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REVIEW

Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology practice recommendations for medical management and monitoring of inflammatory bowel disease in Asia

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Abstract

Inflammatory bowel disease (IBD) has increased in incidence and prevalence in Asian countries since the end of the 20th century. Moreover, differences in the cause, phenotypes, and natural history of IBD between the East and West have been recognized. Therefore, the Asian Organization for Crohn's and Colitis and the Asia Pacific Association of Gastroenterology have established recommendations on medical management of IBD in Asia. Initially, the committee members drafted 40 recommendations, which were then assessed according to Grading of Recommendations Assessment, Development and Evaluation. Eight statements were rejected as this indicated that consensus had not been reached. The recommendations encompass pretreatment evaluation; medical management of active IBD; medical management of IBD in remission; management of IBD during the periconception period and pregnancy; surveillance strategies for colitis-associated cancer; monitoring side effects of thiopurines and methotrexate; and infections in IBD.

Introduction

Inflammatory bowel disease (IBD) has become common in Asia over the past few decades. Some countries/areas are experiencing a more rapid increase than in Western countries, which has been attributed to rapid urbanization and industrialization.[1] The highest incidence of IBD has been reported in East Asia (Korea, Japan, and China) and South Asia (India). Also, differences in the clinical manifestations of IBD between the East and West have been noted: in Asia, there is a higher male predominance of Crohn's disease (CD); more perianal involvement in CD; and fewer extraintestinal manifestations and worse clinical outcomes among older-onset patients with ulcerative colitis (UC).[1,2] There are also different genetic risk factors between the East and West: nucleotide

oligomerization domain (NOD2) variants present in Caucasians have not been identified in many Asian ethnicities (Han Chinese, Japanese, Korean, Indian, and Malaysian), and among Asian populations, tumor necrosis factor (TNF) superfamily 15 polymorphisms was identified as a CD-susceptible gene and the TNF-α-308 polymorphism as a UC-susceptible gene. Recently, a Korean group[3] discovered a single nucleotide polymorphism in NUDT15, which may partially explain the higher incidence of thiopurine-induced leukopenia in Asians.

In the West, many guidelines are used for the management of IBD, for example, the European Crohn's and Colitis Organization guidelines and the American College of Gastroenterology guidelines.[4–8] Some countries in the East have developed their own guidelines tailored for their patients' needs. In consideration of differences among Asian and Western IBD patients, the Asian Organization for Crohn's and Colitis (AOCC) and Asia Pacific Association of Gastroenterology have jointly developed recommendations on medical management and monitoring for IBD in Asia.

Methods

This clinical practice recommendation was developed using the Grading of Recommendations Assessment, Development and Evaluation methodology and was drafted by an AOCC recommendation panel. A professional group was formed of 251 experts from 12 Asian countries and regions, including Mainland China, Hong Kong, Taiwan, India, Indonesia, Japan, Malaysia, Philippines, Saudi Arabia, Singapore, South Korea, Thailand, and United Kingdom. Recommended indicators were established by clinical practitioners through subcommittee meetings and discussions. The votes of each recommendation guideline were graded according to level of agreement: completely agree, partially agree, as appropriate, and disagree. Recommendations were approved when over 80% of the participants answered "completely agree" or "agree." The members of the guideline panel met with the authors of the technical review at AOCC 2018 meeting in Shanghai. For each item, the group came to an agreement regarding the overall quality of the evidences. When consensus was not reached on the first vote, panel members went through a discussion and modification process. If consensus was still not reached, the statement was rejected. The result was presented as a percentage under the classification of recommendation, as "level of agreement."

Pretreatment evaluation

Differential diagnosis with intestinal tuberculosis.

1. Intestinal tuberculosis should be excluded before IBD diagnosis, and patients should receive diagnostic anti-tuberculosis treatment when differential diagnosis is difficult.
Level of agreement: strongly agree 81.3%, agree 15.5%, uncertain 2.8%, disagree 0.4%

Crohn's disease and intestinal tuberculosis frequently have similar clinical and endoscopic features, making it difficult to differentiate between the two diseases, especially in Asia, where tuberculosis is prevalent.[9] Moreover, the misdiagnosis of intestinal tuberculosis as CD can result in the inappropriate treatment of tuberculosis patients with immunosuppressive drugs, such as corticosteroids, thiopurines, and anti-TNF agents, which can lead to disseminated tuberculosis.[10] Conversely, the misdiagnosis of CD as intestinal tuberculosis can expose CD patients to the toxicity of anti-tuberculosis drugs and delay proper treatment of CD.

Concomitant pulmonary tuberculosis, ascites, night sweats, involvement of fewer than four segments of the bowel, patulous ileocecal valve, transverse ulcers, scars, or pseudopolyps strongly indicate intestinal tuberculosis. In doubtful cases, a therapeutic trial of anti-tubercular drugs is often used in attempts to confirm the diagnosis. Patients with intestinal tuberculosis will have clinical and endoscopic improvement after 2–3 months of anti-tuberculosis therapy; however, symptom persistence after a therapeutic trial of 3 months of anti-tubercular therapy may indicate the diagnosis of CD.[11]

Latent tuberculosis screening and chemoprophylaxis.

2. IBD patients should be screened for tuberculosis by chest radiography and PPD skin test or/and IGRA before anti-TNF-α therapy.
Level of agreement: strongly agree 82.1%, agree 15.5%, uncertain 2.0%, disagree 0.4%

3. IBD patients with latent tuberculosis infection should receive biological agents in combination with prophylactic anti-tuberculosis treatment with at least isoniazid during the first 6 months.
Level of agreement: strongly agree 64.3%, agree 31.3%, uncertain 2.8%, disagree 1.6%

Chest radiograph may be insufficient for screening Asian IBD patients for tuberculosis because of the high prevalence of the disease. Reactivation of latent tuberculosis infection is a major challenge in IBD patients. A Korean study found that the incidence rate, standardized incidence ratio, and number needed to screen for incident tuberculosis in IBD patients compared with that in the general population were 223.9/100 000 person-years, 2.64 (2.30–3.01), and 446.6 (392.8–517.6), respectively.[12] Screening for and treating latent tuberculosis before the use of anti-TNF-α therapy has decreased the risk of active tuberculosis. There is no gold standard test for the detection of latent tuberculosis infection; the definitive diagnosis is based on the medical history, tuberculin skin test, or interferon gamma release assay results, and chest radiography. Song *et al.*[13] have reported that 102 of 447 (22.8%) patients who had chest computed tomography had findings suggestive of latent tuberculosis infection. Therefore, chest computed tomography is recommended as an adjunctive to interferon gamma release assay for latent tuberculosis screening in IBD patients before commencing immunosuppressive therapy in high-prevalence regions.

Preventive therapy is given to reduce the risk of progression from latent tuberculosis infection to active disease and should be offered to all patients with evidence of latent disease before an anti-TNF-α agent is started. Available regimens for the treatment of latent tuberculosis infection have an efficacy of 60% to 90% and a duration of protection of up to 19 years.[14] A study from Korea[15] has reported that the incidence rate of tuberculosis per 1000 person-years was lower in new TNF antagonist users treated for latent tuberculosis (4.07; 95% confidence interval [CI], 1.55–6.60) than in those not treated (12.34; 95% CI, 9.96–14.72) (incidence rate ratio, 0.33; 95% CI, 0.17–0.63).

Screening for opportunistic infection.

4. IBD patients should be screened for HBV, HCV, HIV and syphilis before corticosteroids, immunomodulators or biologics treatment.
Level of agreement: strongly agree 75.4%, agree 21.4%, uncertain 2.8%, disagree 0.4%
5. All IBD patients with positive HBsAg, even with normal liver transaminases and negative HBV-DNA, should receive antiviral therapy with Entecavir or Tenofovir at least 1 week before biologics application. Liver transaminases and HBV-DNA should be checked regularly.
Level of agreement: strongly agree 65.9%, agree 23.4%, uncertain 5.6%, disagree 5.1%

Reactivation of viral hepatitis has been widely reported in patients undergoing immunosuppressive therapy, with a potentially fatal outcome. Morisco *et al*.[16] reported on 20 IBD patients with HBV or HCV infection who received immunosuppressive therapy (six HBsAg+, four isolated anti-HBc+, and 10 anti-HCV+). Hepatitis was reactivated in one of the six patients with HBsAg+ and one of the four with isolated anti-HBc+. Although data for IBD patients are scarce, prophylaxis has proven beneficial in patients undergoing immunosuppressive therapy. Shibolet *et al*.[17] reported that lamivudine appeared to be protective against reactivation of hepatitis B infection in HBsAg-positive patients treated with immunosuppression for non-hepatic disorders. However, alternative anti-viral medications for HBV, such as tenofovir or entecavir, are preferred in these cases, as they have the lowest rates of resistance with long-term use.[18]

Evaluation of perianal involvement.

6. IBD patients should receive pelvic MRI or perianal ultrasound to exclude perianal disease before deciding treatment plans.
Level of agreement: strongly agree 48%, agree 37.3%, uncertain 13.1%, disagree 1.6%

Abscess is a complication of penetrating CD and is considered a contraindication to immunosuppressive therapies. Perianal fistulas affect about 5% to 40% of patients with CD, and the incidence increases with more distal disease (i.e. colonic and rectal involvement) and with increased duration and severity of disease.[19] In about 10% of patients with CD, perianal disease predates other symptoms. In a prospective, blinded comparison,[20] endoscopic ultrasound, magnetic resonance imaging, and examination under anesthesia had $>$ 85% accuracy for classification of fistulas, and accuracy reached 100% when a combination of any two of the tests was used.

Medical management of active inflammatory bowel disease

Treatment strategy for inflammatory bowel disease.

7. We recommend step-up strategy to induce remission in patients with mild to moderate ulcerative colitis.
Level of agreement: strongly agree 76%, agree 22%, uncertain 2%, disagree 0%

Induction therapy for mild-to-moderate UC generally consists of 5-aminosalicylate therapy (sulfasalazine or mesalamine), which is highly effective.[21,22] However, a subanalysis of the Active Ulcerative Colitis Trials 1 failed to demonstrate any difference in response rates to infliximab among patients with disease duration of less than 3 years versus greater than 3 years.[23] Therefore, there may be little rationale for a universal top-down approach in treating UC.

5-Aminosalicylic acid(5-ASA)/Sulfasalazine (SASP).

8. We recommend using 5-ASA/SASP to induce remission in patients with mild to moderate ulcerative colitis.
Level of agreement: strongly agree 84%, agree 14%, uncertain 2%, disagree 0%
9. We recommend combining oral and topical 5-ASA/SASP preparations for proctitis, left-side colitis or pancolitis to induce remission in patients with mild to moderate ulcerative colitis.
Level of agreement: strongly agree 67%, agree 29%, uncertain 4%, disagree 0%

Aminosalicylates still remain the treatment of choice in mild-to-moderate UC in the biologic era. A double-blind, placebo-controlled trial for mildly to moderately active UC demonstrated 24% complete and 50% partial responses in those receiving 4.8 g of 5-aminosalicylic acid (5-ASA) per day as compared with 5% complete and 13% partial responses in those receiving

placebo.[24] In addition, mesalazine has been found as effective as sulfasalazine for inducing response or remission (relative risk [RR], 0.90, 95% CI, 0.77–1.04) and is better tolerated.[25] Although oral mesalazine is effective, combination with topical mesalazine is better: oral mesalazine 4 g/day plus a 1-g mesalazine enema in 116 patients induced clinical remission at 8 weeks in 64% compared with 43% with oral mesalazine alone ($P = 0.03$).[26]

Steroid.

10. We recommend using corticosteroids to induce remission in patients with severe ulcerative colitis.
Level of agreement: strongly agree 76.6%, agree 21.8%, uncertain 1.6%, disagree 0%
11. We recommend the maximum duration of intravenous corticosteroids use before switching to rescue therapy is 5 days.
Level of agreement: strongly agree 35.3%, agree 51.2%, uncertain 9.9%, disagree 3.6%

A systematic review of 32 trials with 1991 patients of corticosteroid therapy for acute severe colitis found a combined response to intravenous hydrocortisone, methylprednisolone, or betamethasone of 67% (95% CI, 65–69%).[27] Corticosteroid treatment should be given for a limited period of 5–7 days. For patients who do not respond to the intravenous steroid therapy after 5–7 days, treatment beyond 7 to 10 days carries no additional benefit.

Immunosuppressive and biological agents.

12. We recommend using anti-TNF-α agents to induce remission in patients with moderate to severe Crohn's disease and severe ulcerative colitis.
Level of agreement: strongly agree 46%, agree 46%, uncertain 7.5%, disagree 0.4%
13. We recommend using anti-TNF-α agents monotherapy over thiopurine monotherapy to induce remission in patients with moderate to severe Crohn's disease and severe ulcerative colitis.
Level of agreement: strongly agree 48%, agree 38.5%, uncertain 10.3%, disagree 3.2%
14. We recommend using anti-TNF-α agents in combination with thiopurines over anti-TNF-α agents monotherapy to induce remission in patients with moderate to severe Crohn's disease when blood ATI increases and/or drug concentration decreases.
Level of agreement: strongly agree 61.1%, agree 32.9%, uncertain 5.2%, disagree 0.8%

A 12-week multicenter, double-blind, placebo-controlled trial of infliximab in 108 patients with moderate-to-severe CD resistant to treatment was conducted in 1995.[28] At 4 weeks, 22 of 27 patients (81%) given 5 mg of infliximab per kilogram, 14 of 28 (50%) given 10 mg of infliximab per kilogram, and 18 of 28 (64%) given 20 mg of infliximab per kilogram had a clinical response compared with response in 4 of 24 (17%) patients in the placebo group. In the CLASSIC-I trial of 299 infliximab-naïve patients with active CD treated with adalimumab (induction dose of 160 mg followed by 80 mg at 2 weeks), 36% achieved remission at 4 weeks compared with 12% who received placebo.[29] In a study of Swedish and Danish patients with severe to moderately severe UC who had not responded to conventional treatment, 7 of 24 (29.2%) patients treated with infliximab compared with 14 of 21 (66.7%) in the placebo group required a colectomy within 3 months ($P = 0.017$; odds ratio [OR] 4.9, 95% CI, 1.4–17).[30] Colombel *et al*.[31] conducted a randomized, double-blind trial that evaluated the efficacy of infliximab monotherapy, azathioprine monotherapy, and the two drugs combined in 508 adults with moderate-to-severe CD who had not received previous immunosuppressive or biologic therapy. Of the 169 patients who received combination therapy, 96 (56.8%) were in corticosteroid-free clinical remission at week 26 (the primary end point) compared with 75 of 169 patients (44.4%) who received infliximab alone ($P = 0.02$). Patients with moderate-to-severe CD who were treated with infliximab plus azathioprine or infliximab monotherapy were more likely to have a corticosteroid-free clinical remission than those receiving azathioprine monotherapy. A systematic review and meta-analysis also showed that combination therapy with adalimumab and immunomodulator was modestly superior to adalimumab monotherapy for induction of remission in CD.[32,33] Another randomized, double-blind trial evaluated the efficacy and safety of 16-week treatment with infliximab monotherapy, azathioprine monotherapy, or the two drugs combined in TNF-α antagonist-naïve adults with moderate-to-severe UC.[34] Anti-TNF-α–naïve patients with moderate-to-severe UC treated with infliximab plus azathioprine were more likely to achieve corticosteroid-free remission at 16 weeks than were those receiving either drug monotherapy. Combination therapy also resulted in significantly better mucosal healing than did azathioprine monotherapy.

In a multivariate analysis within a pivotal study by Farrell and colleagues,[35] scheduled maintenance dosing and use of a concomitant immunosuppressive agent independently protected against the development of anti-drug antibodies. A post-hoc analysis of the ACCENT I study[36,37] suggested that concomitant immunosuppression resulted in lower rates of anti-drug antibody formation, whereas episodic maintenance therapy was associated with the development of antibodies (8% vs 30%; OR, 0.21; 95% CI, 0.13–0.36; $P < .0001$; Janssen research ELISA).

Treatments: Miscellaneous.

15. We recommend nutrition support during the induction of remission in patients with Crohn's disease.
Level of agreement: strongly agree 62%, agree 26%,

uncertain 12%, disagree 0%

16. IBD patients should routinely receive nutritional risk assessment and undertake nutritional support based on the result.

Level of agreement: strongly agree 69.4%, agree 24.6%, uncertain 6%, disagree 0%

17. IBD patients should receive iron supplement if they have hypoferric anemia.

Level of agreement: strongly agree 69.4%, agree 27%, uncertain 3.6%, disagree 0%

18. IBD patients should receive calcium and vitamin D3 supplements if they have osteoporosis.

Level of agreement: strongly agree 67.9%, agree 27.4%, uncertain 4.7%, disagree 0%

It is estimated that up to 85% of hospitalized IBD patients have protein–energy malnutrition, based on abnormal anthropometric and biochemical criteria.[38,39] Patients identified in nutrition screening as malnourished or at risk of malnutrition should have a nutrition assessment: nutrition history, physical exam, laboratory tests, and clinical judgment. Based on the results of the assessment, a tailored nutrition care plan can be developed. A systematic review of CD children[40] found that 83% (24/29) on enteral nutrition achieved remission compared with 61% (17/28) of steroid-treated patients (RR 1.35, 95% CI, 0.92–1.97).

Anemia is the most frequent, although often neglected, comorbidity of IBD. A placebo-controlled, double-blinded, randomized study in women with iron deficiency but without anemia[41] found that intravenous iron administration resulted in an improvement of fatigue in 82% of patients in the intervention group compared with 47% in the placebo group and that the effect of iron supplementation on fatigue was most pronounced in women with an initial ferritin concentration of less than 15 ng/mL Osteopenia and osteoporosis are frequent complications in IBD patients. According to Abitbol *et al*.,[42] the fracture risk for IBD patients is about 40% to 60% greater than that in control subjects. Treatment with calcium and vitamin D is likely beneficial for IBD patients who have low bone mineral density, and T scores in sequential dual-energy X-ray absorptiometry scans are increased in patients with calcium and vitamin D supplementation.

Medical management of inflammatory bowel disease in remission

5-Aminosalicylic acid/SASP.

19. We recommend using 5-ASA/SASP to maintain remission in patients with ulcerative colitis.

Level of agreement: strongly agree 82%, agree 15%, uncertain 3%, disagree 0%

20. 5-ASA/SASP should be continued long-term in maintenance treatment.

Level of agreement: strongly agree 73%, agree 24%, uncertain 3%, disagree 0%

In a study by Wang *et al*.,[43] 5-ASA was superior to placebo for maintenance of clinical or endoscopic remission in UC patients; 41% of patients treated with 5-ASA had relapse compared with 58% of placebo patients (seven studies, 1298 patients; RR 0.69, 95% CI, 0.62–0.77). There did not appear to be any difference in efficacy among the various 5-ASA formulations used.

Long-term continuous treatment with high dose mesalazine (4.0 g/day) may be more effective than short-term treatment for maintenance of remission in UC patients.[44] One hundred fifteen patients who clinically improved or who achieved clinical remission after treatment with 4.0 g/day mesalazine were categorized into two subgroups according to median duration of treatment: a short-term treatment group of 28 patients (48.3%) ($\leq$ 105 days, n = 58) and a long-term treatment group of 17 patients (29.8%) ($>$ 105 days, n = 57). The relapse-free rate in the long-term treatment group was significantly higher than in the short-term treatment group ($P < 0.05$). The mean time to relapse in the long-term treatment group was significantly longer than in the short-term treatment group (425.6 ± 243.8 vs 277.4 ± 224.5 days; $P < 0.05$).[44]

Steroid.

21. We recommend against using corticosteroid for maintenance of remission.

Level of agreement: strongly agree 71%, agree 9%, uncertain 5%, disagree 15%

The role of oral corticosteroids as maintenance therapy after patients have been brought into remission was first studied by Truelove and Witts,[45] followed by Lennard-Jones *et al*.[46] Both groups found that prednisone was not superior to placebo in preventing relapses of UC. Four randomized placebo-controlled clinical trials have evaluated budesonide for maintenance of medically induced remission in ileocolic CD.[47–50] Although two of the studies found a lengthening of the median time to relapse with budesonide (6 mg daily) compared with placebo, the rate of relapse after 12 months was not different. These data indicate that corticosteroids are not effective for maintenance of medically induced remission in CD.

Immunosuppressants.

22. We recommend using thiopurines over no immunomodulator therapy to maintain remission in patients with Crohn's disease.

Level of agreement: strongly agree 52%, agree 40%, uncertain 7%, disagree 1%

A pooled analysis of six studies (489 participants) found that azathioprine (1.0 to 2.5 mg/kg/day) was superior to placebo for

maintenance of remission in CD patients over 6 to 18 months[51]; remission was maintained in 73% of patients in the azathioprine group compared with 62% in placebo patients (RR 1.19, 95% CI, 1.05–1.34), and the number needed to treat for an additional beneficial outcome was nine.

Management of inflammatory bowel disease during the periconception period and pregnancy

23. Female IBD patients should cease methotrexate for at least 3 months while thalidomide should be completely prohibited before conception.
Level of agreement: strongly agree 82%, agree 14%, uncertain 3%, disagree 1%

24. Female IBD patients could be treated with corticosteroids or biologics only under the full consideration of the pros and cons during gestation.
Level of agreement: strongly agree 61%, agree 34%, uncertain 5%, disagree 0%

25. Female IBD patients could use biological agents till 22–24 weeks of gestation to minimize fetal exposure.
Level of agreement: strongly agree 47%, agree 40%, uncertain 11%, disagree 2%

26. Female IBD patients should take 2 mg/d folic acid supplement daily to prevent neural tube deformity if they receive SASP treatment at least 3 months before conception or during pregnancy.
Level of agreement: strongly agree 53%, agree 34%, uncertain 12%, disagree 1%

In a systematic review of studies evaluating 101 patients with rheumatoid arthritis exposed to methotrexate (5–25 mg/week) from conception to the first trimester, 23% of pregnancies resulted in miscarriages, 5% of infants had minor malformations, and there were only 66% live births (induced abortions were excluded from analysis).[52] Methotrexate exposure was associated with a 3.4-fold increased risk of cardiovascular defects and a 2.6-fold increased risk of oral clefts compared with no exposure. Thalidomide should never be used by women who are pregnant or who could become pregnant while taking the drug. Product labeling states that if thalidomide is taken during pregnancy, it can cause severe birth defects or embryo-fetal death.

A meta-analysis of cohort and case–control studies reported a marginally increased risk of major malformations after first-trimester exposure to corticosteroids.[53] In a meta-analysis of five studies that included pregnant women with IBD who received anti-TNF therapy, there were no significant differences in rates of unfavorable pregnancy outcomes (OR 1.00, 95% CI, 0.72–1.41), abortion (OR 1.53, 95% CI, 0.97–2.41), preterm birth (OR 1.00, 95% CI, 0.62–1.62), low birth weights (OR 1.05, 95% CI, 0.62–1.78), or congenital malformation (OR 1.10, 95% CI, 0.58–2.09) compared with rates in women with IBD who were not exposed to anti-TNF therapy.[54] In a small case–control study, there were significantly increased risks of preterm births and low birth weights associated with corticosteroid exposure; however, the significance of these findings is questionable because the patients were hospitalized for severe, active disease.[55]

In pregnant women with IBD in remission, discontinuation of anti-TNF therapy (before week 30) was associated with low relapse rates (8%) in a small case series (n = 25) and in a case–control study (14%) (n = 85).[56] One study reported an increased risk of pregnancy-related complications with exposure to anti-TNF therapy in the third trimester in a univariate analysis, but this was not significant in the multivariate analysis.[57]

Periconception folic acid supplementation reduces the risk of neural tube defects.[58] Sulfasalazine may inhibit absorption and lower the serum concentrations of folic acid; therefore, folic acid supplementation may be required.

Surveillance strategies for colitis-associated cancer

27. UC patients, or CD patients with colon involvement should routinely receive endoscopy with multiple biopsies from multiple segments starting from the 8th year after diagnosis.
Level of agreement: strongly agree 52.4%, agree 34.9%, uncertain 11.5%, disagree 1.2%

28. UC patients with low grade dysplasia in flat mucosae should reexamine endoscopy in 3–6 months and receive pancolectomy when necessary.
Level of agreement: strongly agree 58.7%, agree 32.5%, uncertain 6.4%, disagree 2.4%

Bopanna *et al*.[59] found that the risk of colorectal cancer in Asian UC patients was like that of recent estimates in Europe and North America; the overall prevalence in Asia was 0.85% (95% CI, 0.65–1.04). The risks for colorectal cancer in UC patients were 0.02% (95% CI, 0.00–0.04) at 10 years, 4.81% (3.26–6.36) at 20 years, and 13.91% (7.09–20.72) at 30 years. A similar risk for colitis-associated cancer was also calculated for patients with Crohn's colitis, based on the severity and extent of colonic involvement. The pooled standardized incidence ratio of colorectal cancer was 1.9 (95% CI, 1.4–2.5).[60] Multiple biopsy specimens throughout the entire colon are helpful in determining the microscopic extent and degree of inflammation, even in mucosa that appears normal on endoscopy. Regarding the initiation of surveillance colonoscopy, the European Crohn's and Colitis Organization guidelines recommended that colonoscopy be started at 6–8 years after onset of UC.[5] Hata *et al*.[61] recommend that patients with late-onset UC (> 40 years of age) undergo screening

colonoscopy earlier because of the high incidence of colorectal cancer within 8 years of the onset of UC, and Lutgens *et al*.[62] reported that about 17–28% of the cancers developed even earlier. Chromoendoscopy is the preferred method for dysplasia surveillance in patients with IBD rather than white-light colonoscopy. Meta-analysis by Feuerstein *et al*. showed that chromoendoscopy ($n = 249$) was more effective at identifying dysplasia than standard white-light endoscopy ($n = 248$) (RR, 2.12; 95% CI, 1.15–3.91).[63] Furthermore, in a randomized controlled trial, Watanabe *et al*. found that targeted and random biopsies detect similar proportions of neoplasias, but a targeted biopsy appears to be a more cost-effective method.[64] In a systematic review,[65] it was found that among UC patients with low-grade dysplasia under surveillance, the annual incidence of progression to colorectal cancer was 0.8%, and the pooled annual incidence of advanced neoplasia was 1.8% (95% CI, 0.9–2.7). Navaneethan *et al*.[66] assessed the risk of progression of low-grade dysplasia to advanced neoplasia for UC patients; of their 102 patients with low-grade dysplasia (65 raised and 37 flat), five (4.9%) patients had progression to advanced neoplasia (three high-grade dysplasia and two colorectal cancer) after a median follow up of 36 months (interquartile range 18–71 months). Compared with proximal colon, flat low-grade lesions in the distal colon were more likely to progress to advanced neoplasia (hazard ratio = 3.6; 95% CI, 1.3–10.6). Twenty of the 102 patients (15 with flat and 5 with raised lesions) underwent colectomy.

Monitoring adverse events of thiopurines and methotrexate

29. IBD patients should routinely receive Full Blood Count, liver, renal and pancreatic function tests during thiopurine or methotrexate treatment.
Level of agreement: strongly agree 70.6%, agree 24.6%, uncertain 4.8%, disagree 0%

About one-fifth of IBD patients treated with thiopurines develop dose-dependent (mainly myelotoxicity and hepatotoxicity) or idiosyncratic (pancreatitis, hepatitis, or flu-like syndrome) adverse events. Late leukopenia, unrelated to the activity of thiopurine methyltransferase, may develop.[67] The most common adverse events caused by methotrexate are gastrointestinal symptoms, but they rarely lead to cessation of treatment. Other significant adverse events of methotrexate are hepatotoxicity, bone marrow suppression, hypersensitivity pneumonitis, gastrointestinal toxicity, and infections.[68]

Infections in inflammatory bowel disease

30. *Clostridium difficile* should be tested for in IBD patients who have recurrence or aggravation of diarrhea during treatment.
Level of agreement: strongly agree 85.3%, agree 12.7%, uncertain 2%, disagree 0%

31. CMV should be tested for in IBD patients with colon involvement if their conditions steadily deteriorate during treatment.
Level of agreement: strongly agree 82.1%, agree 15.5%, uncertain 1.6%, disagree 0.8%

32. Acute severe UC patients should be routinely tested for *Clostridium difficile* and CMV.
Level of agreement: strongly agree 77%, agree 18.6%, uncertain 3.6%, disagree 0.8%

Clostridium difficile infection is frequent in patients hospitalized for IBD flare. Sokol *et al*.[69] have reported that *C. difficile* infection was present in 35 of 461 patients (7.6%) hospitalized for IBD flare and non-toxigenic *C. difficile* was identified in 10 (2.2%) cases.

The first case of UC-associated cytomegalovirus (CMV) infection was reported in 1961, in a patient whose colonic biopsies had viral cytoplasmic inclusions.[70] The reported prevalence of CMV reactivation during moderate-to-severe IBD flare is 21% to 34%,[71,72] and among steroid-refractory patients, the prevalence has exceeded 30%.[70,73] Kojima *et al*.[74] reviewed 126 surgical specimens of UC patients to explore the clinicopathologic features of CMV infection. They found that the prevalence of CMV was higher in patients with severe UC undergoing surgery (16% and 25% by HE staining and immunohistochemistry, respectively) than in those with refractory UC (1.3% and 8.3% by HE staining and immunohistochemistry, respectively, $P < 0.05$). The CMV prevalence was much lower in patients with UC-related dysplasia (0% for both HE staining and immunohistochemistry). These results may suggest that CMV infection is related to the severity of colitis rather than the nature of UC therapy.

Discussion

Eight statements were rejected as this indicated that consensus had not been reached. The statement "IBD patients should receive TPMT and NUDT15 polymorphism test before thiopurine treatment" was rejected. In Asian patients, it is strongly recommended to detect NUDT15 genotype rather than TPMT before initiating thiopurine therapy.[75] Vedolizumab with an excellent safety profile is approved for the treatment of IBD that is refractory to conventional therapy, and it has been shown to be effective in the induction and maintenance of remission in IBD. Ustekinumab was approved in 2016 for the treatment of moderate-to-severe CD, which targets the interleukin-12/23 shared p40 subunit, blocking the receptors for these pro-inflammatory cytokines on cells. Many novel biologics are not available in most of Asian countries, so we did not discuss this as part of management of IBD. In the future, we will update the consensus with the clinical application of new biological agents.

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