Updated treatment strategies for intestinal Behçet’s disease

Yong Eun Park1 and Jae Hee Cheon1,2

1Department of Internal Medicine and 2Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

INTRODUCTION

Behçet’s disease (BD) is a chronic, multi-systemic immune disorder with an unknown etiology, characterized by recurrent oral and genital aphthous ulcerations, arthritis, and skin manifestations, with ocular, vascular, neurological, and gastrointestinal (GI) involvement [1,2]. The diagnosis of intestinal BD is based on GI symptoms in BD patients and typical intestinal ulcerative lesions documented by objective measures [3]. Although the GI symptoms can range from asymptomatic or mild abdominal discomfort to severe abdominal pain, involvement of the GI tract often leads to severe morbidity and mortality [4]. Additionally, these patients can have further complications such as massive hemorrhage, fistula, or bowel perforation [3,5]. Similar to inflammatory bowel disease (IBD), intestinal BD is accompanied by different clinical courses [6] with chronic continuous symptoms or repeated episodes of relapse and remission [7,8]. Along with proper intervention with surgical management, the appropriate use of medical therapy given the life-long duration of the disease is of great importance in the management of intestinal BD [9,10]. Empirical medical therapies include 5-aminosalicylic acids (5-ASAs), corticosteroids, immunomodulators such as azathioprine and 6-mercaptopurine (6-MP), thalidomide, and anti-tumor necrosis factor α (TNF-α) agents. Therefore, we will cover and review the current therapeutic strategies and new clinical data for the treatment of intestinal BD.

Keywords: Intestinal Behcet disease; Biological products; Tumor necrosis factor-alpha; Infliximab; Adalimumab
treatment modalities that might have the potential to be developed as novel therapeutic agents in the near future will also be discussed.

**PRINCIPLES OF APPROACH TO THE MANAGEMENT OF INTESTINAL BD**

According to the 2008 European League Against Rheumatism (EULAR) guidelines, there are unfortunately no evidence-based treatment guidelines that can be recommended for the management of intestinal BD [11]. There are a few large, randomized and controlled trials of potential management for patients with intestinal BD. Therefore, the management of intestinal BD has been empirically based on the treatment guidelines for Crohn’s disease (CD) following opinions of expert physicians [2]. Correspondingly, according to the Japanese consensus of intestinal BD published in 2007, 5-ASAs, corticosteroids, immunomodulators, enteral nutrition, total parenteral nutrition, and surgical therapy were included in standard therapy for intestinal BD [12]. In addition, in 2014, the 2nd edition of consensus statements for intestinal BD suggested that anti-TNF-α agents such as adalimumab and infliximab should be considered as standard therapy for intestinal BD [13]. Cheon and Kim [2] and Lee et al. [14] proposed a treatment algorithm for intestinal BD based on expert opinion and accumulated published data (Fig. 1).

**MEDICAL TREATMENT**

5-Aminosalicylic acids

5-ASAs can reduce inflammation and have immunomodulatory actions in the intestine [15]. 5-ASAs widely used for IBD are sulfasalazine and mesalamine [15]. Although evidence of efficacy in intestinal BD is still insufficient, the Japanese consensus statements recommended 5-ASA as a first option for induction and maintenance therapy for mild or moderate intestinal BD [13]. 5-ASA is usually administered at a dose of 2 to 4 g/day [2]. Sulfasalazine, a colon-selective drug that contains a sulfon group, is usually administered 3 to 4 g/day in intestinal BD [2].

In 1997, a case study reported that sulfasalazine use was associated with clinical improvement in 79% (11 of 14, p < 0.005) of intestinal BD patients in Korea [16]. In contrast, Matsukawa et al. [17] reported the ineffectiveness of 5-ASA in recurrent intestinal ulcers. However, Jung et al. [18] showed that 5-ASA/sulfasalazine therapy has a positive effect on maintaining remission in Korean patients with intestinal BD, although younger age (< 35 years), higher C-reactive protein (CRP) level, and higher disease activity were associated with a poor response to 5-ASA/sulfasalazine. Another retrospective study on the effect of 5-ASA compounds reported that among 16 patients who were treated with 5-ASA compounds, 62.5% (n = 10) achieved clinical remission with a disease-free duration of 89.3 ± 64.5 months (Table 1) [13,16,18-34]. This discrepancy between studies possibly originates from differences in disease heterogeneity, especially disease severity.

**Corticosteroids**

Corticosteroids are fast-acting anti-inflammatory drugs that have been commonly used for patients with acutely moderate-to-severe and refractory intestinal BD [13,20-22,35]. However, evidence on the efficacy of corticosteroids in intestinal BD also remains insufficient, because prospective/randomized studies are lacking. Treatment with corticosteroids is considered the first-line therapy during the acute phase of the disease, initially at doses of 0.5 to 1.0 mg/kg/day of prednisolone for 1 to 2 weeks with tapering by 5 mg each week and stoppage within 3 months (Table 1) [2,36-38]. Prolonged use of prednisolone in excess of 10 mg/day is not recommended. Some

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Figure 1. A proposed algorithm for the treatment of intestinal Behçet’s disease. Adapted from Lee et al. [14]. 5-ASA, 5-aminosalicylic acid; anti-TNF, anti-tumor necrosis factor.
## Table 1. Studies of medical treatments of intestinal BD: 5-ASA, corticosteroids, immunomodulators, thalidomide, IVIG

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Study</th>
<th>Type of study</th>
<th>No. of patients or articles</th>
<th>Dose of medication</th>
<th>Indication/Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>Yoo et al. (1997) [16]</td>
<td>Case report</td>
<td>Total: 31 Sulfasalazine user: 14</td>
<td>1 g/day → 2–4 g/day → 1–2 g/day (maintenance)</td>
<td>Symptom improved: 79%</td>
</tr>
<tr>
<td></td>
<td>Sonta et al. (2000) [34]</td>
<td>Case report</td>
<td>Total: 1</td>
<td>1,200 mg/day</td>
<td>Lesion: esophageal ulcers Positive clinical efficacy</td>
</tr>
<tr>
<td></td>
<td>Jung et al. (2012) [18]</td>
<td>Retrospective cohort study</td>
<td>Total: 292</td>
<td></td>
<td>Maintaining remission; mild-to-moderate intestinal BD Clinical remission: 143</td>
</tr>
<tr>
<td></td>
<td>Hisamatsu et al. (2014) [13]</td>
<td>Japanese consensus statements</td>
<td>Relevant articles: 15</td>
<td>5-ASA: 2.25–3.00 g/day Sulfasalazine: 3–4 g/day</td>
<td>Indication: maintenance therapy</td>
</tr>
<tr>
<td></td>
<td>Hatemi et al. (2016) [19]</td>
<td>Retrospective cohort study</td>
<td>Total: 60 5-ASA user: 16</td>
<td></td>
<td>Remission: 10 of 16 patients (62.5%) Disease free duration: 89.3 ± 64.5 months</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Nakase et al. (2001) [20]</td>
<td>Case report</td>
<td>Total: 2</td>
<td></td>
<td>Case 1: PD 30 mg → 40 mg → no improved: IV 2.5 mg dexamethasone every 2 weeks Case 2: PD 40 mg → 25 mg/day → recur: IV 2.5 mg limethasone every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Toda et al. (2002) [21]</td>
<td>Case report</td>
<td>Total: 1</td>
<td>1 g/day of IV methylprednisolone, 3 days → IV PD 40 mg/day → 20 mg PD IA injection</td>
<td>Disease remission</td>
</tr>
<tr>
<td></td>
<td>Yasuo et al. (2003) [22]</td>
<td>Case report</td>
<td>Total: 1</td>
<td>PD 0.5 mg/kg daily</td>
<td>Lesion: esophageal ulcer Symptom improved &amp; esophagoscopy after 4 weeks: mucosa healing</td>
</tr>
<tr>
<td></td>
<td>Park et al. (2010) [23]</td>
<td>Retrospective cohort study</td>
<td>Total: 54</td>
<td>Median dosage: 0.58 mg/kg (range, 0.39–1.20)</td>
<td>Clinical remission: 25 (46.3%) 1 Year treatment response: 26 (48.1%) Cumulative probability of surgery: 17.5% at 1 year; 49.1% at 3 years</td>
</tr>
<tr>
<td></td>
<td>Hisamatsu et al. (2014) [13]</td>
<td>Japanese consensus statements</td>
<td>Relevant articles: 15</td>
<td>The initial dose of corticosteroids: 0.5–1 mg/kg/day for 1–2 weeks Clinical improvement → tapered by 5 mg every week &amp; stopped</td>
<td>Indication: induction therapy Severe symptoms (i.e., abdominal pain, diarrhea, GI bleeding) Complications with deep ulcers confirmed by radiology or endoscopy</td>
</tr>
<tr>
<td>Drugs</td>
<td>Study</td>
<td>Type of study</td>
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<tr>
<td>Immunomodu-</td>
<td>Choi et al. (2000) [24]</td>
<td>Retrospective cohort study</td>
<td>Total: 43</td>
<td>AZA: 50 mg/day</td>
<td>Re-operation rates: decreased in AZA user group (7% vs. 25% at 2 years; 25% vs. 47% at 5 years) maintenance therapy in patients who require surgery Remission: 16 (38%)</td>
</tr>
<tr>
<td>lators</td>
<td>Matsumura et al. (2010) [28]</td>
<td>Case report</td>
<td>Total: 1</td>
<td>Oral tacrolimus: 10–12 ng/mL (induction) → 5–10 ng/mL (maintenance)</td>
<td>Refractory case to 5-ASA, steroid, immunomodulators, thalidomide, infliximab Remission: 33 months after starting tacrolimus</td>
</tr>
<tr>
<td></td>
<td>Jung et al. (2012) [26]</td>
<td>Retrospective cohort study</td>
<td>Total: 272</td>
<td>AZA: Initial dose 25 or 50 mg daily → 2.0–2.5 mg/kg (gradually increased every 2–4 weeks) 6-MP: Initial dose 0.5 → 1.0–1.5 mg/kg (gradually increased)</td>
<td>Indication: maintenance therapy Remission: 39 (58.2%) of 67 (maintaining medically or surgically induced remission) Clinical relapse: 13 (33.3%) of 39 Relapse risk factors: younger age (&lt; 25 years) at diagnosis, lower hemoglobin level (&lt; 11 g/dL)</td>
</tr>
<tr>
<td></td>
<td>Lee et al. (2015) [25]</td>
<td>Retrospective cohort study</td>
<td>Total: 77</td>
<td>AZA: 2–2.5 mg/kg/day</td>
<td>Postoperative recurrence rate: lower in patients who received post-operative thiopurines than 5-ASA user (p = 0.050)</td>
</tr>
<tr>
<td></td>
<td>Park et al. (2015) [27]</td>
<td>Retrospective cohort study</td>
<td>Total: 196 (IBD) Intestinal BD: 83</td>
<td>AZA: 2–2.5 mg/kg/day</td>
<td>Cumulative relapse-free survival rate: higher in the leukopenic group than in the non-leukopenic group (p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>Hatemi et al. (2016) [19]</td>
<td>Retrospective cohort study</td>
<td>Total: 44</td>
<td>AZA</td>
<td>Remission and no relapse: 24 (65%) Mean follow-up duration: 68.6 ± 43.6 months</td>
</tr>
<tr>
<td></td>
<td>Park et al. (2017) (unpublished data)</td>
<td>Retrospective cohort study</td>
<td>Total: 10</td>
<td>MTX: various dose (subcutaneously &amp; oral) AD: 160 mg in week 0, 80 mg in week 2, and 40 mg every other week</td>
<td>Steroid free remission: 3 patients (30%) at 3 months, 4 patients (50%) at 6 months CRP levels: significantly decreased at 6 months compared with the baseline (p = 0.039).</td>
</tr>
</tbody>
</table>
case studies have reported the efficacy of an intravenous administration of a lipid emulsion of dexamethasone [20,21]. However, corticosteroid use was paradoxically associated with increased risk of GI bleeding and perforation [39]. Additionally, Park et al. [40] reported that corticosteroid use was significantly associated with re-bleeding in patients with intestinal BD. Despite these side effects, Park et al. [23] in 2010 performed a retrospective study of clinical outcomes after corticosteroid use in patients with moderate-to-severe intestinal BD. A total of 54 patients were enrolled and the median corticosteroid dosage was 0.58 mg/kg (interquartile range, 0.39 to 1.20). In this study, 46.3% of patients (n = 25) achieved complete remission after 1 month of treatment. Three months after treatment, 40.7% of patients (n = 22) showed treatment response. After 1 year, 48.1% (n = 26) remained responsive to treatment. However, after 1 year, 35.2% of the patients (n = 19) exhibited corticosteroid dependency, and 7.4% (n = 4) received surgery. Treatment response at three months was independently associated with a decreased risk of surgery in the long term (p = 0.009). Therefore, the authors suggested that short-term response rate to initial corticosteroid therapy was high in patients with intestinal BD [23].

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Study</th>
<th>Type of study</th>
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<th>Dose of medication</th>
<th>Indication/Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>Sayarlioglu et al. (2004) [32]</td>
<td>Case report</td>
<td>Total: 1</td>
<td>100 mg/day</td>
<td>Lesion: recurrent intestinal perforation cecum, transverse colon, terminal ileum Remission: 4 months follow-up</td>
</tr>
<tr>
<td></td>
<td>Yasui et al. (2008) [31]</td>
<td>Case report</td>
<td>Total: 7</td>
<td>Initial dose: 2 mg/kg/day → if necessary, 3 mg/kg/day (increase) or 1–0.5 mg/kg/day (decreased)</td>
<td>Inclusion case: conventional therapy failure, severe steroid toxicity Clinical improvement: all patients</td>
</tr>
<tr>
<td></td>
<td>Lee et al. (2010) [33]</td>
<td>Case report</td>
<td>Total: 4</td>
<td>Case 1: 200 mg/day           Case 2: 100 mg/day     Case 3: 100 mg/day     Case 4: 50 → 100 mg/day</td>
<td>Inclusion case: refractory to steroid, 5-ASA, immunomodulators Clinical improvement: 3 of 4</td>
</tr>
<tr>
<td></td>
<td>Beales (1998) [30]</td>
<td>Case report</td>
<td>Total: 1</td>
<td>400 mg/kg/day for 5 days</td>
<td>Lesion: oral, genital ulcer, uveitis, acniform rash, arthralgia, intestine Previous therapy: cyclosporine, thalidomide maintenance → IV methyl PD, oral mesalamine add → no effect Clinical improvement: after 30 months</td>
</tr>
<tr>
<td></td>
<td>Cantarini et al. (2016) [29]</td>
<td>Case report</td>
<td>Total: 4</td>
<td>Case 3: 400 mg/kg/day for 5 days per month</td>
<td>Lesion: mucocutaneous, ocular, neurological, GI Previous therapy: prednisone, cyclosporine, AZA, mesalazine Clinical improvement: after 14 months</td>
</tr>
</tbody>
</table>

BD, Behçet’s disease; 5-ASA, 5-aminosalicylic acid; IVIG, intravenous immunoglobulin; PD, prednisolone; IV, intravenous; IA, intra-arterial; GI, gastrointestinal; AZA, azathioprine; 6-MP, 6-mercaptopurine; TNF-α, tumor necrosis factor α; mAb, monoclonal antibody; IBD, inflammatory bowel disease; MTX, methotrexate; ADA, adalimumab; CRP, C-reactive protein.
this background, the Japanese consensus recommended that corticosteroids should be considered for induction therapy when patients have severe symptoms such as abdominal pain, diarrhea, or GI bleeding due to deep ulcers [13].

**Immunomodulators**

Immunomodulators included in this review are thiopurines (6-mercaptopurine, 6-MP, and its prodrug azathioprine), methotrexate, tacrolimus, interferon, cyclosporin, and intravenous immunoglobulin [41].

**Thiopurines**

Thiopurines are the most commonly prescribed immunomodulators for patients with intestinal BD, especially those with moderate-to-severe disease and those who are corticosteroid-dependent/resistant or secondarily lose response to anti-TNF-\(\alpha\) agents (Table 1) [1,2,13,24].

Thiopurine drugs such as azathioprine and 6-MP are also used in postoperative patients after intestinal resection to reduce the postoperative recurrence rate [25], and they were reported to be relatively useful in the maintenance of remission after surgery in intestinal BD patients [26]. The initial dose of azathioprine is 25 to 50 mg/day, and if the azathioprine therapy is tolerated without side effects such as leukopenia and liver dysfunction, the dose can be gradually increased every 2 to 3 weeks up to 2.0 to 2.5 mg/kg [13,26,42]. The dose for the initial use of 6-MP is 0.5 mg/kg, which can also be gradually increased up to 1.0 to 1.5 mg/kg in a similar manner to that of azathioprine [26]. Jung et al. [26] reported positive effects of thiopurine maintenance therapy in patients with intestinal BD in Korea. They retrospectively evaluated patients with intestinal BD who received prolonged thiopurine monotherapy for over 6 months in a tertiary single center [26]. Of the 272 patients with intestinal BD, 67 patients (24.6%) received thiopurine therapy, and 39 of these 67 patients (58.2%) maintained medically or surgically induced remission. However, a younger age at diagnosis and a lower hemoglobin level were significantly associated with a poor response to thiopurines in this study [26].

Choi et al. [24] and Lee et al. [25] independently reported the effects of postoperative thiopurine use in patients with intestinal BD (Table 1). Choi et al. [24] compared the reoperation rate between azathioprine users and non-users. Reoperation rates were significantly lower in azathioprine users (7%) than in non-users (25%) at 2 years, and 25% and 47% at 5 years, respectively [24]. In addition, Lee et al. [25] investigated the postoperative protective effect of thiopurine. In their study, the postoperative recurrence rate was significantly lower in patients who received postoperative thiopurines (\(p = 0.050\)) [25].

The most common side effect of thiopurine drugs was leukopenia, which is defined as a white blood cell (WBC) count lower than 3,000 or 4,000 cells/mm\(^3\) [26,27]. Following the American Gastroenterological Association recommendations, it is suggested that when patients are treated with azathioprine or 6-MP, routine laboratory monitoring, including complete blood count, should be frequently performed [43]. Park et al. [27] reported that lower WBC count during thiopurine maintenance therapy was associated with prolonged remission.

**Methotrexate**

The efficacy of other immunomodulators has also been reported. The use of methotrexate in patients with intestinal BD remains relatively poorly understood; however, Iwata et al. [44] reported the efficacy and safety of the combination of infliximab and methotrexate in 10 patients with refractory intestinal BD. All the 10 patients had improved symptoms and disease-related complications within 4 weeks. In addition, 50% of the patients (five of 10) showed disappearance of ileocecal valve ulcers at 6 months, and 90% of the patients (nine of 10) showed disappearance of the ulcers at 12 months (Table 2) [44-67]. Recently, Park et al. (unpublished data) also reported the efficacy of methotrexate in patients with intestinal BD as either mono- or combination therapy with adalimumab. In a retrospective review of 10 intestinal BD patients who received methotrexate treatment, four of the 10 patients received methotrexate monotherapy and the other six patients received combination therapy with adalimumab. In methotrexate monotherapy, three patients (30%) had steroid-free remission at 3 months, and four patients (50%) did at 6 months (unpublished data) (Table 1).

**Tacrolimus**

Oral tacrolimus is a macrolide antibiotic with potent immunosuppressive activity [68], and it is widely used for the prevention of allograft rejection in patients who...
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Study</th>
<th>Type of study</th>
<th>No. of patients</th>
<th>Dose of medication</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Hassard et al. (2001)</td>
<td>Case report</td>
<td>Total: 1</td>
<td>5 mg/kg, at 0, 2, 7, and 23 weeks</td>
<td>Disease activity: CDAI 270 (baseline) → 13 (at 2 weeks) Remission: after 10 weeks</td>
</tr>
<tr>
<td></td>
<td>Travis et al. (2001)</td>
<td>Case report</td>
<td>Total: 2</td>
<td>Case 1: 3 mg/kg (dose reduced because of recent sepsis) Case 2: 5 mg/kg</td>
<td>Case 1: CRP 72 mg/L → 45 (on steroids) → 70 (sepsis) → 29 (on infliximab) → 12 (12 weeks later) Case 2: CRP 109 mg/L → 25 (on steroids) → 73 (recur) → 51 &lt; 6 (on infliximab)</td>
</tr>
<tr>
<td></td>
<td>Kram et al. (2003)</td>
<td>Case report</td>
<td>Total: 1</td>
<td>5 mg/kg dose over a 6-week period (3 infusions)</td>
<td>CRP 18.7 → normal (on infliximab) → 22.5 mg/mL (relapse) → normal (on infliximab + MTX)</td>
</tr>
<tr>
<td></td>
<td>Lee et al. (2007)</td>
<td>Case report</td>
<td>Total: 1</td>
<td>5 mg/kg</td>
<td>CRP: 70 → 6.7 mg/L (on infliximab) CDAI: 183 → 88 (on infliximab) HBI: 10 → 2 (on infliximab)</td>
</tr>
<tr>
<td></td>
<td>Byeon et al. (2007)</td>
<td>Case report</td>
<td>Total: 1</td>
<td>5 mg/kg</td>
<td>Lesion: unhealed anastomosis site, early recurrent ulcers after a distal ileocecectomy Remission: on endoscopy at 15 days after the infliximab infusion</td>
</tr>
<tr>
<td></td>
<td>Ugras et al. (2008)</td>
<td>Case report</td>
<td>Total: 1</td>
<td>5 mg/kg at weeks 0, 2, and 6</td>
<td>Remission: 7 months</td>
</tr>
<tr>
<td></td>
<td>Naganuma et al. (2008)</td>
<td>Case report</td>
<td>Total: 6</td>
<td>5 mg/kg at 0, 2, 6 weeks (induction) &amp; every 8 weeks (maintain)</td>
<td>Clinical remission: 4 of 6 (induction), 4 of 4 (maintain) Surgery: 2 of 6 (case 5-ileum ulceration, case 6-ileum ulceration with internal fistula)</td>
</tr>
<tr>
<td></td>
<td>Maruyama et al. (2012)</td>
<td>Case report</td>
<td>Total: 1</td>
<td>5 mg/kg at 0, 2, and 6 weeks (induction) &amp; every 8 weeks (maintain)</td>
<td>Remission: 6 years</td>
</tr>
<tr>
<td></td>
<td>Iwata et al. (2011)</td>
<td>Retrospective study</td>
<td>Total: 10</td>
<td>Infliximab (3 mg/kg at 0, 2, and 6 weeks &amp; every 8 weeks) + MTX (3 mg/kg to 200 mg)</td>
<td>Short-term response: improved clinical symptoms &amp; decreased ESR, CRP within 4 weeks Long-term response: remain remission at 6, 12, and 24 months</td>
</tr>
<tr>
<td></td>
<td>Lee et al. (2013)</td>
<td>Retrospective multicenter study</td>
<td>Total: 28</td>
<td>5 mg/kg at weeks 0, 2, and 6 &amp; every 8 weeks</td>
<td>Moderate to severe disease Clinical response: 2 weeks (75%), 4 (64.3%), 30 (50%), 54 (39.1%) Clinical remission: 2 (32.1%), 4 (28.6%), 30 (46.2%), 54 (39.1%) Biological response rate: 2 (82.1%), 4 (57.1%), 30 (53.8%), 54 (43.5%) Sustained response: 15 (53.6%)</td>
</tr>
<tr>
<td>Drugs</td>
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<tr>
<td>Kinoshi-ta et al. (2013) [64]</td>
<td>Retrospective study</td>
<td>Total: 15</td>
<td>5 mg/kg at 0, 2 and 6 weeks &amp; every 8 weeks</td>
<td>Short-term response at week 10: 12 of 15 (80%) Clinical remission: 8 of 15 (53%) Clinical response: 4 of 15 (27%) Long-term response after 12 months: 7 of 11 (64%) Clinical remission: 3 of 11 (27%) Clinical response: 4 of 11 (36%) After 24 months: 4 of 8 (50%) Clinical remission &amp; response: 3 of 8 (38%)</td>
<td></td>
</tr>
<tr>
<td>Ideguchi et al. (2014) [65]</td>
<td>Retrospective study</td>
<td>Total: 43</td>
<td>Infliximab user: 7</td>
<td>-</td>
<td>1 of 7: remission 2 of 7: insufficient efficacy 1 of 7: AE, sepsis 2 of 7: unchanged 1 of 7: for concurrent rheumatoid arthritis</td>
</tr>
<tr>
<td>Hibi et al. (2016) [47]</td>
<td>Prospective, open-label, single-arm phase 3 study</td>
<td>Total: 18</td>
<td>Intestinal BD (11), NBD (3), VBD (4)</td>
<td>5 mg/kg at weeks 0, 2, 6 (induction) &amp; every 8 weeks (maintain) until week 46 10 mg/kg (patients who showed inadequate responses after week 30)</td>
<td>Complete responder: 61% (11 of 18) Intestinal BD: improvement in clinical symptoms &amp; decrease in CRP levels after week 2</td>
</tr>
<tr>
<td>ADA</td>
<td>De Cassan et al. (2011) [58]</td>
<td>Case report</td>
<td>Total: 2</td>
<td>Induction dose of 160 mg subcutaneously 80 mg 2 weeks later Maintenance: 40 mg every other week</td>
<td>Intestinal BD Repeated steroid-dependent flares and failure of maintenance Clinical response, remission: 1-year follow-up</td>
</tr>
<tr>
<td>Shimizu et al. (2012) [66]</td>
<td>Case report</td>
<td>Total: 1</td>
<td>40 mg every other week</td>
<td>Lesion: marginal ulcer after surgery (total gastrectomy) in stomach Improvement: after 3 months</td>
<td></td>
</tr>
<tr>
<td>Tanida et al. (2015) [48]</td>
<td>Multicenter, open-label, uncontrolled study</td>
<td>Total: 20</td>
<td>160 mg at the start 80 mg at 2 weeks 40 mg, every other week &amp; 80 mg for inadequate response/flare for 52 weeks</td>
<td>Intestinal BD Symptom relief &amp; endoscopic assessment scores of 1 or lower at week 24 of treatment: 9 of 20 (45%) At week 52: 12 patients (60%)</td>
<td></td>
</tr>
<tr>
<td>Tanida et al. (2016) [57]</td>
<td>Case report</td>
<td>Total: 8</td>
<td>ADA: 160 mg in week 0, 80 mg in week 2, 40 mg every other week over 52 weeks</td>
<td>Refractory intestinal BD (failed to respond to conventional treatments) Primary outcome MI: at 10 weeks; 5 of 8 (62.5%); at 52 weeks; 6 of 8 (75%) Improvement of Global GI symptoms to score 0: at 10 weeks; 3 of 8 (37.5%); at 52 weeks; 4 of 8 (50%)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2. Continued

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Study</th>
<th>Type of study</th>
<th>No. of patients</th>
<th>Dose of medication</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vitale et al. (2017) [59]</td>
<td>Multicenter retrospective observational study</td>
<td>Total: 100</td>
<td>40 mg subcutaneously every 14 days (5 patients: initially treated with 40 mg every 7 days)</td>
<td>GI involvement: 47 of 100 at 12 weeks: ADA induced clinical efficacy in 81 patients At 24 months: 67 of 100 patients were still on ADA therapy Combination therapy with DMARDs: no significantly superior to monotherapy</td>
</tr>
<tr>
<td></td>
<td>Inoue et al. (2017) [46]</td>
<td>Open label study following a phase 3 clinical trial</td>
<td>Total: 20</td>
<td>Initiated at 160 mg: 10 mg every 14 days, followed by 40 mg every other week until the study end</td>
<td>Intestinal BD Incidence of AEs through week 100: 544.4 events/100 person-years MI at weeks 52: 60.6% MI at weeks 100: 40.6% CR at weeks 52: 20.6% CR at weeks 100: 15.0%</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Ma et al. (2014) [49]</td>
<td>Retrospective comparative study based on observation</td>
<td>Total: 54</td>
<td>Etanercept, subcutaneously at the dose of 25 mg twice a week</td>
<td>Intestinal BD Primary outcome: 4 criteria for diagnosis of BD Remission rate, ulcer healing, recovery rate of ESR and CRP: significantly higher in Etanercept group than conventional group Less adverse reactions in intestinal BD: etanercept group</td>
</tr>
<tr>
<td>ANA/CAN</td>
<td>Cantarini et al. (2015) [50]</td>
<td>Case report</td>
<td>Total: 9</td>
<td>ANA, 100 or 150 mg/day With prednisone (5–25 mg/day)</td>
<td>GI involvement BD: 3 of 9 On refractory to TNF blockers, standardized therapies Response to ANA: 8 of 9 Relapse: 8 of 9 Remain completely under control on ANA monotherapy: 1 patient</td>
</tr>
<tr>
<td></td>
<td>Emmi et al. (2016) [60]</td>
<td>Retrospective study</td>
<td>Total: 30</td>
<td>ANA, 100 mg/day, subcutaneously CAN, 150 mg, subcutaneously every 6–8 weeks</td>
<td>GI involvement BD: 13% (4 of 30) CR at 12 months: 13 of 27 Maintain therapy: 6 of 13 Maintained the same drug: 1 of 6 Shifted from ANA to CAN: 6 AE: ANA, 4 of 27 (15%); CAN, 6 of 27</td>
</tr>
<tr>
<td></td>
<td>Vitale et al. (2014) [51]</td>
<td>Case report</td>
<td>Total: 3</td>
<td>CAN, 150 mg every 6 weeks</td>
<td>Case 1: GI involve (+), symptom-free, 6-month follow-up Case 2: GI involve (+), symptom-free, 12-month follow-up Case 3: GI involve (−), symptom-free, 6-month follow-up</td>
</tr>
</tbody>
</table>
underwent organ transplantation [28]. Matsumura et al. [28] reported improvement after using tacrolimus in a patient refractory to conventional therapeutic agents such as 5-ASA, corticosteroids, immunomodulators, and infliximab. In our experience at Severance Hospital, four patients underwent tacrolimus therapy after failure of conventional agents, but none had a response to that drug (unpublished data).

Interferon
In 1957, Isaacs and Lindenmann [69] first introduced interferon (IFN), a large family of glycoproteins known to produce cellular responses to various antigens such as microbes, viruses, and tumors [70,71]. Several studies reported the efficacy of IFN alfa-2a in the treatment of BD, especially in patients with mucocutaneous lesions, arthritis, and ocular manifestations [70,72,73]. Alpsoy et al. [70] reported a randomized, placebo-controlled, and double-blind study in 50 patients with BD. Of the 50 patients, 23 received IFN alfa-2a therapy, two of whom showed complete response while another 13 showed partial response. Eight patients showed no response. Grimbacher et al. [74] reported the efficacy of IFN alfa-2a in a patient who had eye and GI tract involvement. The patient experienced improved retinal infiltrates, skin lesions, and abdominal complaints within 2 weeks of treatment [74]. Monastirli et al. [75] presented a case demonstrating improvement of clinical symptoms in a patient who had intestinal BD and acute myelitis that were initially unresponsive to high-dose steroids; the patient remained drug-free until 12 months of follow-up. However, until now, there has been little research on the effect of IFN in patients with intestinal BD, and therefore it is difficult to clearly define the effect of IFN on intestinal BD.

Cyclosporin
Cyclosporin is one of the most potent immunosuppressive agents, which decreases T-cell activity and blocks the immune response of inflammatory cytokines [76]. Several studies reviewed the positive effect of cyclosporin on the ocular manifestations of BD [11,77,78]. Following the EULAR guidelines, cyclosporin should not be used in BD patients with central nervous system involvement [11]. With regard to intestinal BD, Bayraktar et al. [7] reported cyclosporin had no benefit on intestinal BD. Therefore, further study is needed to clarify the efficacy of cyclosporin in intestinal BD.

Intravenous immunoglobulin
Since 1952, immune globulin products from human plasma have been used to treat immune deficiency [29,79]. Intravenous immunoglobulin (IVIG) is an immunomodulating agent that has multiple activities and has been used for autoimmune and systemic inflammatory diseases [29]. There are a limited number of studies regarding the role of the IVIG in intestinal BD. Beales [30] reported a case of IVIG treatment without additional corticosteroids in a BD patient with colon involvement after initial failed treatment with corticosteroids.
and other immunomodulators. She significantly improved after IVIG initiation, and bowel lesions disappeared after 6 weeks. Cantarini et al. [29] reported successful treatment with IVIG in patients with severe and resistant BD. Of four patients, all had mucocutaneous involvement with BD and one patient had intestine involvement (Table 1) [29]. Therefore, the effect of IVIG on intestinal BD still warrants further study.

Thalidomide
Thalidomide, a synthetic derivative of glutamic acid, was first introduced in 1957 and used as a sedative agent with a teratogenic side effects; however, recent research has shown growing interest in its anti-inflammatory and immunomodulatory properties [2,31]. Therefore, there have been several studies of thalidomide treatment in pediatric patients with BD who were refractory to other immunomodulators, or those who developed undesirable side effects [80,81].

Sayarlioglu et al. [32] reported beneficial effects of thalidomide on recurrent perforating intestinal ulcers in an adult patient with BD. Additionally, Yasui et al. [31] reviewed a case of thalidomide for the treatment of juvenile-onset intestinal BD, which included seven patients with severe and recurrent intestinal involvement. The initial dose of thalidomide was 2 mg/kg/day, with dose adjustment according to response; if necessary, the dose of thalidomide was increased up to 3 mg/kg/day or decreased to 0.5 to 1 mg/kg/day [31]. All the seven patients achieved clinical improvement and were allowed to stop corticosteroid therapy [31]. In Korea, Lee et al. [33] also reported the efficacy of thalidomide in four patients who had chronic relapse of intestinal BD that repeatedly required corticosteroids and was refractory to conventional therapy such as 5-ASA and immunomodulators. Three of the four patients showed clinical symptom improvements; however, two of the four patients had to stop the therapy due to side effects such as general edema, leukopenia, and sepsis (Table 1).

It has been reported that thalidomide reduces TNF-α levels via degradation of its encoding messenger RNA, and thus shows immunomodulatory effects [82]. Hatemi et al. [83] investigated 13 patients with intestinal BD who were refractory to conventional therapy were treated with anti-TNF-α and/or thalidomide. Of those, 10 patients (75%) achieved clinical and endoscopic remission [83]. Therefore, thalidomide may become a therapeutic option for intestinal BD, but it should be carefully selected and monitored due to its teratogenicity and side effects such as edema, leukopenia, and sepsis. Further well-designed studies are necessary to conduct proper use.

Others
Colchicine
Colchicine is an anti-inflammatory drug that suppresses the secretion of cytokines and chemokines, and is used for the management of patients with gout and BD [35,84]. Some studies reported the improvement of arthralgia and erythema nodosum in patients with BD, but the effect on mucocutaneous manifestations was controversial in several studies [85-87]. Therefore, the EULAR recommended that colchicine is preferred when the dominant lesion is erythema nodosum [11]. However, currently, there is no evidence on the use of colchicine for intestinal BD. Choi et al. [24] suggested that there are no beneficial effects on intestinal lesions from their retrospective study. There is an insufficient number of studies to prove efficacy of colchicine in intestinal BD.

Stem cell transplantation and leukocytapheresis
Hematopoietic stem cell transplantation (HSCT) has been used to treat severe autoimmune and inflammatory conditions that are unresponsive to traditional therapies [38,88]. HSCT in patients with BD has been reported several times in forms of case reports either for refractory BD or patients with associated hematological conditions such as aplastic anemia or myelodysplastic syndrome (MDS) [88-90]. This treatment is based on the rationale that a vigorous immunoablative regimen can remove autoaggressive lymphocyte clones [2]. Yamato [89] and Rossi et al. [90] reported cases of successful stem cell transplantation for MDS with BD and severe/refractory BD. HSCT could be an alternative therapy in BD patients with severe organ involvement, including GI involvement, that is refractory to immunomodulators [88]. Allo-stem cell transplants have high transplant-related morbidity and mortality; therefore, autologous transplants have been performed more frequently in BD patients, and non-myeloablative regimens may be preferred over myeloablative ones [88].
According to the Japanese consensus statements for intestinal BD in 2014 [13], leukocytapheresis was classified into an experimental treatment to mechanically remove WBCs in patients with intestinal BD who are steroid-dependent or resistant [2]. This is because activated neutrophils in patients with severe intestinal BD increase leukocytosis or cytokines [91]. However, this procedure also warrants further well-designed studies [2].

**Anti-TNF-α agents and biologics**

Intestinal BD is associated with abnormal T-cell immune response and T helper type 1-associated cytokines such as TNF-α, IFN-γ, interleukin-12 (IL-12), and IL-18, which play a critical role in disease pathogenesis [92,93]. In patients with BD, the number of γδ cells producing TNF-α increases, TNF-α and its receptor levels are elevated in the blood, and the expression of TNF-α increases when the clinical course becomes worse [93]. Therefore, the importance of anti-TNF-α agents has been reported in several studies based on this background (Table 2) [45,46,67,94-97]. According to the Japanese consensus [33], anti-TNF-α mAbs (infliximab and adalimumab) should be considered as the standard therapy in patients with intestinal BD [2,13]. Infliximab is a chimeric monoclonal antibody against TNF-α [2] that can be considered for induction therapy with 5 mg/kg at 0, 2, and 6 weeks [13]. Responders should be administered maintenance therapy with infliximab every 8 weeks [13]. Adalimumab is a fully human anti-TNF-α monoclonal antibody [48], and can also be used for induction therapy with a dose of 160 mg at week 0 (baseline), 80 mg at week 2, and 40 mg at week 4 subcutaneously. Responders should be considered for maintenance therapy every other week at a dose of 40 mg [13]. In addition, several studies on the effects of various biologics such as etanercept, anakinra, canakinumab, and tocilizumab have been conducted [49-52].

**Infliximab**

Hassard et al. [53] reviewed a patient with chronically active, steroid-dependent intestinal BD who received 4 doses of infliximab during 6 months. The patient achieved remission, with a reduced Crohn’s Disease Activity Index score (from 270 to 13) at 2 weeks of infliximab use, and maintained remission after 10 weeks (Table 2) [53]. Naganuma et al. [54] also reported on the efficacy of infliximab induction and maintenance therapy. Four of six patients with intestinal BD achieved remission, and all four patients maintained remission with infliximab therapy (Table 2) [54]. In 2013, Lee et al. [45] reported a multicenter retrospective study of 28 patients with active moderate-to-severe intestinal BD who had been treated with infliximab at eight tertiary hospitals in Korea. At 2, 4, 30, and 54 weeks post-infliximab infusion, patients showed clinical response rates of 75%, 64.3%, 50%, and 39.1%, and clinical remission rates of 32.1%, 28.6%, 46.2%, and 39.1%, respectively. In addition, independent factors of maintenance response were older age at diagnosis (≥ 40 years), female sex, a longer disease duration (≥ 5 years), concomitant immunomodulator use, and achievement of remission at week 4 on multivariate analysis (Table 2) [45]. In a prospective open-label, single-arm phase 3 study in Japan, 18 patients with BD were enrolled, including 11 patients with intestinal BD, three patients with neurological BD, and four patients with vascular BD with poor response or resistance to conventional therapy [47]. Induction infliximab therapy was administered at 5 mg/kg at weeks 0, 2, and 6, with maintenance therapy every 8 weeks thereafter until week 46. Eleven of 18 of the patients (61%) were complete responders at weeks 14 and 30 and remained in remission until week 54. In addition, laboratory findings such as CRP levels were diminished, and 80% of patients showed healing or scarring ulceration at week 14. However, three patients with intestinal BD had to increase the dose of infliximab up to 10 mg/kg after week 30 due to loss of response, and two of three patients had symptoms that could not be controlled and worsened (Table 2) [47].

The efficacy of infliximab induction and maintenance therapy for intestinal BD has been widely accepted in many studies [13,47,55]. However, there is still insufficient evidence on the effect of combination therapy with immunomodulators as well as whether it can be used as a postoperative therapy in patients who underwent bowel resection. Byeon et al. [56] reviewed a patient with an unhealed postoperative anastomotic site and recurrent ulcers after a distal ileocecectomy, and reported endoscopic remission after 15 days of infliximab infusion. Iwata et al. [44] reported that concomitant therapy of infliximab with methotrexate was effective to achieve short-term remission and long-term response until 24 months. Well-designed further studies are needed.
Adalimumab

Adalimumab is a humanized anti-TNF-α monoclonal antibody [98] and is widely used in patients with rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, psoriasis, juvenile idiopathic arthritis, uveitis, and IBD [48,57,99]. In 2011, De Cassan et al. [58] first reported adalimumab efficacy in patients with intestinal BD with repeated steroid-dependent flares and failure of conventional therapy. After that, several studies showed the efficacy of adalimumab in patients with intestinal BD. Tanida et al. [48] performed a multicenter, open-label, uncontrolled study of adalimumab for the treatment of Japanese patients with intestinal BD who were refractory to conventional therapy, including corticosteroids and/or immunomodulators. A total of 20 patients with intestinal BD were treated with adalimumab with dose of 160 mg at induction, 80 mg 2 weeks later, and 40 mg every other week for 52 weeks; for some patients with incomplete response, the dose of adalimumab increased up to 80 mg every other week. After 24 weeks of adalimumab therapy, nine of 20 patients (45%) had alleviated GI symptoms and diminished endoscopic assessment scores to 1 or lower than at pre-treatment. In addition, 12 of 20 patients (60%) had reduced endoscopic assessment scores at week 52. Additionally, no newly discovered safety problems or deaths were reported (Table 2) [48]. Recently, Inoue et al. [46] published an open-label phase 3 study (NCT01243671) in Japan to evaluate the safety and efficacy of adalimumab for the treatment of the same patients included in the 52 week follow-up study from weeks 52 to 100. Long-term efficacy of adalimumab was assessed on the basis of marked improvement, defined as both a GI symptom score of ≤ 1 (did not affect patient’s daily life) and an endoscopic score of ≤ 1 (largest ulcer is ≤ 1/4 original size), and complete remission, defined as a GI symptom score of 0 (symptom-free) and an endoscopic score of 0 (complete ulcer healing). At weeks 52 and 100, 12 of 20 patients (60%) and eight of 20 patients (40%) showed marked improvement, while four of 20 patients (20%) and three of 20 patients (15%) showed complete remission, respectively (Table 2) [46]. In addition, Kimura et al. [95] reported that a patient with intestinal BD and MDS successfully improved in GI symptoms, CRP levels, leukocytopenia, and anemia 4 months after starting adalimumab.

Combination therapy with adalimumab and immuno-modulators has not yet been established, but Vitale et al. [59] conducted a multicenter retrospective study with 100 BD patients for the comparison of adalimumab monotherapy and combination therapy with disease modifying anti-rheumatic drugs. Although the study was not limited to patients with intestinal BD, it did not show a significant difference in clinical outcomes between adalimumab monotherapy and combination therapy (Table 2) [59].

Etanercept

Etanercept is a dimeric human TNF receptor (TNFR) p75-Fc fusion protein that inhibits TNF-α activity [100,101]. Only a few studies have focused on etanercept as a treatment option for intestinal BD [49]. Ma et al. [49] reported on the outcomes of etanercept in the treatment of intestinal BD with 19 patients who were refractory to conventional therapy. Forty-three patients were enrolled; however, 39% of the etanercept-treated patients had a clinical response compared with 45% of the placebo group (p = 0.763) at week 4 [102]. Furthermore, some recent studies have suggested a paradoxical development of IBD in patients receiving etanercept therapy. Forty-four (41 CD, three ulcerative colitis [UC]) of 443 cases (297 CD, 146 UC) were reported to develop de novo IBD after the initiation of etanercept, and 43 cases of flares of existing IBD patients were reported in association with etanercept therapy [104]. Therefore, the therapeutic efficacy of etanercept in patients with intestinal BD is also questionable.

Anakinra

Anakinra is a recombinant version of the IL-1 receptor antagonist (IL1-RA) and a biologic agent used to modify the immune response of IL-1 [105]. Although the exact etiology of BD is still unclear, it has been reported that IL-1 is a proinflammatory cytokine [106] which can
be increased in patients with BD. Zou and Guan [106] reported increased susceptibility to BD due to polymorphisms in the IL-1-related gene. Cantarini et al. [50] reported on the effects of anakinra in patients with conventional therapy-resistant BD. Nine patients were refractory to anti-TNF agents and conventional therapy, and most of them received anakinra (100 mg daily) with low doses of corticosteroids. Eight of nine patients had symptom improvement after using anakinra; however, the eight had recurrence over time and 15% of patients experienced adverse events (AEs) [50]. Although the efficacy of anakinra has been shown in a few studies, the long-term effect is unclear and most of the studies were not limited to patients with intestinal BD; therefore, more studies are required to clarify the relationship between recurrence and dosage, and to determine the exact efficacy in intestinal BD.

Canakinumab
Canakinumab is a fully human anti-IL-1β antibody which could also be considered as a therapeutic option for resistant or refractory BD [51,60]. Vitale et al. [51] reported successful use of canakinumab in three patients with BD. Two patients had GI involvement and had failed to respond to conventional therapy such as sulfasalazine, methotrexate, cyclosporin, azathioprine, corticosteroids, anti-TNF agents, and anakinra (100 mg/day). Therefore, canakinumab was used at a dose of 150 mg every 6 (case 2) and/or 8 weeks (case 1) by subcutaneous injection, which led to clinical improvement and achieved clinical remission [51]. Recently, Emmi et al. [60] reported outcomes on the use of IL-inhibitors including canakinumab in patients with BD. Three patients used canakinumab (150 mg every 6 to 8 weeks for 12 months) and achieved complete remission at 12 months with no serious AEs (Table 2) [60]. However, the study was not limited to intestinal BD. Therefore, further studies are required.

Tocilizumab
Tocilizumab is a recombinant-humanized anti-human IL-6 receptor monoclonal antibody [107]. IL-6 is a cytokine that plays an important role in immune function, and some studies have shown that circulating IL-6 level is elevated in patients with BD [52,108]. Deroux et al. [52] reported four experienced cases using tocilizumab and reviewed the cases in the literature to evaluate the safety and efficacy of tocilizumab in patients with refractory BD. Three of the four patients were BD patients with GI involvement and all patients were previously unresponsive to conventional therapy. All patients received tocilizumab (8 mg/kg every 4 weeks) and experienced significantly decreased disease activity [52]. However, tocilizumab failed in clinical trials for patients with CD because of serious adverse effects such as bowel perforation and abscess [109,110]. This is because IL-6 is known to play an important role in stimulating intestinal epithelial proliferation and repairing intestinal injury [111]. Therefore, we should pay attention to the use of tocilizumab in patients with intestinal BD in whom intestinal perforation is one of the important complications, and further studies are required.

CONCLUSIONS

Although intestinal BD is not common, GI manifestation occurs more frequently in East Asia, including Korea, than in the Mediterranean region [2,36,112,113]. In addition, complications such as intestinal perforation and bleeding considerably increase morbidity and mortality [2,3]; therefore, it is important to manage and treat patients properly. Appropriate medical therapy in intestinal BD is important to prevent poor outcomes such as frequently recurred ulcer, surgery, complications, and mortality. 5-ASA, corticosteroids, immunomodulators, and anti-TNF agents have been proposed as standard therapy in intestinal BD. However, there is still no definite guideline for established medical therapy because of its rarity and lack of clinical data. Studies on the pathogenesis of BD have been carried out, and studies on new therapies such as the therapeutic effects of related biological agents have been actively under investigation. We anticipate more advanced treatment strategies and established treatment guidelines in intestinal BD in the near future.

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

Acknowledgments
This study was supported by a grant (NRF-2017R1 A1A1A05001011) from the Basic Science Research Pro-
gram through the National Research Foundation of Korea, which is funded by the Ministry of Science, ICT, and Future Planning; and a faculty research grant (2012-31-0477) from the Department of Internal Medicine, Yonsei University College of Medicine.

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