

REVIEW

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Inflammatory Bowel Disease in Korea: Epidemiological, Genomic, Clinical, and Therapeutic Characteristics

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Inflammatory bowel disease (IBD) describes chronic inflammatory disease of the intestines and has a variable course; Crohn's disease and ulcerative colitis comprise the two main forms of the condition. Although IBD occurs worldwide, its epidemiologic and clinical characteristics vary depending upon the geographic location and the ethnicity of the population. Identifying the characteristic features of IBD in populations living in different geographical locations and with different ethnicities may provide significant clues about its etiology and pathophysiology, which in turn may be helpful in the development of more appropriate treatment strategies for IBD for these different populations. Therefore, it is important for each country and region to evaluate critically the epidemiology, genomics, and clinical characteristics of IBD among its own population. We have performed a critical review of the recent data in Korea, and describe herein the current epidemiologic and genotypic status, as well as the clinical manifestations and therapeutic responses of IBD that are unique to Korean patients. (***Gut Liver* 2010;4:1-14**)

Key Words: Inflammatory bowel diseases; Crohn's disease; Ulcerative colitis; Korea

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disorder of the bowel, consisting mainly of Crohn's disease (CD) and ulcerative colitis (UC). The incidence of IBD has been rising not only in Western countries, but also in Asia, including Korea.¹ Intriguingly, the characteristics of Western and Asian IBD patients differ

in epidemiology, phenotype and genetic susceptibility.²⁻⁷ Evaluating these geographically unique features may provide substantial clues for identifying the pathophysiology and the etiology of IBD. However, such efforts have been challenging in most Asian countries, where there are lack of population-based registries, limited access to health care facilities, limited availability of diagnostic devices, and the occurrence of infectious diseases that mimic IBD, which hindered the accurate assessment of the incidence and the prevalence, the risk factors and the clinical characteristics of IBD.⁸ Until recently, only Japan has been able to report the reliable data, as it has the accessible and efficient health care system and maintains a national IBD registry under the Ministry of Health, Labor and Welfare.³ In Korea, the Korean Association for the Study of Intestinal Diseases (KASID) has recently taken a leading role in establishing the organizational structural bases for investigating IBD and has performed a series of nationwide studies.^{1,9,10} Korea has a relatively small nation of territory and the population is ethnically homogeneous. Members of KASID from each province of the nation participate to perform multicenter studies and patients with IBD have been registered by members of KASID.^{1,9} This review will describe the updated data on Korean IBD patients based on the recent publications.^{1,8,11-20}

EPIDEMIOLOGY

Despite the advances in scientific technologies used to study IBD, its etiology and pathogenesis remain unclear. Traditionally, it has generally been thought that IBD occurs predominantly in the industrialized Western coun-

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tries. However, as many other parts of the world including Asia, South America and Eastern Europe became industrialized since the middle of the last century, the incidence and the prevalence of IBD in these areas increased dramatically, suggesting that urbanization may be a risk factor for IBD.^{2,3,8,21-27} On the other hand, in Western Europe and North America, the incidence and the prevalence of IBD have stabilized or only slightly increased over time.²⁸⁻³¹

In Korea, the incidence and prevalence of CD and UC are low compared to those of Western countries, but are increasing rapidly. According to a recent update on the descriptive epidemiology of IBD in Korea¹ based on the population-based data from an urban district in Seoul, the mean annual incidence rates of CD and UC increased from 0.05 to 0.34 per 100,000 inhabitants in 1986-1990, and from 1.34 to 3.08 per 100,000 inhabitants in 2001-2005, respectively. The adjusted prevalence rates of CD and UC per 100,000 inhabitants were 11.24 (95% CI, 9.29-13.18) and 30.87 (95% CI, 27.47-34.27), respectively. In addition, it was observed that the ratio of the incidence rates of UC to CD was decreasing in Korea, indicating that CD showed a trend of more accelerated incidence rate compared to UC. This finding is similar to that observed in many Western countries.^{28,32,33} Male predominance in the prevalence rate of CD was observed in the Korean population, a finding similar to those reported in the recent studies from China² and Japan³⁴ while the incidence of CD in females is predominant or equal to that in males in Western countries.^{28,32}

DIAGNOSIS

Regarding the diagnosis of IBD, two factors should be considered: first, distinguishing IBD patients from alternative inflammatory disease patients and secondly, correctly differentiating between UC and CD.³⁵ Before establishing a diagnosis of IBD, other various forms of intestinal inflammation with identifiable causes should be excluded using relevant history, careful physical examination, prudent laboratory tests, and thorough review of the radiographic, endoscopic and pathologic data. The differential diagnosis of intestinal inflammation is outlined in Table 1. In some Asian countries including Korea, where intestinal tuberculosis is still prevalent, the distinction between intestinal tuberculosis and CD is extremely difficult because of their clinical similarities. Studies from Korea have shown that the proportion of patients receiving anti-tuberculosis treatment before confirmation of CD was nearly 50% of all CD patients.³⁶ In a study conducted in Korea, four endoscopic characteristics were identified

Table 1. Differential Diagnosis of Intestinal Inflammation

Self limited colitis
Diverticulitis
Intestinal tuberculosis
Ischemic colitis
Intestinal Behçet's disease
Radiation colitis
Amebic colitis
Bacterial infectious colitis
Cytomegalovirus colitis
Appendicitis
Eosinophilic gastroenteritis
Henoch-Schonlein purpura
Graft-versus-host disease
Diversion colitis
Microscopic colitis
Gastrointestinal sarcoidosis
Drug-related (NSAIDs, diuretics, antihypertensives)

for each disease: anorectal lesions, longitudinal ulcers, aphthous ulcers, and a cobblestone appearance for CD, and involvement of fewer than four segments, a patulous ileocecal valve, transverse ulcers, and scars or pseudopolyps for intestinal tuberculosis. Using these endoscopic parameters, the diagnosis of either intestinal tuberculosis or CD was correctly made in 87.5% of patients.¹⁸ In Asia, if a patient has an ulceration in the ileocecal region, intestinal Behçet's disease (BD) should be included as a differential diagnosis.³⁵ In an effort to differentiate intestinal BD and CD, a Korean study reported that round ulcerations, ≤ 5 in number, focal distributions, and absence of aphthous and cobblestone lesions were dominant features in intestinal BD.¹² The authors stated that these characteristics enabled the correct diagnosis of intestinal BD or CD in 92% of patients with ulcers on colonoscopy.

As the two main subforms of IBD, UC and CD have similar clinical manifestations, it is very challenging for the clinicians to correctly diagnose IBD. While there are several diagnostic criteria available for IBD including Mendeloff's criteria,³⁷ Lennard-Jones criteria,³⁸ the international multicentre scoring system of the Organization Mondiale de Gastroenterologie (OMGE),³⁹ and the diagnostic criteria of the Japanese Research Society on IBD,³ there is no single gold standard for the diagnosis of IBD. All diagnostic criteria use an integrating assessment of the clinical presentation, endoscopic, radiographic, and pathologic findings for diagnosis. More recently, serologic assays, utilizing antineutrophil cytoplasmic autoantibody (ANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA) have been added as diagnostic tools with an adjunctive role in differentiating UC and CD.^{40,41} A Korean study demonstrated that the sensitivity (49.4%) and the specif-

icity (79.2%) of ASCA for CD are comparable to those seen in Western countries and that the sensitivity (44.2%) and the specificity (95.8%) of the pANCA for UC are also similar to those previously reported in Western countries.⁴² However, in a recent Korean study, Lee *et al.* reported that the prevalence of pANCA in Korean patients with UC was relatively low compared to patients in Western countries (22% vs 59-84%).¹⁷ The major distinctive clinical, morphological, structural and pathological features between the two subforms of IBD are listed in Table 2.

As genome-wide association studies have been introduced in an effort to identify the etiologic factors of IBD, many genetic polymorphisms related to an increased risk of IBD have been discovered.⁴³⁻⁵² In the near future, it is expected that a more specific genetic map will be identified to improve the diagnosis of IBD. Combined with serologic assays, genetic testing is promising for a number of reasons. First, genetic testing is non-invasive. Second, genetic testing can be used to predict the phenotypic features of disease.⁵³ Serologic tests serve as effective means to predict a complicated course of the disease by showing high associations with disease activity and the sites of involvement in IBD.^{54,55} A judicious combined utilization of genetic and serologic tests may be more reliable for predicting complicated behavior than the use of either test alone and may be helpful in developing a risk-stratified approach for the selection of medical therapy.⁵⁶ Moreover, genetic evidence could allow clinicians to identify IBD patients before they become symptomatic and to choose appropriate early preventive measures.

Genotypic features and clinical characteristics of Korean IBD are somewhat different from those of Western

countries. In Korea, a recent population based study showed that the most common location of the involvement CD is in both small bowel and colon (66.7%) followed by isolated segments of either small bowel (21.0%) or colon (12.3%).¹ This finding is similar to that reported by a Japanese study.⁵⁷ This contrasts with recent European studies that reported isolated colonic disease as the most common type of CD at diagnosis.^{29,58} In a genetic polymorphism study with a large number of Northern European and Korean patients with CD and normal controls, CARD15 (NOD2) mutations were not found to be associated with susceptibility to CD in Korean patients, although they were in European populations.⁵⁹ This finding was confirmed by another study also conducted in Korea.¹⁵ On the other hand, recent studies showed that genetic variants in IL23R, tumor necrosis factor superfamily member 15 (TNFSF15), and tumor necrosis factor- α (TNF- α) gene but not autophagy-related 16-like 1 (ATG16L1), which are known to be associated with CD in European populations also contribute to CD susceptibility in Koreans.⁶⁰⁻⁶² In Japan^{63,64} and Korea⁶⁵ studies, the HLA-DRB1*1502 allele was shown to be positively associated with UC, whereas the results showed discord about this association in Western populations.⁶⁶⁻⁶⁸

The clinical features of UC at diagnosis are reported to be similar in Koreans and Westerners.²⁰ For instance, there are no differences in the extent and the severity of disease at diagnosis or in the male to female ratio of patients with UC between Korea and Western countries.

EVALUATION OF CLINICAL ACTIVITY

To develop an optimal treatment strategy for IBD, it is essential to fully understand the disease's activity and ex-

Table 2. Differences in Clinical, Endoscopic, and Histological Features between Ulcerative Colitis and Crohn's Disease

	Ulcerative colitis	Crohn's disease
Hematochezia	Common	Rarely
Palpable abdominal mass	Rarely	Occasionally in right lower abdomen
UGI involvement	No	Yes
Distribution	Diffuse and continuous	Focal and asymmetric with skip segments
Fistulas and abscesses	Rarely	Common
Strictures	Rarely	Common
Perianal lesion	Rarely	Common
Mucosal appearance	Diffuse friability, large ulcers	Aphthous ulcers, linear or serpiginous, cobblestone ulcers
Granulomas	Absent	15-60% present
Crypt abscesses	Common	May be present
Fissures	Rarely	Common
Transmural mucosal inflammation	No	Yes
ANCA	Common	Rarely
ASCA	Rarely	Common

UGI, upper gastrointestinal; ANCA, anti-neutrophil cytoplasmic antibodies; ASCA, anti-saccharomyces cerevisiae antibodies.

tension of disease. The Truelove and Witts severity index is one of the most commonly used disease activity indexes for UC, and comprises six items: number of stools per day, presence of blood in stools, temperature, pulse, hemoglobin and erythrocyte sedimentation rate (ESR).⁶⁹ Another popular activity index is the Mayo Score, which is composed of four variables: frequency of bowel movements, rectal bleeding, findings of sigmoidoscopy and Physician Global Assessment.⁷⁰ Generally, the anatomic extent of UC is divided into “distal” when the lesions are not found beyond the splenic flexure and “extensive” when the mucosal inflammation is extended proximally to the splenic flexure.⁷¹ In a Korean study of 304 UC patients, 44.1% of patients were diagnosed with proctitis, 22.7% with left side colitis and 33.2% with extensive colitis. The clinical severity was mild in 49.0% of patients, moderate in 41.1% and severe in 8.6%.²⁰ As serologic markers for the clinical activity of UC, pANCA and triggering receptors expressed on myeloid cells-1 (TREM-1) have been reported to be useful. The UC activity index was found to be higher in pANCA-positive patients than in pANCA-negative Korean patients.¹⁷ The serum TREM-1 level correlated better with disease activity than ESR or CRP, irrespective of disease extent in Korean patients with UC.¹⁹

Since CD affects various sites of the intestine and manifests as different endoscopic appearances of involvement, it is suggested that CD is a heterogeneous entity and that different genetic backgrounds may explain the different clinical patterns observed for the disease.^{72,73} It is, therefore, important to develop a simple classification of CD based on stable and reproducible clinical variables in order to study its genetic or environmental bases. In 1998, the World Gastroenterology Meeting in Vienna proposed a new classification based on three clinical variables including age at diagnosis, location and disease behavior (Table 3).⁷⁴ According to the Vienna classification, pa-

tients are categorized into the A1 group if the diagnosis is made before 40 years of age and A2 if it is made thereafter. Patients are regarded as L1 when the disease is located in the terminal ileum, L2 when it is located in the colon, L3 when it is located in the ileocolon, and L4 when it involves the upper gastrointestinal tract. The B1 group includes patients with non-stricturing non-penetrating disease, the B2 group includes patients with stricturing disease, and the B3 group includes patients with penetrating disease. Among these variables, disease location appears to remain stable, while significant sustained changes are noted in disease behavior over time.⁷⁵ Recently, the Vienna classification was revised and a new Montreal classification was proposed.⁷⁶ Regarding age-of-onset, the Montreal revision categorizes early onset of disease as an A1 category for those with an age of diagnosis of 16 years or younger. With respect to disease location, the Montreal classification allows upper gastrointestinal disease to coexist with more distal disease. Lastly, in terms of disease behavior, perianal disease is recognized as a separate subclassification. The data from Severance Hospital in Korea following the Vienna classification showed that patients in groups A1 and A2 made up 88.9% and 11.1%, respectively, of the entire patient population, and that L1, L2, L3, and L4 made up 19.5%, 13.9%, 45.8%, and 20.8%, respectively.⁷⁷ Notably, the most common location was L3, which is different from the pattern normally seen in Western countries. During the follow-up period, the proportion of B1 and B2 diminished from 48.6% and 27.8% to 37.5% and 25%, respectively, while that of B3 increased from 23.6% up to 37.5% (Fig. 1). The Crohn's disease activity index (CDAI), the most widely applied activity index for CD, consists of eight variables: the number of liquid stools, the extent of abdominal pain, general well-being, the occurrence of extraintestinal symptoms, the need for anti-diarrheal drugs, the presence of abdominal masses,

Table 3. The Vienna and Montreal Classifications of Crohn's Disease

	Montreal	Vienna
Age at diagnosis	A1, ≤16 years 16 years < A2 ≤ 40 years A3, 40 years <	A1, <40 years A2, ≥40 years
Location	L1, Terminal ileum L2, Colon L3, Ileocolon L4, Isolated upper gastrointestinal	L1, Terminal ileum L2, Colon L3, Ileocolon L4, Upper gastrointestinal
Behavior	B1, Non-stricturing non-penetrating B2, Stricturing B3, Penetrating p perianal disease modifier	B1, Non-stricturing non-penetrating B2, Stricturing B3, Penetrating

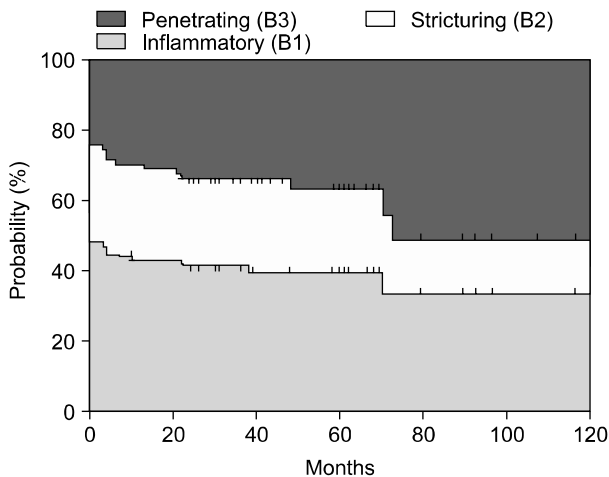


Fig. 1. Changes in disease behavior in Korean CD patients according to the Vienna classification.

hematocrit and body weight.⁷⁸ The range of scores is 0 to 600 and in clinical trials, active CD is indicated when the CDAI score is over 150. As the CDAI has been frequently used in clinical trials over two decades and vigorously validated, this index is considered the gold standard for evaluation of disease activity.⁷⁹ The Harvey Bradshaw index is another convenient and commonly used activity index for CD.⁸⁰

MANAGEMENT OF IBD

IBD is characterized by its chronicity, with cycles of remission and relapse that occur over the patient's lifetime. The goals of therapy for IBD, therefore, are not only the induction but also the maintenance of remission of symptoms without the use of corticosteroids.

CROHN'S DISEASE

1. Medical management

1) Induction of remission

Clinical trials have documented that sulfasalazine, budesonide, and conventional corticosteroids are effective at inducing remission in mild to moderately active CD.

Although oral aminosalicylates have been widely used in clinical practice to treat active CD, their use is controversial evidence. In the case of mild to moderate CD, clinical trials demonstrate that sulfasalazine administered at 2-6 g/day is more effective than placebo for inducing remission.^{81,82} This effect is most notable in patients with active colonic or ileocolonic disease.^{83,84} In contrast, mesalazine has failed to show consistent results in various controlled studies.⁸⁵⁻⁸⁷ Some patients are intolerant of the

adverse effects of sulfasalazine, including headache, nausea, skin rash, fever, hepatitis, autoimmune hemolysis, aplastic anemia, leucopenia, folate deficiency, pancreatitis and male infertility. Most of these effects are related to the sulfapyridine moiety of sulfasalazine. Considering that the intestinal bacterial flora probably plays a role in the pathogenesis of CD, antibiotics have been used as therapeutic agents. Although metronidazole and ciprofloxacin are often used for the treatment of CD, controlled trials have failed to show convincing evidence of their efficacy for the induction of remission in active CD.⁸⁸⁻⁹¹ Budesonide undergoes extensive first-pass hepatic metabolism, which reduces the side effects associated with systemic corticosteroids. Well controlled studies have revealed that budesonide is significantly more effective than placebo and 5-ASA, and is about as effective as conventional corticosteroids for inducing remission in active CD.⁹²⁻⁹⁴ Therefore, budesonide has been recommended as a first-line therapy for mild to moderate CD of the ileum and proximal colon in an American Gastroenterological Association position statement and in the European Crohn's and Colitis Organization Consensus.^{95,96}

For those patients who do not respond to the first-line therapy described above and for those with moderate to severe CD, oral prednisone 40-60 mg/day should be given. In the case of fulminant and refractory inflammatory CD, remission may be induced with intravenous corticosteroids, such as methylprednisolone at 1-1.5 mg/kg per day. A Korean study showed that serum albumin level could be a significant predictive factor for response to initial steroid therapy in active CD patients.⁹⁷ Compared to steroid responders, a steroid dependent group was characterized by lower serum albumin levels. According to the data from a Korean study, when a median dosage of oral steroids at 0.59 mg/kg was administered, the overall response rates to the steroid at one month and one year were as high as 88.5% and 58.3%, respectively.⁹⁸ These rates were comparable to the best response rates from Western studies (Fig. 2). Patients with moderate to severe disease who fail to respond to 5-ASA, budesonide and conventional corticosteroids, and patients intolerant of corticosteroids, may be treated with anti-TNF- α antibody agents including infliximab (intravenous, 5 mg/kg at 0, 2, and 6 weeks) and adalimumab (subcutaneous, 160 mg at 0 and 80 mg at 2 weeks). The results of a nationwide survey conducted in Korea,⁹⁹ showed that the clinical response rate for infliximab in luminal CD was 51%, and that the clinical remission rate was 36%. Thirteen percent of patients did not respond to infliximab treatment. In patients with fistular disease, the clinical response rate was 45%, clinical

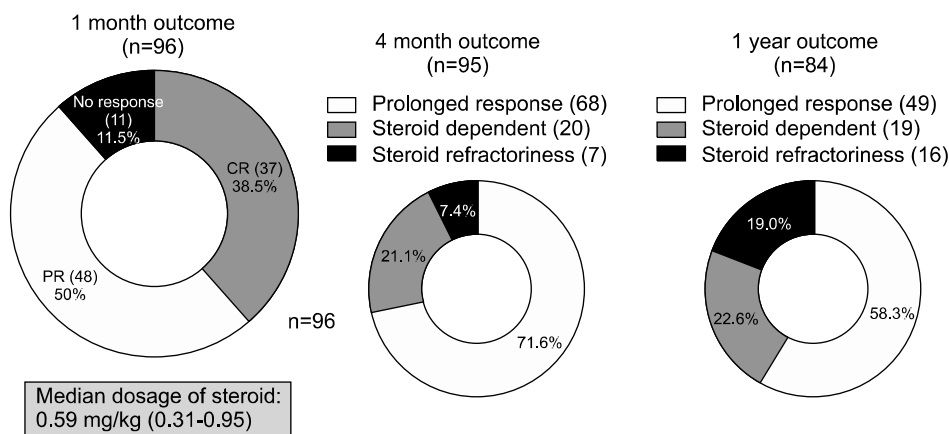


Fig. 2. Overall response rates to steroids in Korean Crohn's disease patients.

remission 31%, and no response 24%. These results are similar to the clinical response rates reported in Western studies. Interestingly, the most common reason for infliximab cessation in Korea was the limitation of the standard national health insurance reimbursement, as it previously covered only one year of infliximab treatment for active CD patients. However, the national health insurance coverage for infliximab has been extended up to 28 injections, regardless of period in a recent amendment.¹⁰⁰

2) Maintenance therapy

Despite the widespread use of 5-ASA in clinical practice for the maintenance of medically induced remission in CD patients, this application is not evidence-based. Clinical studies have revealed that sulfasalazine and mesalazine are not actually effective for maintaining medically induced remission in CD patients. In general, corticosteroids are not recommended for maintaining remission due to related systemic adverse effects and lack of efficacy. The results of a Korean study showed that preoperative corticosteroid treatment increased the risk of postoperative infections in patients with CD.¹⁰¹ Treatment with budesonide at 6 mg/day, however, has been shown to prolong the time to relapse and to be effective at maintaining remission for at least six months, but less than one year.¹⁰²

Immunosuppressive agents such as azathioprine (AZA) and 6-mercaptopurine (6-MP) have been reported to be effective as maintenance therapy and to be advantageous for reducing or discontinuing steroid usage in steroid-dependent CD patients.¹⁰³⁻¹⁰⁵ However, due to slow onset of action, these drugs are not used as induction therapy in patients with active CD.¹⁰³ Because azathioprine or mercaptopurine are frequently continued indefinitely as maintenance therapy,¹⁰⁶ their long term side effects should be kept in mind. These agents, therefore, are

currently reserved for steroid-dependent or refractory patients. Myelotoxicity is one of the significant adverse effects of thiopurine drugs and is reported to be associated with decreased thiopurine methyltransferase (TPMT) and deficiency of inosine triphosphate pyrophosphatase (ITPA).¹⁰⁷ Korean patients with IBD who are treated with AZA/6-MP experience myelotoxicity more frequently than similarly treated Europeans. Among 133 IBD patients treated with azathioprine in Korea, leucopenia occurred in 75 cases (56.4%), which is a higher incidence than that reported in Western studies.¹⁰⁸ Another Korean study revealed that there is no correlation between TPMT genotype and AZA toxicity.¹⁰⁹ Methotrexate is another effective immunosuppressive agent for maintaining remission of CD.

For patients who are unable to maintain remission or who are dependent on steroids in spite of treatment with AZA or 6-MP, infliximab can be used for maintenance of remission, steroid-sparing and mucosal healing (5 mg/kg every eight weeks).¹¹⁰ Alternatively, adalimumab can be given subcutaneously for maintenance therapy at 40 mg every other week. With advances in the understanding of the pathophysiology of CD, a range of new therapeutic agents apart from anti-TNF drugs are under investigation. Among these innovative drugs are the T-cell blocking agents,¹¹¹ anti-adhesion molecules,¹¹² anti-vascular adhesion protein-1 monoclonal antibody¹¹³ and avidity multimers (avimers)¹¹⁴ with high ligand affinity and specificity that allows binding to many targets at the same time.

2. Medical management of fistulizing CD

One of the distinct characteristics of Korean CD patients is the high incidence of perianal fistulas. The incidence rate of perianal fistulas in Korea is 48.5%, which is higher than that reported in other countries (13-38%).¹³ Because the incidence of CD in Korea has been increasing substantially, the possibility of CD should

be considered in Korean patients with perianal fistulas. The first-line therapy for fistulas in patients with CD is antibiotic treatment with metronidazole or ciprofloxacin,^{96,104,115,116} with AZA or 6-MP being the typical second-line treatment. In cases in which active fistulizing disease fails to respond to treatment with antibiotics and immunosuppressive agents, infliximab or adalimumab can be administered.

3. Surgical management

A significant proportion of CD patients will need surgical management an average of 20 years after diagnosis. Failure of medical therapy remains the most common indication for surgical treatment of CD.^{117,118} The occurrence of complications despite medical treatment is an additional indication for surgical management.

Worsening obstruction is a frequent complication of CD, especially with small bowel involvement. Whereas acute obstructions are often resolved with medical treatment, chronic obstructions are usually caused by fibrostenotic lesions and require surgical management.¹¹⁹

Not all fistulas require surgery. Although intestinal fistulas occur in one-third of CD patients, only a few patients require surgical management.¹²⁰ Generally, fistulas associated with abscesses or strictures, that are connected to the genitourinary tract, or that cause intestinal malabsorption are indications for surgical management.

The lifetime risk for intraabdominal abscess in CD patients is approximately 25%.¹²¹ Almost all abscesses require drainage either surgically or percutaneously. Although there is controversy as to whether or not intraabdominal CD abscess should be managed surgically, surgical resection is required when an abscess has enteric contents.¹²² Korean data have shown that nonsurgical treatment including percutaneous catheter drainage can be considered an initial therapy for a CD-related abscess. The overall success rate and cumulative recurrence rate at seven months were 66.7% and 12.5%, respectively.¹⁶ A recent Korean study reported that the clinical efficacy of nonsurgical treatment is comparable to that of surgical treatment.¹²³ Other indications for surgical management in CD include free perforation, bleeding and cancer.

In CD, 70-90% of patients will require surgical management during the disease course. Another study reported that the cumulative operation rate was 44%, 61%, and 71% at one, five, and 10 years after diagnosis, respectively.¹²⁴ Unlike the above Western studies, the rate was much lower in the results of a Korean study with 11.5%, 13.1%, and 18.2% at one, three, and six years after diagnosis, respectively.³⁶ The rate reported in another Korean study was also lower than that reported for

Western countries.¹²⁵ This disparity could be attributed to the different perspectives of different backgrounds toward surgical intervention in CD patients. Another possible reason could be that the Western study was conducted early, when aggressive surgery for CD was prevalent and Korean studies are more recent, when surgical treatment is rarely performed due to the advances in medical treatment.

The rate of complications with surgical management for CD in Korea is 13.6%, which is comparable to that of other countries.¹²⁶

ULCERATIVE COLITIS

1. Medical management

UC can be treated according to anatomical extent of the disease. In distal UC, in which disease involvement is limited to below the splenic flexure, a topical agent can be effectively applied. Similar to CD, the management of UC is focused on both induction and maintenance of disease remission. In addition, the therapeutic decision depends mainly on clinical severity rather than on histologic severity of inflammation.

1) Induction of remission

In mild to moderate active UC patients, the first line regimen is 5-ASA, including oral and rectal formulations. Effective oral doses for each drug are as follows; sulfasalazine 4-6 g/day, mesalamine 2-4 g/day, balsalazide 6.75 g/day, olsalazine 1.5-3 g/day. The effects of these drugs are usually observed within 2-4 weeks in 40-80% of patients.^{127,128} Left side colitis can also be managed with topical agents such as rectal mesalazine or rectal corticosteroid. Controlled trials show that topical mesalamine is superior to oral 5-ASA or topical corticosteroid alone in inducing clinical improvement in patients with mild to moderate distal colitis.^{110,129,130} Furthermore, the combination of oral and topical 5-ASA may produce a better response in the management of mild to moderate distal colitis than administration of either oral or topical formulations alone.¹³¹

If the patients fail to respond to 5-ASA agents, they should be managed with oral prednisone 40-60 mg daily for one to two weeks. At one year after starting corticosteroids, a prolonged response is observed in 49% of patients, and 22% of patients become steroid dependent.¹³²

Patients with severe active UC showing aggravated symptoms despite treatment with oral corticosteroids should be hospitalized for intravenous steroid therapy. Further failure to respond to intravenous steroid might require the use of cyclosporine, tacrolimus and a biologic

agent such as infliximab. If patients do not respond to maximal medical treatment, superimposed infection with cytomegalovirus or *C. difficile* should be considered as a potential cause of aggravation.

Although there have been many studies in Western countries indicating the usefulness of cyclosporine in the treatment of severe UC, the efficacy of cyclosporine has been disappointing in Korea, with a reported response rate of only 14%.¹³³ One Korean study was conducted to evaluate the efficacy of cyclosporine and corticosteroid combination therapy in patients with severe UC that was refractory to an initial intravenous corticosteroid treatment. Unlike Western studies, the Korean study concluded that this combination failed to present any additional benefit over corticosteroid therapy alone in terms of short-term response.¹³⁴ These results suggest that there might be differences in the metabolism of this agent or differences in phenotypes, in terms of responsiveness, based on differences in genetic backgrounds.

Korean UC patients seem to show a better clinical response to medical treatment than their Western counterparts. The overall remission rate in the first attack was 90% in Western population-based studies, whereas the rate in the Korean study with 311 first diagnosed UC

patients was 97.4%.²⁰

2) Maintenance management

5-ASA agents are the mainstay of effective treatment for relapse-prevention of UC. Topical 5-ASA reduces the relapse rates in proctitis or left sided colitis, but topical corticosteroids have not shown effectiveness as a maintenance treatment in distal colitis.^{127,135,136} AZA or 6-MP may be another choice for relapse-prevention in patients who do not respond to 5-ASA or who are dependent on oral steroids. Patients, who have frequent relapses or are steroid-dependent, despite treatment with 5-ASA and immunomodulators, can be treated effectively with infliximab. Recent studies have shown that 45% of infliximab responders remain in the non-relapsed state, compared to 20% of initial responders in the placebo group after 54 weeks of maintenance therapy with infliximab.¹³⁷ These promising results with infliximab encourage further trials for confirmation of the role of infliximab as an effective management of UC.

2. Surgical management

A surgical approach is required for treatment of UC when there are life-threatening complications such as

Table 4. Characteristics of Korean Patients with CD Compared to Those of Western Countries

	Differences	Similarities
Epidemiology	<ul style="list-style-type: none"> Incidence and prevalence of CD in Korea are low, but are increasing rapidly whereas those of Western countries have stabilized or only slightly increased over time^{1,28-31} Male is predominant in the prevalence rate of CD in Korean population while female is predominant or equal to male in Western countries^{1,28,32} 	<ul style="list-style-type: none"> CD shows a trend of more accelerated incidence rate compared to UC¹
Genomics	<ul style="list-style-type: none"> CARD15 (NOD2) and ATG16L1 mutations were not found to be associated with susceptibility to CD^{15,59,62} 	<ul style="list-style-type: none"> Genetic variants in IL23R, TNFSF15, and TNF-α gene were associated with susceptibility to CD⁶⁰⁻⁶²
Diagnosis	<ul style="list-style-type: none"> Intestinal tuberculosis and intestinal Behcet's disease should be included as a differential diagnosis because of their relatively high prevalence in Korean population^{35,36} 	<ul style="list-style-type: none"> Sensitivity and specificity of ASCA for CD are 49.4% and 79.2%, respectively⁴²
Clinical features	<ul style="list-style-type: none"> The most common location of CD is both small bowel and colon type in Korean population while isolated colonic disease is the most common type in Western countries¹ The incidence rate of perianal fistulas in Korea is higher than Western countries (48.5% vs 13-38%)¹³ 	
Therapeutic efficacy	<ul style="list-style-type: none"> The most common reason for infliximab cessation was the limitation of the standard national health insurance reimbursement⁹⁹ Korean patients who are treated with AZA/6-MP experience myelotoxicity more frequently than similarly treated Westerners¹⁰⁸ The cumulative operation rate of Korean CD patients is much lower than that of Western CD patients^{36,125} 	<ul style="list-style-type: none"> The clinical response rate and clinical remission rate for infliximab in Korean luminal CD and fistular disease are similar with those of Western countries⁹⁹ The rate of complications with surgical management for CD in Korea is comparable to that of Western countries¹²⁶

hemorrhage or perforation, and documented dysplasia or cancer. Other indications for surgery include fulminant colitis with or without toxic megacolon refractory to maximal medical management or intolerance to immunosuppression or medical therapy. Growth failure due to intractable disease course in pediatric UC patients can also be an indication for surgery.¹³⁸ Since 20-24% of strictures in UC are malignant¹³⁹ and biopsies of the stricture site are inadequate for excluding malignancy, strictures should be managed with surgery.¹⁴⁰

Total proctocolectomy with ileal J-pouch anal anastomosis (IPAA) is the most commonly used surgical method for treatment of UC. Large cohort studies have described this method as relatively safe and durable with a low perioperative mortality rate of 0.2-1.0%. In a recent study of 20 Korean UC patients treated with IPAA, postoperative functional outcomes including sexual and urinary function were found to be tolerable. Despite a relatively high postoperative complication rate (35%), most cases were managed conservatively.¹⁴

Pouchitis is the most common long-term complication of IPAA. It develops in 24-48% of IPAA patients and can be controlled with antibiotics including ciprofloxacin or metronidazole. Similar to data from other countries, 37.5% of Korean UC patients undergoing total proctocolectomy with IPAA have pouchitis and most of these cases occur within one year after surgery.¹⁴¹

One of the unique characteristics is that the cumulative probability of colectomy is much lower in Korean UC patients than in Western patients. In Western countries, the

cumulative colectomy rate is shown to be 3-10% after one year,¹⁴²⁻¹⁴⁴ 8-20% after five years,^{144,145} and 24-34% after 10 years.^{146,147} In contrast, studies from Korea reveal that it is 2.0-3.0% after one year and 3.3% after five to 15 years.^{17,20} Furthermore, the author showed that there were no deaths associated with UC in that study, suggesting that Korean UC patients tend to have a milder form of the disease.

CONCLUSION

Although IBD is a worldwide disease, its incidence rates and clinical features vary depending on geographic area and population origin. The incidence and the prevalence rates of IBD have been increasing dramatically in Korea. There are some clinical and genotypic characteristics that are unique to Korean IBD patients (Tables 4 and 5). Most of all, the clinical course of IBD in Korean patients seems milder than that in Western countries, as indicated by the lower rates of surgical intervention and better responses to medical management in Korean patients. These differing characteristics may provide significant clues about the etiology and the pathophysiology of IBD. Further comprehensive population-based studies are required to clarify these differences.

Although biological therapies have shown a promising role and have altered the management of IBD, they must be used judiciously based on the existing evidence of efficacy and safety. The recent emergence of several promising biologic agents suggests that these novel biologic

Table 5. Characteristics of Korean Patients with UC Compared to Those of Western Countries

	Differences	Similarities
Epidemiology	<ul style="list-style-type: none"> Incidence and prevalence of UC in Korea are low, but are increasing rapidly whereas those of Western countries have stabilized or only slightly increased over time^{1,28-31} 	<ul style="list-style-type: none"> Male to female ratio of the in Korean UC patients was 0.94:1²⁰
Genomics	<ul style="list-style-type: none"> HLA-DRB1*1502 allele was associated with UC in Korean population⁶⁵ 	
Diagnosis	<ul style="list-style-type: none"> The prevalence of pANCA in Korean UC patients was relatively low compared to those in Western countries (22% vs 59-84%)¹⁷ 	<ul style="list-style-type: none"> Sensitivity and specificity of pANCA for UC are 44.2% and 95.8%, respectively, which are similar to those in Western countries⁴²
Clinical features		<ul style="list-style-type: none"> The extent and severity of disease at diagnosis in Korean UC patients was similar to that in Western countries²⁰
Therapeutic efficacy	<ul style="list-style-type: none"> The efficacy of cyclosporine has been disappointing in Korea with a response rate of only 14%¹³³ Korean UC patients seem to show a better clinical response to medical treatment than their Western counterparts (97.4% vs 90%)²⁰ The cumulative colectomy rate is much lower in Korean UC patients than that in Western patients^{17,20} 	<ul style="list-style-type: none"> The rate of pouchitis after IPAA in Korean UC patients was similar to that in Western patients (37.5% vs 24-48%)¹⁴¹

agents may replace or be used in combination with TNF antagonists in the near future.

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