



Updates on conventional therapies for inflammatory bowel diseases: 5-aminosalicylates, corticosteroids, immunomodulators, and anti-TNF- α

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The incidence and prevalence of inflammatory bowel diseases (IBDs) are rapidly increasing worldwide. IBDs are considered an emerging problem not only in Western countries but also in developing countries. The relapses and complications of active IBD mandate various medications. Nevertheless, hospitalization, emergency room visits, or surgery may be required, resulting in a socioeconomic burden. Great advances have been made in the development of new therapeutic options for IBD to achieve induction and maintenance remission. Nevertheless, conventional therapy is still the mainstay in the treatment of IBD. This review article provides an update on recent advances in conventional therapies, including 5-aminosalicylates, corticosteroids, immunomodulators, and anti-tumor necrosis factor- α agents to treat IBD.

Keywords: Inflammatory bowel diseases; Mesalamine; Adrenal cortex hormones; Immunologic factors; Anti-TNF agents

INTRODUCTION

Inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD), are characterized by chronic immune-mediated intestinal inflammation of the gastrointestinal tract [1]. Despite the emergence of new biological agents and small molecules for treating IBDs, conventional therapies including 5-aminosalicylates (5-ASA), corticosteroids, immunomodulators, and anti-tumor necrosis factor- α (TNF- α) agents are still the mainstay to induce and maintain clinical remission of IBD because of their effectiveness, safety, and acceptable cost [2]. Medical treatment, personalized care through a multidisciplinary team

approach, and validated information for patients is critical for IBD treatment [3,4]. The International Organization for the Study of Inflammatory Bowel Diseases updated the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)-II statement to optimize IBD treatment; symptomatic remission and normalization of C-reactive protein levels were short-term targets, decreasing the calprotectin level was an intermediate-term target, and endoscopic healing and normalization of quality of life were long-term targets [5,6]. Here, we review the updated data on the current experience and outcomes of conventional IBD therapies for optimizing medical treatments suggested by the STRIDE-II statement. This review provides an overview and practical

treatment tips for conventional IBD therapies useful at primary and secondary medical institutions.

5-ASA

Various 5-ASA-based drug formulations

5-ASA-based drugs include sulfasalazine, olsalazine, balsalazide, and mesalamine and are effective, safe, and inexpensive drugs for treating IBD, particularly UC (Table 1) [7]. Sulfasalazine (brand names include Salazopyrin, Hanlim Pharm Co., Seoul, Korea), which is an azo-bonded prodrug of sulfapyridine, and 5-ASA were originally proposed to treat rheumatoid arthritis in the late 1930s [8]. 5-ASA is metabolized from sulfasalazine by the gut bacterial enzyme azoreductase and was reported to ameliorate the intestinal inflammation of IBD patients in the mid-1970s, but sulfapyridine originating from sulfasalazine can cause intolerance to sulfapyridine and allergic reactions, including fever, nausea, vomiting, headache, angioedema, and diarrhea, and its use is gradually decreasing [9]. However, patients with rheumatic diseases, such as rheumatoid arthritis or ankylosing spondylitis, continue to use this drug because it treats arthritis and UC at the same time.

Second-generation azo-bonded 5-ASA drugs, which do not contain sulfapyridine, were developed in the early 1980s and these are converted into 5-ASA in the colon similar to sulfasalazine. Olsalazine (brand names include Dipentum, Pharmacia AB, Uppsala, Sweden) is a 5-ASA dimer and balsalazide (brand names include Colazal, Chong Kun Dang, Seoul, Korea) is an azo-bonded prodrug of 4-amino-benzoyl- β -alanine and 5-ASA. The adverse events of balsalazide

are significantly less frequent than those of sulfasalazine [10].

In addition, the most commonly used 5-ASA-based drug, mesalamine (brand names include Asacol, Salofalk, Mezavant, and Pentasa, Ferring, Saint-Prex, Switzerland) has been developed in various newer formulations [11]. To reach the colon mucosa without being absorbed in the stomach and small intestine, 5-ASA must be bound to a drug-delivery system or prodrug [12,13]. Asacol, consisting of 5-ASA coated with Eudragit S100 (Daewoong, Seoul, Korea), which is a polymethacrylate copolymer that only dissolves at $\text{pH} \geq 7$, targets the terminal ileum and colon [14]. OPTICORE coated 1,600 mg Asacol tablets were recently developed, and are composed of the two-trigger release technology [15]. The Phloral in the outer layer is composed of Eudragit S100, which is a polymethacrylate copolymer that only dissolves at $\text{pH} \geq 7$, but is also resistant to starch and serves as an energy source for colonic microbiota, to trigger rapid release [15]. In addition, the Duocoat inner layer, which is composed of a partially neutralized enteric polymer with a buffer salt, promotes the dissolution of the outer enteric polymer layer [15]. Salofalk consisting of 5-ASA coated with Eudragit L100, which only dissolves at $\text{pH} \geq 6$, targets the distal ileum and colon [14]. Mezavant consists of 5-ASA and the MMX system (Takeda, Tokyo, Japan) coated combination of Eudragit S100 and Eudragit L100, which delays and prolongs administration of mesalazine throughout the colon and only dissolves at $\text{pH} \geq 7$ [16]. Pentasa consists of 5-ASA coated with a semipermeable ethylcellulose membrane. It is sensitive to moisture, released in a time-dependent manner, and targets from the duodenum through the small bowel to the colon [17]. The new Pentasa sachet formulations (1 and 2 g)

Table 1. 5-ASA preparations

Preparation	Drug	Formulation	Release site
Azo-bonded prodrugs	Sulfasalazine (Salazopyrin)	Sulfapyridine+5-ASA	Colon
	Olsalazine (Dipentum)	5-ASA+5-ASA	Colon
	Basalazide (Colazal)	4-amino-benzoyl- β -alanine+5-ASA	Colon
pH-dependent drugs	Mesalamine (Asacol)	5-ASA coated with Eudragit S100	Terminal ileum and colon
	Mesalamine (Salofalk)	5-ASA coated with Eudragit L100	Distal ileum and colon
	Mesalamine (Mezavant)	MMX system coated combination with Eudragit S100 and Eudragit L100	Terminal ileum and colon
Time-dependent drugs	Mesalamine (Pentasa)	5-ASA coated with a semipermeable membrane of ethylcellulose	Duodenum, small bowel, and colon

5-ASA, 5-aminosalicylate.

were recently launched and are expected to improve medication adherence in patients who have difficulty swallowing large tablets [18].

Mechanisms of action of 5-ASA-based drugs

5-ASA is absorbed in the stomach and the small bowel without a drug-delivery system or prodrug. It is metabolized to an inactive form of N-acetyl-5-aminosalicylic acid by N-acetyltransferase (NAT) and is excreted in the urine or feces [19]. While it has no effect at a low dose because of conversion by NAT, it has a sufficient effect at a higher dose greater than that of the NAT saturation point [19]. It relieves inflammation after it reaches the inflamed terminal ileum or colon.

The mechanisms of action of 5-ASA-based drugs are still not understood, but several plausible hypotheses have been proposed. 5-ASA reduces the synthesis of prostaglandins and leukotrienes by downregulating inducible cyclooxygenase 2/prostaglandin E2 (COX-2/PGE2) signaling [20]. Furthermore, it acts as a peroxisome proliferator-activated receptor γ agonist to inhibit the production of inflammatory cytokines, such as interleukin (IL)-1, IL-6, and TNF- α , as well as the activation of nuclear factor kappa B (NF- κ B) [21,22]. It also scavenges reactive oxygen and nitrogen species, which helps reduce intestinal inflammation [23]. In addition, it reduces intestinal inflammation through other mechanisms. These therapeutic effects have the advantage of producing fewer systemic side effects, as they only act locally on the intestinal mucosa and not systemically.

Induction doses of 5-ASA for UC patients

The various 5-ASA-based drug formulations are effective at inducing remission compared to placebo agents in patients with mild to moderate UC, and no differences in clinical efficacy have been reported between the various formulations [24]. The disease extent, patient preference, dose, and formulation are considered when selecting a 5-ASA drug. In patients with mild to moderate ulcerative proctitis, rectal 5-ASA therapy is recommended at 1 g per day for induction [25,26]. A rectal enema with 5-ASA can cover up to a splenic flexure and is, therefore, effective local treatment for left-sided colitis. In addition, oral 5-ASA therapy of ≥ 2.4 g per day is the standard treatment for induction in patients with mild to moderate left-sided colitis or pancolitis [25,26]. In the Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA (ASCEND) trial, patients treated with 4.8 g per day of 5-ASA achieved more rapid symptomatic relief,

biochemical remission, and endoscopic remission compared to patients treated with 2.4 g per day of 5-ASA, but no difference was observed in clinical remission [27-29]. Combination therapy with oral and topical 5-ASA is superior to oral 5-ASA monotherapy for inducing mild to moderate UC [30] regardless of the disease extent. Therefore, high-dose oral 5-ASA combined with topical 5-ASA is preferred to treat moderate to severe UC patients.

Maintenance doses of 5-ASA for UC patients

In patients with mild to moderate ulcerative proctitis, 0.5 to 1 g per day of rectal 5-ASA therapy is recommended for maintenance remission [25,26]. In patients with mild to moderate left-sided colitis or pancolitis, ≥ 2 g per day of oral 5-ASA therapy is the standard treatment for maintenance remission [25,26]. A dose escalation of 5-ASA from 1.2 g per day to 2.4 g per day or 2.4 g per day to 4.8 g per day reduces fecal calprotectin levels and is associated with less frequent disease relapse [31]. Combination therapy of oral and topical 5-ASA is superior to oral 5-ASA monotherapy for maintenance of mild to moderate UC [32]. The efficacy and adherence between once-daily and divided dosing were not different in several meta-analyses [33,34]. However, a randomized control trial once-daily dosing group achieved a higher rate of clinical remission and adherence compared to a three-times-daily dosing group [35]. Simplifying drug dosing would improve real-world long-term drug adherence for maintenance therapy [36,37].

Use of 5-ASA in CD patients

The use of 5-ASA in CD patients is common in routine clinical practice, but recent evidence suggests no benefit of 5-ASA compared to placebo for induction and maintenance in CD patients [38,39]. To minimize financial burden and diminish unnecessary drug use, the Stopping Aminosalicylate Therapy in Inactive Crohn's Disease (STATIC) study, which is an ongoing open-label, randomized, noninferiority randomized trial that compares a continuing group and a withdrawing group with CD during remission [40]. Nevertheless, the safety and effectiveness of 5-ASA for luminal CD patients has led physicians to use it in some cases, particularly in mild colonic disease, to avoid corticosteroids [41]. In a previous study, high-dose mesalamine was superior to placebo, but sulfasalazine was not significantly superior to placebo [41].

In one previous study, the clinical outcomes were not different between a 5-ASA withdrawal group and a 5-ASA

continuation group of IBD patients initiated on immunomodulators or biologic agents [42]. Although further large-scale prospective studies are needed, discontinuing 5-ASA should be considered for patients in remission who are receiving immunomodulators or biologic agents.

Side effects of 5-ASA-based drugs

5-ASA-based drugs are generally safe and tolerable, but adverse reactions occur in some cases. 5-ASA can cause fever, headache, rash, vomiting, paradoxical diarrhea, muscle pain, and abdominal pain [43]. It rarely causes serious side effects, including pleuritis, pericarditis, pancreatitis, interstitial nephritis, or hepatotoxicity [44]. Side effects usually occur between 1 and 4 weeks and improve immediately after discontinuation. They are more common when taking sulfasalazine than when taking mesalamine. Sulfasalazine-treated patients should take a folic acid supplement because this drug decreases folic acid absorption.

CORTICOSTEROIDS

Corticosteroids are effective, rapidly acting drugs that induce remission of active moderate to severe IBD. They rapidly inhibit intestinal inflammation by reducing intestinal permeability, decreasing TNF- α production, and blocking NF- κ B [45]. Systemic corticosteroids, including 40 to 60 mg (or 0.5 to 1 mg/kg) per day of prednisolone or 40 to 60 mg per day of methylprednisolone or 300 to 400 mg per day of hydrocortisone, should be initiated and tapered over 8 to 12 weeks depending on the initial drug response [24,26]. Steroid administration for < 3 weeks and prednisolone < 15 mg/day usually do not induce active IBD [46]. Long-term steroid use for more than 3 months is not recommended due to a lack of an effect in preventing flare-ups [47].

Despite the effectiveness of corticosteroids, their long-term use should be avoided because of their short-term adverse effects, such as acne, headache, electrolyte imbalance, hyperglycemia, and hypertension, and their long-term adverse effects, such as susceptibility to infection, osteoporosis, aseptic joint necrosis, and adrenal insufficiency [48]. Budesonide, a synthetic glucocorticosteroid with a high affinity for the glucocorticoid receptor, has higher topical potency and lower systemic bioavailability than systemic corticosteroids [49]. Budesonide MMX at a daily dose of 9 mg achieves clinical remission in active mild to moderate left-sided

UC and in ileocecal CD patients who fail 5-ASA-based therapy [49,50]. However, this drug is currently not available in Korea. Beclomethasone dipropionate, a second-generation corticosteroid, at a 5 mg daily dose for 4 weeks and every other day for an additional 4 weeks is not inferior to 40 mg prednisolone per day for the initial 2 weeks and tapering 10 mg every 2 weeks during the 8 weeks of treatment for active left-sided or extensive UC [51,52]. Topical steroid agents, including beclomethasone dipropionate, are also beneficial for patients with 5-ASA refractory UC [53]. Topical 5-ASA has demonstrated effectiveness for inducing a clinical response or remission and preventing relapse in several studies. In a previous study, combined topical steroids and 5-ASA was more effective than topical 5-ASA or topical steroids alone for inducing a response (100% of patients with combination vs. 70% with beclomethasone alone and 76% with 5-ASA alone) [54]. These oral locally active steroids could be an alternative therapeutic option to reduce systemic side effects [55]. Corticosteroid-dependent patients who initially respond to corticosteroids but relapse after discontinuation or tapering or corticosteroid-refractory patients who do not respond to corticosteroids should consider the use of immunomodulators or biologic agents to reduce long-term inappropriate exposure to corticosteroids [56,57].

IMMUNOMODULATORS

Conventional immunomodulators, such as azathioprine (AZT), 6-mercaptopurine (6-MP), and methotrexate (MTX), are recommended for the maintenance of remission in patients with IBD who fail 5-ASA-based drugs and are dependent on or refractory to corticosteroids [58]. The efficacy of 2.0 to 2.5 mg/kg AZT and 6.0 to 1.5 mg/kg 6-MP once per day was confirmed for the maintenance of CD remission in a clinical study [59]. It is important to start with a low dose and increase to the target dose because the effect is often insufficient while maintaining a low dose. In addition, thiopurine monotherapy but not MTX is effective for long-term maintenance in UC [60]. The combined therapy of an anti-TNF- α agent and an immunomodulator reduces the immunogenicity and efficacy of anti-TNF- α agents in UC and CD [61]. Combination therapy with allopurinol and AZT decreases hepatotoxicity and increases effectiveness by reducing the AZT dose [62]. The subsequent leukocytopenia,

thrombocytopenia, or pancytopenia caused by increases in active metabolites should be carefully monitored.

Thiopurines are metabolized to 6-thioguanine nucleotides (6-TGN) with therapeutic effects and to 6-methylmercaptopyrimidine ribonucleotides without any therapeutic effect but are related to adverse events [63]. Therapeutic drug monitoring (TDM) and 6-TGN measurement have been suggested to optimize the efficacy of thiopurine therapy before step-up medical therapy [64,65]. In addition, 10% to 28% of IBD patients discontinue thiopurine therapy because of intolerable short-term adverse events or long-term adverse events including cervical neoplasia [66]. AZT-intolerant patients who develop dose-dependent side effects, including nausea, vomiting, hepatotoxicity, leukopenia, and pancreatitis, can switch to 6-MP therapy to gain comparable efficacy and tolerability with a half-dose of AZT [67,68].

Leucopenia needs special attention. Thiopurine S-methyltransferase (*TPMT*) gene variants in Western countries have been associated with leukopenia, but are very rare in East Asian countries [69]. In East Asian countries, nudix hydrolyase 15 (*NUDT15*) gene variants (T/T genotype) are more frequent than *TPMT* gene variants and they more accurately predict severe thiopurine-related leukopenia [70]. Blood tests for full blood counts, renal, and liver biochemistry, TDM of thiopurines, and genotyping of *NUDT15* and *TPMT* in routine practice could improve the efficacy and safety of IBD patients [71,72]. In particular, genotyping *NUDT15* is

essential, and if it is not available, close monitoring should be performed with a complete blood count test at intervals of 1 to 2 weeks for the first 4 weeks.

MTX is often considered a second-line drug when there is resistance or intolerance to the use of AZT/6-MP, and its effectiveness has been proven [73]. In a recent retrospective study, MTX had similar effects in inducing and maintaining remission and achieving mucosal healing compared to AZT/6-MP in CD patients [74]. By contrast, MTX monotherapy is not recommended for maintaining remission in UC patients [75]. In one study, corticosteroid-free remission did not improve in an infliximab (IFX) and MTX combination group compared to an IFX monotherapy group, but MTX lowered the immunogenicity of IFX, which reflects the long-term durability of IFX [76]. Combination therapy with IFX and MTX therapy is recommended to reduce immunogenicity in IBD patients [75]. The American College of Gastroenterology guidelines suggest 15 to 25 mg once weekly parenteral MTX treatment as monotherapy and 12.5 to 15 mg oral MTX once weekly as combination therapy for CD patients [77]. In addition, MTX is superior to AZT/6-MP in that it is administered once a week, the dosing effect appears more quickly, and the incidence of tumors is low. Therefore, adolescent or young male patients and those with a homozygous mutation in *NUDT15* should receive MTX therapy. The adverse events of MTX include nausea, vomiting, diarrhea, hepatotoxicity, and cytopenia.

Table 2. Checklist for patient screening for immunomodulators and/or anti-TNF- α agents

General considerations	Checkpoint
Contraindications to anti-TNF- α agents	Grade 3, 4 heart failure
	Previous lymphoma or current malignancy history
	Demyelinating disease
	History of recurrent infection
Precautions and screening	Tuberculosis: tuberculin skin test, chest x ray, interferon gamma release assay
	HBV: HBsAg, anti-HBc, anti-HBs
	HCV: anti-HCV
	HIV: antigen/antibody HIV-1/2 immunoassay VZV: IgM/IgG anti-VZV
Vaccination status	Live vaccination (MMR, herpes zoster, BCG, varicella): contraindicated
	Inactive vaccination (COVID-19, DTP, HAV, HPV, influenza, pneumococcus): safe

TNF- α , tumor necrosis factor- α ; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBc, anti-hepatitis B core antibody; anti-HBs, anti-hepatitis B surface antibody; HCV, hepatitis C virus; HIV, human immunodeficiency virus; VZV, varicella zoster virus; IgM, immunoglobulin M; MMR, measles, mumps and rubella; BCG, Bacillus Calmette-Guérin; COVID-19, coronavirus disease 2019; DTP, Diphtheria-Tetanus-Pertussis; HAV, hepatitis A; HPV, human papillomavirus.

Concomitant administration of folate of at least 5 mg per week (1 mg daily) helps reduce the side effects on the digestive system. MTX should not be used in women planning to become pregnant, because it may cause teratogenesis. It must be discontinued for 3 to 6 months before planning pregnancy.

Due to the increased infection risk with immunomodulators, IBD patients should undergo a screening test for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and active or latent tuberculosis (Table 2) [24]. Vaccination history should be checked, as live vaccinations are contraindicated during immunosuppressive therapy [24]. Live vaccinations should be administered at least 4 weeks before the start of immunomodulators or 3 to 6 months after stopping the immunomodulators.

ANTI-TNF- α AGENTS

Indications of anti-TNF- α agents

The development of anti-TNF- α agents in 1998 for CD and 2005 for UC changed the paradigm of medical treatment for moderate to severe IBD patients [78]. Anti-TNF- α agents are recommended for induction and maintenance remission

in moderate to severe active IBD patients who are refractory to corticosteroids and/or immunomodulators or dependent on corticosteroids [78]. Anti-TNF- α agents are also effective for treating complex perianal fistulizing CD and preventing the postoperative recurrence of CD [79,80]. However, anti-TNF- α agents are not indicated for patients with an intra-abdominal abscess and/or a fibrotic stricture, and surgical resection is preferred.

Utilization of anti-TNF- α agents

IFX (Remicade, Janssen, Seoul, Korea; Remsima, Celltrion, Incheon, Korea; and Remaloce, SAMSUNG BIOEPIS, Incheon, Korea) is a chimeric monoclonal antibody biologic drug that is infused intravenously at 5 mg/kg over 2 hours (shortened to 1 hour if well tolerated) at 0, 2, and 6 weeks and every 8 weeks thereafter in IBD patients (Table 3) [81,82]. A subcutaneous formulation of the IFX biosimilars, CT-P13 (Remsima) or SB2 (Remaloce), is now available for IBD patients. Subcutaneous CT-P13 has comparable efficacy, safety, and immunogenicity as intravenous CT-P13 [83]. Adalimumab, a completely humanized immunoglobulin G1 monoclonal anti-TNF- α antibody, is administered subcutaneously at an induction dose of 160 mg, followed by 80 mg 2 weeks later, and a maintenance dose of 40 mg every other week

Table 3. Anti-TNF- α agents for inflammatory bowel disease

Preparation	Drug	Route of administration	Target disease	Induction dose	Maintenance dose
Infliximab	Remicade	Intravenous	UC, CD	5 mg/kg at weeks 0, 2, and 6	5 mg/kg every 8 weeks
	Remsima (CT-P13)	Intravenous	UC, CD	5 mg/kg at weeks 0, 2, and 6	5 mg/kg every 8 weeks
		Subcutaneous	UC, CD	5 mg/kg at weeks 0, 2 (IV) 120 mg at week 6 (SC)	120 mg every 2 weeks
	Remaloce (SB2)	Intravenous	UC, CD	5 mg/kg at weeks 0, 2, and 6	5 mg/kg every 8 weeks
Adalimumab	Humira	Subcutaneous (citrate-free formulation)	UC, CD	160 mg at week 0 80 mg at week 2 40 mg at week 4	40 mg every other week
	Adallope (SB5)	Subcutaneous	UC, CD	160 mg at week 0 80 mg at week 2 40 mg at week 4	40 mg every other week
	Yuflyma (CT-P17)	Subcutaneous (citrate-free formulation)	UC, CD	160 mg at week 0 80 mg at week 2 40 mg at week 4	40 mg every other week
Golimumab	Simponi	Subcutaneous	UC	200 mg at week 0 100 mg at week 2 50 mg at week 6 (100 mg if weight > 80 kg)	50 mg (or 100 mg) every 4 weeks

TNF- α , tumor necrosis factor- α ; UC, ulcerative colitis; CD, Crohn's disease; IV, intravenous; SC, subcutaneous.

for IBD patients [84,85]. The adalimumab biosimilars, SB5 (Adallope, SAMSUNG BIOEPIS) and CT-P17 (Yuflyma, Celltrion Korea) are now available for IBD patients. Golimumab is generated from genetically engineered mice immunized with human TNF and is administered subcutaneously at an induction dose of 200 mg, followed by 100 mg 2 weeks later, and a maintenance schedule of 100 mg every 4 weeks for UC patients [86].

Adverse events of anti-TNF- α agents

Anti-TNF- α agents are associated with an increase in adverse infectious events in IBD patients [87]. Screening of latent tuberculosis, HBV, HCV, and HIV before beginning an anti-TNF- α agent and preventing pneumocystis jirovecii or herpes zoster infection has benefits in patients treated with an anti-TNF- α agent (Table 2) [87-89]. Routine screening of latent tuberculosis with either an interferon-gamma release assay test or the tuberculin skin test combined with a chest X-ray is mandatory for candidates taking an anti-TNF- α agent. In addition, serological screening with hepatitis B surface antigen and the antibody to hepatitis B surface, and the core (anti-HBc) protein should be performed before immunosuppressive therapy. Anti-TNF- α agents are associated with increased risk for hepato-splenic T cell lymphoma and melanoma [90,91]. The immediate infusion reaction during the anti-TNF- α agent course can cause pruritus, rash, headache, chest discomfort, and anaphylaxis. A late infusion reaction 1 to 3 weeks after administration of an anti-TNF- α agent manifests as arthralgia, joint stiffness, and fever. These infusion reactions occur in 3.5% to 38.6% of cases and can be prevented using antipyretics, antihistamines, and/or corticosteroids [92].

Optimizing anti-TNF- α agents

Although anti-TNF- α agents have advanced the medical treatment of IBD, 10% to 30% of patients experience a primary non-response and do not respond to induction therapy; 23% to 46% of patients eventually experience a loss of response to maintenance therapy [93,94]. TDM is efficacious for optimizing IBD therapy [95]. A recent consensus statement suggested that the IFX trough concentration during week 14 and the maintenance period should be $> 3 \mu\text{g/mL}$ and that the adalimumab trough concentration during week 4 and the maintenance period should be $> 5 \mu\text{g/mL}$ [96]. In the presence of adequate trough drug concentrations, anti-drug antibodies (ADA) are unlikely to

be clinically relevant [97]. In the absence of a detectable biologic drug concentration, patients with undetectable/low ADA can optimize drug therapy by combining them with immunomodulators, shortening the dosing interval, and increasing the drug dose. Patients with high ADA levels should consider switching drug classes [97]. Although reactive TDM performed in response to active inflammation based on biochemical, endoscopic, or radiological assessments is recommended, proactive TDM performed in patients regardless of clinical status is currently under active investigation to demonstrate its superiority [98]. Before changing biologic agents, it is necessary to carefully consider the need for surgery, the existence of consistent infections, or the possibility of combined IBD.

CONCLUSIONS

Conventional therapies, including 5-ASA-based drugs, corticosteroids, immunomodulators, and anti-TNF- α agents are the keystone of medical treatment for IBD. New formulations and delivery systems are being developed for 5-ASA-based drugs to improve patient adherence and convenience. Corticosteroids and second-generation corticosteroids have important roles in inducing clinical remission in moderate to severe IBD patients. To minimize the inappropriate use of corticosteroids, optimal timing and dosing of the immunomodulator is required to maintain remission. The *NUDT15* gene test and TDM monitoring have helped reduce adverse events and maximize the efficacy of immunomodulators. Anti-TNF- α agents have changed the standard of treating refractory moderate to severe IBD patients. Combination therapy with an anti-TNF- α agent and an immunomodulator helps overcome immunogenicity in IBD patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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