased drug clearance. Third, fecal losses from increased gut permeability are associated with severe inflammation.[44] To overcome these factors and achieve successful induction of remission, accelerating IFX dosing is considered for patients with ASUC. Hindryckx *et al.*[45] reported that IFX dose intensification is beneficial in at least 50% of ASUC patients and that an intensified IFX dosing regimen with 1 to 2 additional infusions in the first 3 weeks of treatment could reduce the early (3-month) colectomy rate by up to 80%. In contrast, a recent retrospective multi-center study and meta-analysis involving seven studies, by Nalagatla *et al.*,[46] have shown no significant differences in short- or long-term outcomes between accelerated IFX dosing and standard IFX dosing. These data suggested that in terms of cytokines, the pathogenesis of UC is not simple and that several cytokines, other than TNF-α, are involved in the UC exacerbation.

Herfarth *et al.*[47] have reported data from a survey of inflammatory bowel disease (IBD) specialists regarding IFX treatment of ASUC. The survey indicated that 5 mg/kg IFX is used for initial ASUC, but that 10 mg/kg is used by week 2 if the response to the initial dose is not good (25% of respondents). Additionally, 10 mg/kg is used with flexible timing of dosing (18% of respondents). In terms of criteria for accelerating the dose, 68% of IBD experts decide on dose intensification according to the patients' clinical severity. Interestingly, no more than 25% of respondents agreed with the dose strategy of IFX for patients with

ASUC.[47] Taken together, this indicates that there is a need for guidance from prospective studies in terms of deciding on IFX dosing for patients with ASUC.

1. Sequential therapy

The introduction of IFX has provided an alternative and effective therapeutic option for patients with ASUC in whom IV corticosteroids fail.[38,48] The efficacy and safety of IFX in this setting were considered equivalent to those of CsA in two randomized control studies.[39,49] A systematic review by Narula *et al.*[50] have demonstrated a short-term response to sequential therapies in 62.4% of patients (95% confidence interval [CI], 57.0% to 67.8%) and adverse event in 23% (95% CI, 17.7% to 28.3%). Thus, the risk of sequential therapy in steroid-refractory UC appears to be lower than that initially reported, although the data quality is not high. However, this study did not necessarily support the use of sequential rescue therapies. Physicians should keep in mind that this approach may contribute to delaying surgery in a patient whose physical condition is worsening, and should be performed only at specialized referral centers, that are familiar with the use of calcineurin inhibitors.

2. Tofacitinib

Reports on the therapeutic effect of TOF in ASUC are limited. Berinstein *et al.*[51] first reported the effectiveness of high-dose TOF (30 mg daily) in patients with ASUC. Following this case series, they conducted a retrospective case-control study to evaluate the effectiveness of TOF in biologic-experienced patients with ASUC requiring IV corticosteroid. The study results indicated that 10 mg of TOF three times daily acted protective for colectomy (hazard ratio, 0.11; 95% CI, 0.02 to 0.56; p=0.008), while 10 mg twice daily did not show this effect (hazard ratio, 0.66; 95% CI, 0.21 to 2.09; p=0.5).[52] Kotwani *et al.*[53] and Gilmore *et al.*[54] reported a case series of the effectiveness of TOF in patients with ASUC refractory to biologics. The summarized results of the two cases series showed eight patients achieved clinical remission without 90-day colectomy, except for one patient. Taken together, these results suggest a potential therapeutic effect of TOF on ASUC; however, prospective studies are required, including appropriate doses and safety at high doses.

3. Vedolizumab

The effect of VED on patients with ASUC has not been comprehensively reported. Perry *et al.*[55] have revealed interesting data that dose escalation of VED contributed to the increasing ratio of achieving remission in UC patients who partially responded to the regular doses. Graziano *et al.*[56] have presented a case of remission induction in a patient with ASUC by shortening the interval of VED administration. In the GEMINI trial, the benefit of increasing the dose of VED for induction of remission was unclear.[57]

However, by accumulating real-world data, it becomes evident that the benefits of increasing the dose and shortening the interval of VED for patients with ASUC as well as TOF. Thus, the effectiveness of VED intensive treatment warrants further investigation.

4. Nutrition (parenteral and enteral nutrition)

There has been some debate on whether enteral or IV nutrition is the better management option for ASUC. No difference in colectomy rates or mortality were observed between patients with ASUC receiving IV steroids on bowel rest with parenteral nutrition and those with oral diet.[58] In addition, randomized comparisons between polymeric total enteral nutrition and total parenteral nutrition showed no difference in remission or colectomy rates.[59] These two studies have shown few complications in the enteral nutrition group. Based on the results, we may consider the appropriateness of enteral nutrition in the management of ASUC by carefully monitoring the patient's condition, including the presence of toxic megacolon, ileus, and other complications.

5. Thromboprophylaxis

It is well recognized that IBD is an independent risk factor for the development of incident and recurrent venous thromboembolism (VTE).[60] Nguyen and Sam[61] have reported that the in-hospital mortality rate of IBD patients with VTE was 2.5 and 2.1 times greater than that of IBD patients without VTE and non-IBD patients with VTE, respectively. Moreover, a retrospective data by Ananthakrishnan *et al.*[62] has indicated a reduced risk of post-hospitalization VTE in IBD patients who received inpatient thromboprophylaxis. Based on data regarding the morbidity and mortality associated with VTE, international guidelines recommend routine subcutaneous low-molecular-weight heparin for hospitalized patients with severe colitis.[63-65]

Additionally, on the day 1 management, checking for VTE is described; however, in the case of hospitalized patients with ASUC, it is important to carefully follow-up VTE by ultrasonography and CT for patients whose hypercoagulability is persistent and in whom peripheral edema occurs. Questions remain about the risk of VTE after discharge with ASUC. Sustained abnormal coagulation status after discharge of patients with ASUC is a significant clinical issue. A cohort study of patients with ASUC has shown that a state of hypercoagulable function was still present 3 months after discharge.[66] This data indicated that some

patients with ASUC who achieved remission may need to continue anticoagulation therapy. However, more data will be required in the Asia IBD cohort in the future.

FUTURE THERAPEUTIC STRATEGY

The therapeutic effect of combination therapy with biologic agents and small molecules on IBD patients has been reported as well, although the data are from pediatric patients.[67] Since the UC pathogenesis is highly diverse,[2] these therapies may be a treatment option for ASUC. However, further accumulation of cases is required to determine safety.

In summary, the management of ASUC remains challenging and requires strict control by IBD experts. Although CsA, TAC, and IFX are effective as rescue therapies, it is critical to determine whether surgical treatment is needed to save patients' lives. Therefore, treating physicians should always be in close contact with surgeons, so that the decision for surgery is not delayed.

CONFLICTS OF INTEREST

H.N. reports receiving personal fees from Abbvie Inc.; Kissei Pharmaceutical Co., Ltd.; KYORIN Pharmaceutical Co., Ltd.; Mitsubishi Tanabe Pharma Corporation; Janssen Pharmaceutical K.K.; Takeda Pharmaceutical Co., Ltd.; Pfizer Japan Inc.; Celgene K.K.; EA Pharma Co., Ltd.; Zeria Pharmaceutical CO., Ltd.; Mochida Pharmaceutical Co., Ltd.; Nippon Kayaku Co., Ltd.; and Daiichi Sankyo Co., Ltd.; JIMRO Co., Ltd.; and grants for commissioned/joint research from Hoya Group Pentax Medical, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Company. Except for that, no potential conflict of interest relevant to this article was reported.

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