



Safety of Biologics and Small Molecules for Inflammatory Bowel Diseases in Organ Transplant Recipients

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Purpose: This study aimed to evaluate the safety of biologics and small molecules for the treatment of inflammatory bowel diseases (IBD) in patients receiving antirejection therapies after organ transplants.

Materials and Methods: We reviewed the medical records of patients with IBD who received organ transplants at the Asan Medical Center between January 1989 and December 2021. We compared the parameters of patients receiving biologics or small molecules to those of patients without those therapies.

Results: This study included a total of 53 patients (ulcerative colitis, 41; Crohn's disease, 6; and gastrointestinal Behçet's disease, 6). Among them, 15 patients were receiving biologics or small molecules and 38 were not. During a mean follow-up of 119 months, the proportion of patients experiencing severe infections was significantly higher in those treated with biologics or small molecules than in those not treated. However, other safety outcomes (e.g., malignancies, adverse events, including organizing pneumonia or hepatic failure, and death) were not different between the two groups. Kaplan-Meier curve analysis revealed no significant difference in the safety outcome rate related to the use of biologics or small molecules. During follow-up, eight patients underwent bowel resections for IBD. The rate of bowel resection was not different between the two groups.

Conclusion: The use of biologics or small molecules for patients with IBD who received organ transplants did not show a significant difference in safety outcomes. However, the possibility of severe infections must be considered.

Key Words: Inflammatory bowel disease, organ transplantation, biologics

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic

and recurrent inflammation of the gastrointestinal tract. IBD consists of two major diseases, ulcerative colitis (UC) and Crohn's disease (CD), and includes gastrointestinal Behçet's disease (GIBD), which is characterized by recurrent intestinal manifestations that cause multisystemic inflammation.

Approximately 30% of patients with IBD, including those who require organ transplantation, are reported to have extraintestinal symptoms and diseases, such as primary sclerosing cholangitis (PSC) or decreased renal function.¹⁻³ PSC is a chronic inflammatory and fibrosing disease of the intra- and extrahepatic bile ducts. Liver transplantation is often required owing to decreased liver function and progression to liver failure. Approximately one-third of patients with IBD who underwent liver transplantation had an increased IBD activity, re-

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quiring more intensive treatment.⁴ In a Taiwanese study, a prevalence of 1.57% for PSC was observed in patients with IBD, and those who were young and male had a greater incidence of IBD with PSC. Of these patients, 25% underwent liver transplantation.⁵ Some studies have reported the need for other organ transplants, such as kidney or heart transplantation. Patients with IBD, especially those with CD, also presented a high incidence of immunoglobulin A nephropathy, a renal complication that can cause end-stage renal disease (ESRD).⁶ For patients with IBD who underwent kidney transplantation, IBD flare occurred in approximately one-third of the patients after transplantation and intestinal resection was required in one-fifth.⁷⁻¹⁰

Treatment for IBD aims to relieve symptoms, maintain long-term remission, and reduce the risk of complications. Biological agents, including anti-tumor necrosis factor- α (e.g., infliximab), anti-integrin antibodies (vedolizumab), anti-interleukin antibodies (ustekinumab), and small molecules (e.g., tofacitinib) are used for maintaining remission in patients with moderate-to-severe IBD, and are effective in patients with refractory IBD.¹¹⁻¹⁴ However, these drugs may have serious side effects, such as increased susceptibility to infections and malignancies. Patients who underwent organ transplantation also have concerns about similar side effects related to the use of immunosuppressants. In particular, infection is an important

cause of mortality in patients after liver transplantation.^{15,16}

In this study, we investigated the safety of biological agents and small molecules for IBD treatment in patients treated with immunosuppressive drugs to prevent transplant rejection after organ transplantation.

MATERIALS AND METHODS

Study population

We reviewed the medical records of patients with IBD who underwent organ transplants at the Asan Medical Center between January 1, 1989 and December 31, 2021. Clinical data of these patients were collected from medical records until November 2022. The transplanted organs of 55 patients were as follows: heart, two patients; kidney and pancreas, one patient; kidney, 16 patients; and liver, 36 patients (Fig. 1). In addition, Fig. 1 shows the causes of transplantation. Among the patients who received biologics before transplantation, two underwent kidney and three underwent liver transplantation. Of these, two patients who underwent liver transplantation had liver cirrhosis and hepatitis caused by hepatitis B virus flare. Biological agents were discontinued after transplantation, and only anti-rejection treatment was maintained for these two patients. Therefore, they were excluded from the final analysis.

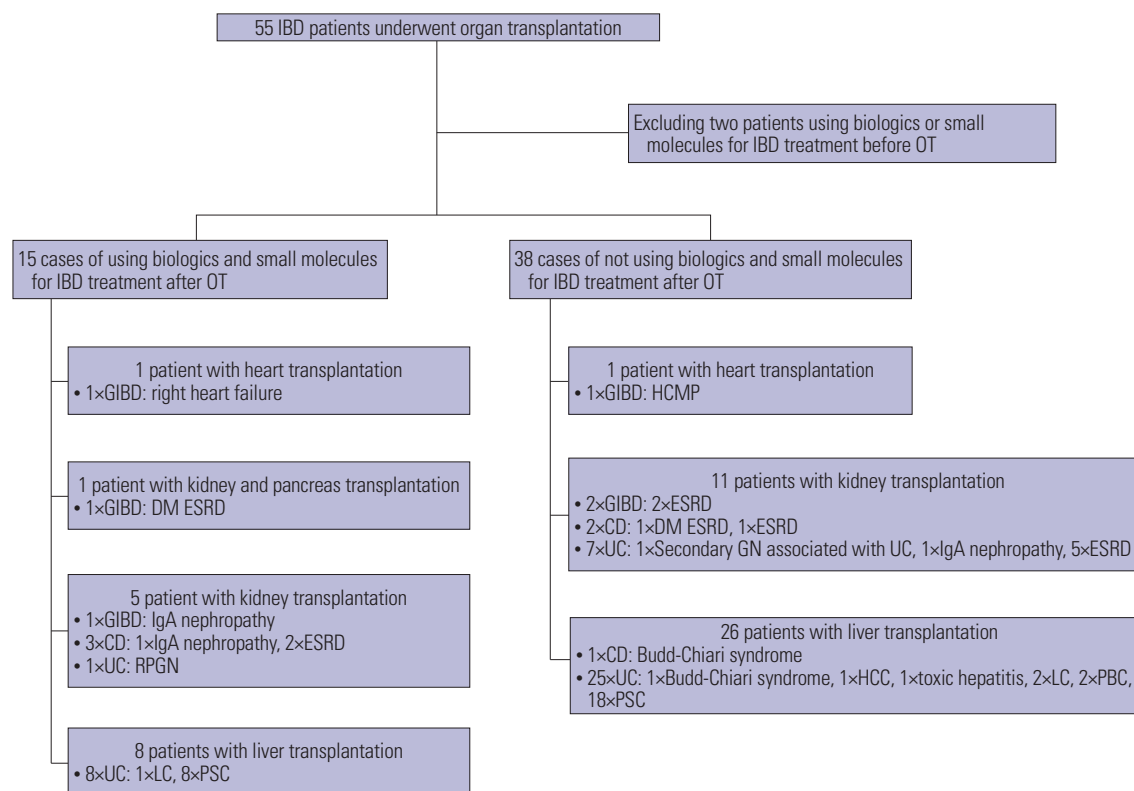


Fig. 1. Flow diagram of study patients and indication for organ transplantation. IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; GIBD, gastrointestinal Behçet's disease; PSC, primary sclerosing cholangitis; ESRD, end-stage renal disease; HCC, hepatocellular carcinoma; LC, liver cirrhosis; PBC, primary biliary cirrhosis.

Study design

The following parameters were evaluated: IBD treatment drugs, surgical history, malignant diseases, and types of immunosuppressants used administered after transplantation. Adverse events were also identified, including major severe infections requiring hospitalization, and mortality caused by concurrent IBD treatment after transplantation were also identified. The study endpoints were adverse events, such as severe infections requiring hospitalization, malignancy, and mortality in patients with IBD who received organ transplants. Patients who did not experience events beyond the end of follow-up or those lost to follow-up at some point were confirmed based on the point of follow-up. Major safety outcomes included severe infections and other adverse events requiring hospitalization, malignancy, and mortality. We compared these parameters between two groups: patients receiving biologics or small molecules (treatment group) and patients without those therapies (control group). Medical records were reviewed to determine the clinical outcomes. IBD activity after organ transplantation was clinically evaluated at the most recent time point during the study period. For clinical assessment of CD, CD Activity Index scores <150 defined CD in remission, 150–220 in mild disease, 220–450 in moderate disease, and >450 in severe disease.¹⁷ For UC, partial Mayo scores of 0 and 1 indicated UC in remission, 2–4 in mild disease, 5–6 in moderate disease, and >6 in severe disease.^{18,19} For GIBD, the disease activity index of intestinal Behçet's disease scores ≤19 defined GIBD as quiescent, 20–39 in mild disease, 40–74 in moderate disease, and ≥75 in severe disease.²⁰

Statistical analysis

Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as mean and standard deviation (SD). The chi-square test was used for categorical variables, and Student's t-test was used for continuous variables. Kaplan–Meier curve analysis with log-rank test was performed to compare the primary outcomes (infection, safety outcomes including malignancy, and other adverse events requiring hospitalization or death). $p < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 21.0, IBM Corp., Armonk, NY, USA).

Ethics statement

The Institutional Review Board (IRB) of Asan Medical Center approved this study (IRB no. 2022-0654).

RESULTS

We included 53 patients in this study (6 with CD, 41 with UC, and 6 with GIBD). Fig. 1 shows the classification of patients included in the study and the causes of organ transplantation.

Liver transplantation for PSC was the most common organ transplant, followed by ESRD-related kidney transplantation. Biologics or small molecules were administered to 15 patients to treat IBD before and after organ transplantation. Table 1 shows the characteristics of the patients. At the time of transplantation, the mean age of patients with IBD receiving biologics or small molecules was 38.4 years, and the mean age of patients with IBD not receiving those medications was 42.8 years. Among patients diagnosed with IBD before organ transplantation, three had CD and 27 had UC. The average duration between IBD diagnosis and transplantation was 82.5, 83.8, and 83.4 months in patients treated with biologics or small molecules, those not treated with biologics or small molecules, and in all patients included in this study, respectively.

The post-transplant antirejection treatment was based on tacrolimus, cyclosporine, mycophenolate mofetil, steroid, and everolimus. The biologics or small molecules for IBD treatment before and after organ transplantation were composed of infliximab (n=8); adalimumab (n=4); ustekinumab (n=3); vedolizumab (n=2); and tofacitinib (n=1) (Table 2). This included patients who sequentially switched to biologics or small molecules due to a loss of response.

Table 3 shows the type of infection and safety outcomes, including malignancy and other adverse events requiring hos-

Table 1. Baseline Characteristics of Patients Taking Biologics or Small Molecules for IBD

	Receiving biologics or small molecules for IBD (n=15)	Not receiving biologics or small molecules for IBD (n=38)	p value
Age at transplant, yr	38.40±11.14	42.76±13.38	0.269
Sex			0.065
Male	12 (80.0)	19 (50.0)	
Female	3 (20.0)	19 (50.0)	
Organ transplantation			0.328
Heart	1 (6.7)	1 (2.6)	
Kidney and pancreas	1 (6.7)	0 (0.0)	
Kidney	5 (33.3)	11 (28.9)	
Liver	8 (53.3)	26 (68.4)	
IBD			0.165
GI Behçet's disease	3 (20.0)	3 (7.9)	
Crohn's disease	3 (20.0)	3 (7.9)	
Ulcerative colitis	9 (60.0)	32 (84.2)	
IBD before OT			0.140
GI Behçet's disease	0 (0.0)	0 (0.0)	
Crohn's disease	2 (13.3)	1 (2.6)	
Ulcerative colitis	5 (33.3)	22 (57.9)	
Mean FU time since OT, months (SD)	124.60 (62.02)	144.82 (85.03)	0.408

FU, follow-up; GI, gastrointestinal; IBD, inflammatory bowel disease; OT, organ transplantation; SD, standard deviation. Data are presented as mean±SD or n (%).

Table 2. Immunosuppressive Regimens after Organ Transplantation and IBD Medication before and after Organ Transplantation (n=53)

	Value
Maintenance antirejection treatment after OT	
CSA/MMF	4
Tacro	17
Tacro/Evero	2
Tacro/MMF	13
Steroid/Tacro	5
Steroid/Tacro/AZA	2
Steroid/Tacro/Evero	1
Steroid/Tacro/MMF	6
Steroid/CSA	1
Steroid/CSA/MMF	2
IBD treatment before OT	
5-ASA	21
Immunomodulator (AZA/6-MP)	2
Infliximab	1
Adalimumab	2
IBD treatment after OT	
5-ASA	32
Immunomodulator (AZA/6-MP)	2
Infliximab	7
Adalimumab	2
Ustekinumab	3
Vedolizumab	2
Tofacitinib	1

AZA, azathioprine; CSA, cyclosporine; Evero, everolimus; IBD, inflammatory bowel disease; MMF, mycophenolate mofetil; OT, organ transplantation; Tacro, tacrolimus; 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine. Data are presented as n.

pitalization, between the two groups; the numbers of events and patients with events for each group are also shown. During the mean follow-up period of 119 months, the proportion of patients experiencing severe infections was significantly higher among those who were treated with biologics or small molecules than in those who were not (40.0% vs. 10.5%, $p=0.022$). Severe infections that required hospitalization included *Clostridioides difficile*, cytomegalovirus (CMV), or fungal infection, bacteremia, and cutaneous herpes zoster. However, other safety outcomes (i.e., malignancies, other adverse events including organizing pneumonia or hepatic failure, and death) were not different between the two groups ($p=0.662$, $p>0.999$, and $p=0.415$, respectively) (Table 3). Although not statistically significant, malignancy incidence and mortality were lower in the group treated with biologics or small molecules. Kaplan–Meier curve analysis revealed no significant differences in the safety outcome rate related to the use of biologics or small molecules ($p=0.305$) (Fig. 2).

Table 4 shows the prognosis of IBD. During follow-up, seven patients underwent bowel resections for IBD. The rate of bowel resection was not different between the two groups ($p=0.078$). IBD activity at the most recent follow-up also showed no significant difference between the two groups.

DISCUSSION

This study investigated the safety and therapeutic effect of bi-

Table 3. Outcomes of Organ Transplantation in Patients with IBD Based on Biologics or Small Molecules Used for IBD

	Receiving biologics or small molecules for IBD treatment (n=15)	Not receiving biologics or small molecules for IBD treatment (n=38)	p value
Number of patients with severe infection	6 (40.0)	4 (10.5)	0.022
Type of infection	3× <i>C. difficile</i> infection 2×Bacteremia 2×CMV infection 1×Fungal infection 1×Cutaneous H. zoster	1× <i>C. difficile</i> infection 1×Bacteremia 3×CMV infection	
Number of patients with malignancies	1 (6.7)	5 (13.2)	0.662
Type of malignancy	1×PTLD	2×PTLD 1×Burkitt lymphoma of terminal ileum 1×Pancreatic cancer 1×Acute lymphocytic leukemia 1×Papillary thyroid carcinoma	
Number of patients with other adverse events	1 (6.7)	2 (5.3)	>0.999
Other adverse events	1×Organizing pneumonia	2×Hepatic failure	
Patient mortality	1 (6.7)	7 (18.4)	0.415
Cause of death	1×Graft failure	3×Graft failure 1×Pancreatic cancer 1×Lymphoma 1×Recurred PSC 1×Unknown	

C. difficile, *Clostridioides difficile*; CMV, cytomegalovirus; H. zoster, Herpes zoster; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; PTLD, post-transplant lymphoproliferative disease.

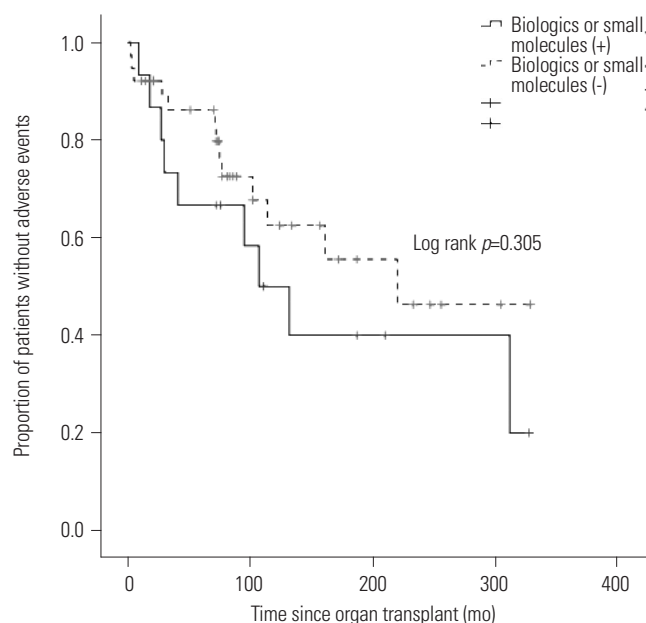


Fig. 2. Comparison of Kaplan–Meier curves (patients without adverse events) of patients with inflammatory bowel disease receiving biologics or small molecules and those of patients without those therapies.

Table 4. Bowel Resection and IBD Activity after Organ Transplantation Based on Biologics or Small Molecules Used for IBD

	Receiving biologics or small molecules for IBD treatment (n=15)	Not receiving biologics or small molecules for IBD treatment (n=38)	p value
Bowel resection after OT			0.078
Ileocecal resection	2 (13.3)	0 (0.0)	
Right hemicolectomy	1 (6.7)	1 (2.6)	
TPC with IPAA	0 (0.0)	3 (7.9)	
IBD activity at most recent FU			0.358
Remission	8 (53.3)	25 (65.8)	
Mild	7 (46.7)	11 (28.9)	
Moderate	0 (0.0)	2 (5.3)	
Severe	0 (0.0)	0 (0.0)	

FU, follow-up; IBD, inflammatory bowel disease; OT, organ transplantation; TPC with IPAA, total proctocolectomy with ileal pouch-anal anastomosis. Data are presented as n (%).

ologics and small molecules for IBD treatment in patients receiving immunosuppressive drugs to prevent transplant rejection after organ transplantation. A higher number of patients with UC underwent organ transplantation than patients with CD, possibly because the prevalence of PSC-associated liver transplantation was higher in patients with UC. Most patients underwent liver transplantation (n=34), followed by kidney (n=16), heart (n=2), and kidney and pancreas transplantation (n=1). Among them, 15 patients received treatment with biologics or small molecules after transplantation.

Infection was the leading cause of death in the first year after organ transplantation. Owing to the similarity of immunosuppressants administered, the causes of infection are similar

in various types of organ transplantation.^{21,22} Among previous studies that have reported PSC-associated liver transplantation outcomes in patients with IBD, infection was the most common adverse event. A recent meta-analysis on the safety of anti-tumor necrosis factor treatment after liver transplantation in patients with IBD did not show a significant increase in severe infection.²³ However, when our study compared the results of using biologics or small molecules among patients with IBD who underwent other solid organ transplantation, including liver transplantation, the rate of serious infection was significantly higher in these groups. The rate of *Clostridioides difficile* infection was high, followed by CMV infection and bacteremia, although the number of patients was small. Additionally, patients who had recurrent infections in the biologics or small molecules treatment group had poor IBD control and often had to change IBD treatment medications due to loss of response.

Recent meta-analyses do not suggest a clear association with safety outcomes, including malignancy and death after transplantation, in patients with IBD.^{24,25} Among 15 patients with IBD who received biologics or small molecules after transplantation in this study, one died due to graft failure during the study period, whereas one case of post-transplant lymphoproliferative disorder and one case of drug-related organizing pneumonia were identified. No colorectal cancer or IBD-related deaths were identified. Similar to the results of a previous study, this study did not show a significant difference between the two groups regarding the incidence of malignancies, death, and other safety outcomes requiring hospitalization. However, further studies are needed since cancer development after organ transplantation is a serious problem.

In this study, the prognosis of IBD was confirmed by bowel resection after organ transplantation and IBD activity at the most recent follow-up. No significant differences were observed between the two groups. A previous study has reported that the rate of bowel resection and discontinuation of biologics use in patients with IBD with organ transplantation were similar to those without organ transplantation.^{26–28}

Previous studies on immunosuppressive drugs after organ transplantation have reported that tacrolimus-included regimen was a risk factor for IBD recurrence after transplantation.^{4,29,30} Furthermore, a recent study has reported that patients with UC who were administered calcineurin inhibitors had higher incidence rate of infections requiring hospitalization, herpes zoster, and malignancies than those not administered these therapies.³¹ However, most patients in this study received tacrolimus, followed by tacrolimus and mycophenolate mofetil, as immunosuppressive agents after transplantation. No association with safety or prognosis was observed in patients with IBD after transplantation. No guidelines or general practices have been developed yet for the treatment of IBD in organ transplanted patients. As in this study, however, similar conclusions were confirmed in various studies including a recent meta-analysis, which reported that biologics therapy was well toler-

ated in patients with IBD who received organ transplants and used immunosuppressive drugs. Further studies will be needed to establish general practices for IBD patients who have received organ transplants in the future.

This study had some limitations. First, since the number of patients included in this study was small and patients with heterogeneous baseline characteristics were classified according to drug use, performing a subgroup analysis was challenging. Therefore, explaining the clinical significance of patients with IBD who received biologics or small molecules after organ transplantation is difficult. Second, a comparison with patients with IBD who did not receive organ transplantation was not performed; therefore, the explanation of whether additional use of immunosuppressive drugs after organ transplantation is associated with IBD activity is limited.

Despite these limitations, this is the first Asian study on the outcomes following solid organ transplantation in patients with IBD. In addition, our study was conducted in a single tertiary center in Korea, where organ transplantation is relatively common, and is expected to provide helpful information for treating transplanted patients with IBD. Furthermore, many studies on Western patients with IBD focus on single organ transplantation or only include patients with CD or UC. In this study, a wide range of patients with CD, UC, and GIBD who received solid organ transplantation, including liver, kidney, and heart, were identified. In particular, GIBD is rare in Western countries but relatively prevalent in Asia and Mediterranean regions; therefore, we focused on the inclusion of GIBD patients in this study.

In conclusion, the use of biologics or small molecules for patients with IBD who received organ transplantation did not show a significant difference in safety outcomes. However, paying attention to the possibility of serious infections is still necessary. Additional large-scale studies on the safety and prognosis of biologics or small molecules treatment after organ transplantation in patients with IBD are needed.

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AUTHOR CONTRIBUTIONS

Conceptualization: Sang Hyoung Park. **Data curation:** Ga Hee Kim. **Formal analysis:** Ga Hee Kim. **Funding acquisition:** Sang Hyoung Park. **Investigation:** Ga Hee Kim. **Methodology:** Sang Hyoung Park and Ga Hee Kim. **Project administration:** Sang Hyoung Park. **Resources:** all authors. **Software:** Ga Hee Kim. **Supervision:** Sang Hyoung Park, Seung Wook Hong, Sung Wook Hwang, Dong-Hoon Yang, Byoung Duk Ye, Jeong-Sik Byeon, Seung-Jae Myung, and Suk-Kyun Yang. **Val-**

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