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ORIGINAL RESEARCH

Safety and Effectiveness of SB2 (Infliximab Biosimilar) in Adult Patients with Immune-Mediated Inflammatory Diseases: A Post-Marketing Surveillance in Korea

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ABSTRACT

Introduction: SB2 is a biosimilar of infliximab (IFX), which is approved for rheumatoid arthritis (RA), ankylosing spondylitis (AS), adult and pediatric Crohn's disease (CD), adult and pediatric ulcerative colitis (UC), psoriatic arthritis (PsA), and plaque psoriasis (PsO). The drug approval process in Korea includes post-marketing surveillance (PMS) studies to re-examine the safety and effectiveness of approved new medications.

Methods: This was a prospective, multi-center, open-label, observational, phase 4 PMS study of IFX-naïve patients or patients switched from reference IFX or another IFX-biosimilar to SB2 in all approved indications. The primary end-

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point was to evaluate the safety of SB2 reported as adverse events (AEs) and adverse drug reactions (ADRs). The secondary endpoint was to evaluate the effectiveness measured as investigators' overall effectiveness assessment, categorized as improved, stable, or worsened. Furthermore, disease-specific activity scores were collected for each indication [28-joint Modified Disease Activity Score (DAS28) for RA, Korean Bath Ankylosing Spondylitis Disease Activity Index (KBASDAI), Crohn's Disease Activity Index (CDAI), and Full Mayo Score for UC].

Results: In the safety and effectiveness analysis, 180 and 128 patients were included, respectively. Most patients (83.9%) were IFX-naïve patients and 16.1% were switched patients. RA (48.9%) and AS (31.1%) were the most frequent indications. Overall, 23 (12.8%) patients reported AEs and 14 (7.8%) patients reported ADRs. Serious adverse events (SAEs) were reported by 3 (1.7%) patients. As per investigators' overall effectiveness assessments, SB2 was effective in 94.6% (105/111) of IFX-naïve patients and 82.4% (14/17) of switched patients. In IFX-naïve patients, disease activity scores decreased significantly from baseline to week 30 (week 24 for AS); mean (SD) changes of disease scores for each indication were DAS28 − 1.9 (0.79) for RA, KBASDAI − 3.8 (1.68) for AS, CDAI − 200.4 (112.47) for CD, and Full Mayo Score − 6.6 (2.92) for UC. The persistence rate of SB2 treatments was 88.3% with median treatment duration of 30.1 weeks.

Conclusion: This PMS study of the IFX-biosimilar SB2 in Korea confirmed the safety and effectiveness of SB2 in major indications.

Keywords: Remaloce; SB2; Biosimilar; TNF inhibitor; Real world evidence; Rheumatoid arthritis; Ankylosing spondylitis; Crohn's disease; Ulcerative colitis; Psoriatic arthritis

Key Summary Points

SB2 is a biosimilar of infliximab, a monoclonal anti-TNFα antibody used to treat immune-mediated inflammatory diseases (rheumatoid arthritis, ankylosing spondylitis, adult and pediatric Crohn's disease, adult and pediatric ulcerative colitis, psoriatic arthritis, and psoriasis).

This study collected real-world evidence (RWE) about the safety and effectiveness of SB2 across approved indications in Korea.

SB2 was well tolerated (12.8% patients reporting AEs) and effective in both IFX-naïve and switched patients (94.5% of IFX naïve patients had their disease activity improved and 82.4% of switched patients improved or remained stable).

This post-marketing surveillance study of the IFX-biosimilar SB2 in Korea confirmed the safety and effectiveness of SB2 in major indications.

INTRODUCTION

Infliximab (IFX), a tumor necrosis factor alpha (TNF-α) inhibitor, is a monoclonal antibody (mAb) that binds to soluble and transmembrane TNF-α and thereby neutralizes the biological activity of TNF-α [1, 2]. After first approvals in 1998 and 1999 in the United States (US) and the European Union (EU), respectively [3, 4], IFX has become a mainstay in the treatment of rheumatic and other inflammatory diseases [5]. SB2 (Samsung Bioepis, Incheon, Republic of Korea) is a biosimilar of IFX that is approved in the EU (Flixabi®), the US (Renflexis®) and Korea (Remaloce®) in all indications as reference infliximab, comprising rheumatoid arthritis (RA), Crohn's disease (CD), ulcerative colitis (UC), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis (PsO).

Biosimilars are biological products that are highly similar to an already approved reference product. The development and approval of biosimilars follows stringent regulatory pathways which were implemented in the EU in 2004 and in the US in 2010 to ensure that there are no clinically meaningful differences between a biosimilar and its reference product in terms of quality characteristics, biological activity, effectiveness, and safety, including immunogenicity [6, 7]. In general, comparability of a biosimilar and its reference product is assessed in a stepwise process comprised of extensive in vitro quality studies to demonstrate high similarity in physicochemical properties, non-clinical comparisons, and clinical head-to-head clinical data in a study population that is relevant and most sensitive for detecting any potential differences between the biosimilar and its reference product [8].

In Korea, post-marketing surveillance (PMS) studies are part of the drug approval process by the Korean Ministry of Food and Drug Safety (MFDS), allowing re-examination of the safety and effectiveness results of new medications that are already approved and on the market for a designated period (4–6 years) [9]. The objective of this PMS study was to evaluate the safety and effectiveness of Remaloce® (hereinafter referred to as "SB2") in actual clinical practice in Korea. In addition, the safety and effectiveness of SB2 were analyzed in patients who were IFX-naïve or switched from another IFX-product to SB2.

METHODS

Study Design

This was a prospective, multi-center, open-label, observational, phase 4 PMS study conducted in 10 centers with 12 principal investigators in Korea between December 4, 2015 and December 3, 2019. The final study protocol and the informed consent form were approved by the local Institutional Review Boards of all the study sites (supplemental Table S1), and the study was conducted in accordance with applicable local regulatory requirements and laws, the Declaration of Helsinki (1996), and the International Council for Harmonization Good Clinical Practice guidelines. Written informed consent was obtained from each subject before enrollment.

Study Population

Upon agreement with the MFDS, the target sample size was set to 160 or more patients to be enrolled within the official re-examination period of 4 years after domestic approval in South Korea. The study prospectively enrolled all consecutively presenting patients using SB2 according to the indications and contraindications of SB2, as per the approved Korean label. Accordingly, the population was comprised of IFX-naïve patients or patients switched from reference IFX or another IFX-biosimilar to SB2, with RA, AS, CD, UC, PsA, or PsO. CD and UC also included pediatric patients aged 6–17 years. Only patients who signed the informed consent form and were willing to participate in the study were enrolled. Patients with contraindications as per the label, i.e., a medical history of hypersensitivity to study drug ingredients, excipients or murine proteins, tuberculosis, severe or opportunistic infections, and moderate to severe heart failure (New York Heart Association NYHA Class III/IV), were excluded.

Patient Management and Outcome Assessment

The investigator determined decisions on diagnostic tests and treatments according to their routine practice. An overview of the doses of SB2 and the treatment schedules for each indication is shown in supplemental Table S2. In general, treatment could be combined with a corticosteroid or an immunosuppressant as per the investigator's discretion.

The primary endpoint was to evaluate the safety of SB2 reported as incidences of adverse events (AEs) and adverse drug reactions (ADRs) for each indication. The secondary endpoint was to evaluate effectiveness reported as investigators' overall effectiveness assessment, categorized as improved, stable (if the disease

activity remained unchanged), or worsened. Disease activity scores were also collected to measure effectiveness, i.e., 28-joint Modified Disease Activity Score (DAS28) for RA, Korean Bath Ankylosing Spondylitis Disease Activity Index (KBASDAI) for AS, Crohn's Disease Activity Index (CDAI) for CD, Full Mayo Score for UC, number of joints with tenderness and edema for PsA, and Psoriasis Area and Severity Index (PASI) for PsO.

Use and administration of SB2 and safety were assessed at baseline (Week 0) and at Weeks 2, 6, 12–14, 18–22, and 24–30 for naïve patients, and at Weeks 2, 8, 14–16, 20–24, and 26–32 for switched patients. Investigator's overall effectiveness assessment was solely evaluated by the principal investigator at the last follow-up visit. DAS28 was measured at Baseline and Week 30 (naïve patients) or Week 32 (switched patients). KBASDAI was measured at Baseline and Weeks 6 and 24–30 (naïve patients) or Weeks 8 and 28–32 (switched patients). Measurement of disease activity indices in patients with fistulizing CD, UC, PsA, or PsO were planned at Baseline and Weeks 14 and 30 (naïve patients) or Weeks 16 and 32 (switched patients). In patients with moderately to severely active CD, measurement of CDAI was planned at Baseline and Weeks 2 and 30 (naive) or Week 32 (switched patients).

Safety Assessment

An AE refers to any undesirable and unintended sign, symptom, or disease that occurs during the administration and use of drugs, and does not necessarily have to have a causal relationship to the relevant drug. An AE whose causal relationship to the administered drug cannot be ruled out is called an adverse drug reaction (ADR). AEs were coded using the Medical Dictionary for Regulatory Affairs, version 22.1, analyzed for seriousness, severity, causal relationship to SB2, and outcome, and summarized as overall incidence with 95% confidence interval (CI) of all AEs and ADRs.

Effectiveness Assessment

Treatment outcomes were evaluated at the last follow-up visit compared to baseline and categorized into three groups: improved, stable, or worsened. Stable in switched patients was defined as an outcome with response which remained unchanged after switching to SB2.

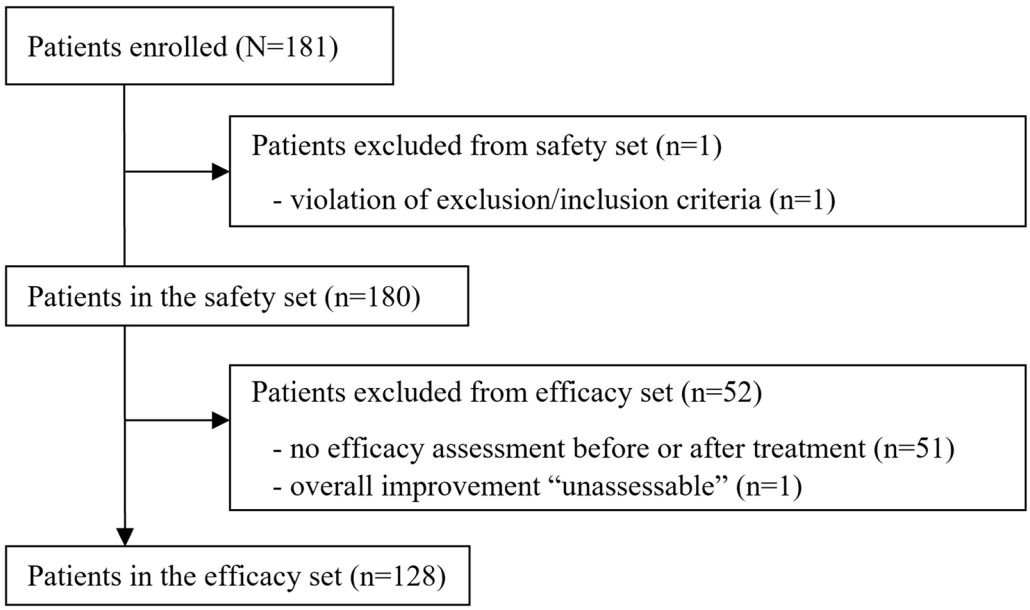

Fig. 1 Patient disposition

Table 1 Baseline demographics and disease characteristics

Category	Overall $N = 180$		Naïve $N = 151$		Switched $N = 29$	
Sex, *n* (%)						
Male	85	(47.2)	66	(43.7)	19	(65.5)
Female	95	(52.8)	85	(56.3)	10	(34.5)
Age (years), mean (SD)	49.3	(15.56)	50.6	(15.21)	42.6	(15.89)
BMI (kg/m^2), mean (SD)	23.2	(3.50)	23.2	(3.57)	23.3	(2.99)
BMI group, *n* (%)						
Normal	88	(48.9)	78	(51.7)	10	(34.5)
Overweight	31	(17.2)	26	(17.2)	5	(17.2)
Obese	47	(26.1)	42	(27.8)	5	(17.2)
Diagnosis, *n* (%)						
RA	88	(48.9)	82	(54.3)	6	(20.7)
AS	56	(31.1)	46	(30.5)	10	(34.5)
CD	18	(10.0)	10	(6.6)	8	(27.6)
UC	16	(8.9)	12	(7.9)	4	(13.8)
PsA	2	(1.1)	1	(0.7)	1	(3.4)
Disease duration (years), mean (SD)	5.9	(6.21)	5.4	(6.10)	8.7	(6.17)
Previous biologics, *n* (%)						
Yes	52	(28.9)	23	(15.2)	29	(100.0)
No	128	(71.1)	128	(84.8)	0	(0.0)
Previous immunosuppressant, *n* (%)						
Yes	107	(59.4)	102	(67.6)	5	(17.2)
No	73	(40.6)	49	(32.5)	24	(82.8)
Comorbidity, *n* (%)						
Liver disease	6	(0.6)	5	(3.3)	1	(3.5)
Kidney disease	1	(3.3)	1	(0.7)	0	(0.0)
Other	114	(63.3)	98	(64.9)	16	(55.2)
Smoking history, *n* (%)						
Yes	40	(22.2)	32	(21.2)	8	(27.6)
No	140	(77.8)	119	(78.8)	21	(72.4)

Table 1 continued

Category	Overall*N* = 180		Naïve*N* = 151		Switched*N* = 29	
Disposition, *n* (%)						
Inpatient	26	(14.4)	23	(15.2)	3	(10.3)
Outpatient	154	(85.6)	128	(84.8)	26	(89.7)
Rheumatoid factor for RA, *n*/*N*' (%)						
Positive	77/87	(88.5)	75/82	(91.5)	2/5	(40.0)
Negative	10/87	(11.5)	7/82	(8.5)	3/5	(60.0)
Not measured	0	(0.0)	0	(0.0)	0	(0.0)
Rheumatoid factor for AS, *n*/*N*' (%)						
Positive	5/48	(10.4)	5/42	(11.9)	0	(0.0)
Negative	42/48	(87.5)	36/42	(85.7)	6/6	(100.0)
Not measured	1/48	(2.1)	1/42	(2.4)	0	(0.0)
Rheumatoid factor for PsA, *n*/*N*' (%)						
Positive	0	(0.0)	0	(0.0)	0	(0.0)
Negative	2/2	(100.0)	1/1	(100.0)	1/1	(100.0)
Not measured	0	(0.0)	0	(0.0)	0	(0.0)
Disease location for CD, *n*/*N*' (%)						
L2	1/18	(5.6)	1/10	(10.0)	0/8	(0.0)
L1, L3, or combined and other	15/18	(83.3)	8/10	(80.0)	7/8	(87.5)
Disease location for UC, *n*/*N*' (%)						
E1	1/16	(6.3)	0/12	(0.0)	1/4	(25.0)
E2, E3	12/16	(75.0)	9/12	(75.0)	3/4	(75.0)

N number of patients in the safety analysis set, *N*' number of patients in each indication, *n* number of patients within the category, *AS* ankylosing spondylitis, *min* minimum, *max* maximum, *BMI* body mass index, *CD* Crohn's disease, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SD* standard deviation, *UC* ulcerative colitis

Stable in naïve patients was defined as an outcome with no response and remaining unchanged after SB2 initiation in naïve patients.

In naïve patients, differences in disease activity scores from baseline to the last follow-up visit were calculated. Among IFX-naïve patients with inflammatory bowel disease (IBD), clinical response was defined as reduction of CDAI by > 70 points in CD patients and reduction of Partial Mayo Score by ≥ 3 points in UC patients. Clinical remission at week 30 was defined as CDAI score ≤ 150 or Partial Mayo score ≤ 2, respectively.

Persistence Rate

The persistence rate of SB2 in this study was assessed by Kaplan–Meier analysis with 95% CI. Based on the Kaplan–Meier analysis results, a survival plot for persistence rate of SB2 by

Table 2 Incidence of AE and ADR

	Naïve ($N = 151$)		Switch ($N = 29$)		Overall ($N = 180$)	
	n (%), [E]	95% CI	*n* (%), [E]	95% CI	*n* (%), [E]	95% CI
AE	17 (11.3), [30]	[6.70, 17.41]	6 (20.7), [8]	[7.99, 39.72]	23 (12.8), [38]	[8.28, 18.55]
ADR	12 (7.9), [16]	[4.17, 13.47]	2 (6.9), [4]	[0.85, 22.77]	14 (7.8), [20]	[4.32, 12.71]
SAE	2 (1.3), [6]	[0.16, 4.70]	1 (3.5), [1]	[0.09, 17.76]	3 (1.67), [7]	[0.35, 4.79]
Serious ADR	0 (0.0), [0]	N/A	1 (3.5), [1]	[0.09, 17.76]-	1 (0.56), [1]	[0.01, 3.06]

ADR adverse drug reaction, *AE* adverse event, *CI* confidence interval, *E* number of events, *n* number of patients with adverse event(s), *N* number of patients in safety analysis set, *SAE* serious adverse event

Table 3 Investigator's overall effectiveness assessment by indication

			Effective		Ineffective	
			Improved	Stable[a]	Stable[b]	Worsened
Overall	Naïve ($N = 111$)	*n* (%)	105 (94.6)	n/a	2 (1.8)	4 (3.6)
($N = 128$)	Switch ($N = 17$)	*n* (%)	11 (64.7)	3 (17.7)	n/a	3 (17.7)
	Overall ($N = 128$)	*n* (%)	119 (93.0)		9 (7.0)	
RA ($N = 51$)	Naïve ($N = 49$)	*n* (%)	48 (98.0)	n/a	1 (2.0)	0 (0.0)
	Switch ($N = 2$)	*n* (%)	2 (100.0)	0 (0.0)	n/a	0 (0.0)
	Overall ($N = 51$)	*n* (%)	50 (98.0)		1 (2.0)	
AS ($N = 46$)	Naïve ($N = 42$)	*n* (%)	40 (95.2)	n/a	1 (2.4)	1 (2.4)
	Switch ($N = 4$)	*n* (%)	3 (75.0)	0 (0.0)	n/a	1 (25.0)
	Overall ($N = 46$)	*n* (%)	43 (93.5)		3 (6.5)	
CD ($N = 16$)	Naïve ($N = 10$)	*n* (%)	8 (80.0)	n/a	2 (20.0)	0 (0.0)
	Switch ($N = 6$)	*n* (%)	4 (66.7)	0 (0.0)	n/a	2 (33.3)
	Overall ($N = 16$)	*n* (%)	12 (75.0)		4 (25.0)	
UC ($N = 14$)	Naïve ($N = 10$)	*n* (%)	9 (90.0)	n/a	0 (0.0)	1 (10.0)
	Switch ($N = 4$)	*n* (%)	1 (25.0)	3 (75.0)	n/a	0 (0.0)
	Overall ($N = 14$)	*n* (%)	13 (92.9)		1 (7.1)	
PsA ($N = 1$)	Naïve ($N = 0$)	*n* (%)	0 (0.0)	n/a	0 (0.0)	0 (0.0)
	Switch ($N = 1$)	*n* (%)	1 (100.0)	0 (0.0)	n/a	0 (0.0)
	Overall ($N = 1$)	*n* (%)	1 (100.0)		0 (0.0)	

AS ankylosing spondylitis, *CD* Crohn's disease, *n* number of patients with clinical assessment, *N* number of patients in the effectiveness analysis set, *n/a* not applicable, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *UC* ulcerative colitis

[a]Switched patients who had clinical response with reference IFX that sustained after switch to SB2

[b]Naïve patients who did not have clinical response before starting SB2 and remained unchanged after SB2 initiation

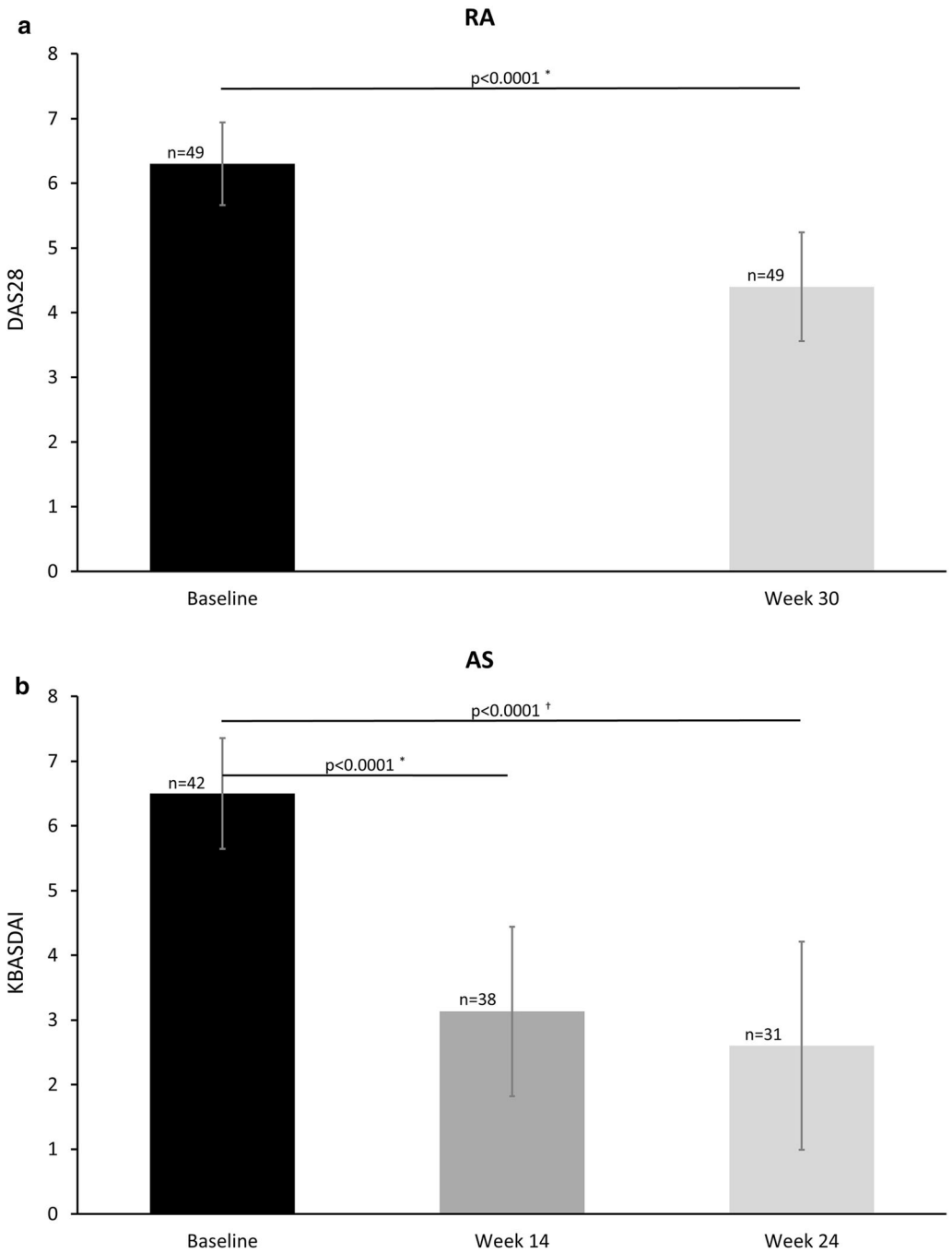

Fig. 2 Mean (SD) disease activity scores of naïve patients with **a** RA, **b** AS, **c** CD, **d** UC. * paired *t* test; †Wilcoxon signed-rank test. *AS* ankylosing spondylitis, *CD* Crohn's disease, *CDAI* Crohn's disease activity index, *DAS28* modified disease activity score, *KBASDAI* Korean Bath ankylosing spondylitis disease activity index, *RA* rheumatoid arthritis, *UC* ulcerative colitis

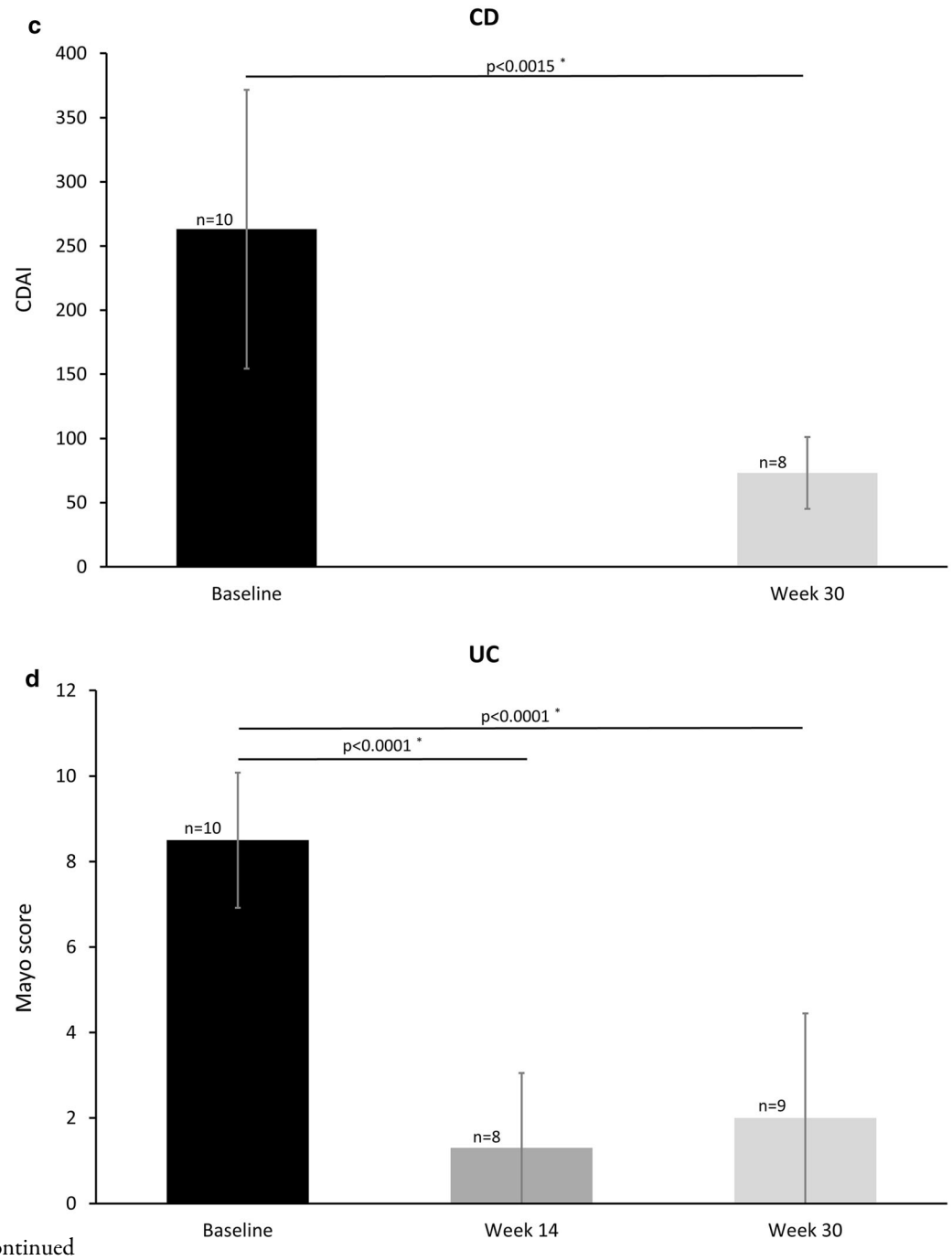

Fig. 2 continued

indication was provided. Patients who did not complete Week 30 for the naïve and Week 32 for the switch groups (Week 24 for naïve and Week 26 for switched patients with AS) due to any reason except the study termination were considered as discontinued patients. Reasons for discontinuation were not reported. Patients who completed or discontinued due to the study termination were censored at patients' last visit date.

Table 4 Treatment duration and discontinuation rate of SB2 treatment by indication

	RA $N = 88$	AS $N = 56$	PsA $N = 2$	CD $N = 18$	UC $N = 16$	Overall $N = 180$
Median treatment duration (weeks)	30.4	30.3	21.5	27.1	24.9	30.1
Number of patients discontinued, n/n' (%)	12/88 (13.6)	6/56 (10.7)	1/2 (50.0)	2/18 (11.1)	0/16 (0.0)	21/180 (11.7)
Number of patients censored, n/n' (%)	76/88 (86.4)	50/56 (89.3)	1/2 (50.0)	16/18 (88.9)	16/16 (100.0)	159/180 (88.3)
Discontinuation rate						
At Week 16, (%) [95% CI]	7.2 [1.64, 12.76]	6.0 [0.00, 12.52]	50.0 [0.00, 100.0]	6.3 [0.00, 18.11]	0.0 [0.00, 0.00]	6.6 [2.81, 10.34]
At Week 32, (%) [95% CI]	15.1 [6.73, 23.40]	10.6 [1.76, 19.36]	50.0 [0.00, 100.0]	14.8 [0.00, 34.01]	0.0 [0.00, 0.00]	12.9 [7.38, 18.36]

AS ankylosing spondylitis, *CD* Crohn's disease, *N* total number of patients in safety set, *n'* number of patients included in the summary statistics, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *UC* ulcerative colitis

Statistical Analysis

Patient demographics and disease characteristics are summarized in three groups: IFX-naïve, switched to SB2, and overall. Continuous variables are presented with descriptive statistics [mean, standard deviation (SD)]. Qualitative variables are summarized by frequency and percentages. Differences in incidences of AEs, ADRs, and effectiveness results by factor were analyzed using a chi-square test or Fisher's exact test. Differences between disease activity score from baseline to following visits were analyzed by paired *t* test or Wilcoxon test. Clinical response and remission for IFX-naïve patients with IBD are summarized by percentages.

The safety analysis set included all patients who have received at least one dose of SB2 without protocol violation, and for whom follow-up was performed in the case of early termination. The effectiveness analysis set included all patients for whom effectiveness has been assessed at least once before and at least once after the SB2 administration.

All analyses were carried out using SAS (v.9.4 or higher).

RESULTS

Patient Disposition and Baseline Characteristics

A total of 181 patients were enrolled, of which 1 patient was excluded due to protocol violation, 180 patients were included in the safety analysis set, and 128 patients in the effectiveness analysis set (Fig. 1). Patient baseline demographics and disease characteristics for the safety analysis set are summarized in Table 1. The majority of patients (151, 83.9%) were IFX-naïve patients and 29 (16.1%) were switched to SB2 from either reference IFX or another IFX-biosimilar (Table 1). The most frequent indications were RA (48.9%) and AS (31.1%). Mean (SD) age was 49.3 (15.56) years and mean duration of the disease was 5.9 (6.21) years. The previous use of immunosuppressant was recorded in 107 (59.4%) patients and the majority of RA patients (73, 83.0%) were on previous immunosuppressant.

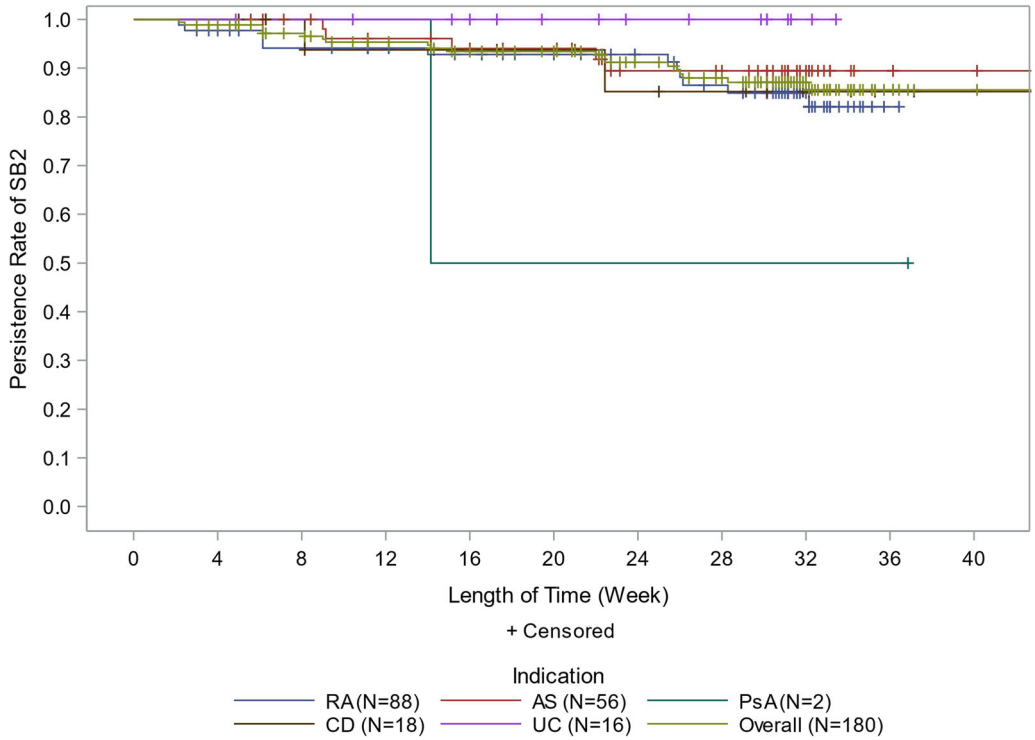

Fig. 3 Kaplan–Meier analysis for persistence rate of SB2 by indication. *AS* ankylosing spondylitis, *CD* Crohn's disease, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *UC* ulcerative colitis

Safety Evaluation

Overall, 23 (12.8%) patients reported 38 AEs (Table 2), with pruritus being the most common AE (3.3% of patients, 6 cases), followed by paresthesia (2.2%, 4 cases), vomiting (1.1%, 2 cases), and headaches (1.1%, 2 cases) (supplemental Table S3). ADRs were reported by 14 (7.8%, 20 cases) patients, with the cases of pruritus and paresthesia being considered ADRs. Three (1.7%) patients reported 7 serious adverse events (SAEs), and 1 event, colitis, was reported as an ADR (Table 2). Eight (4.4%, 10 cases) patients reported infusion-related reactions (pain, pruritus, rash, and urticaria) or hypersensitivity. A detailed overview of incidence rates of AEs and ADRs is shown in supplemental Table S3. The incidence rates of AEs and ADRs in 100 patient-years are described in supplemental Table S4.

Across indications, AEs were reported for 13.6% of patients with RA, 12.5% of patients with AS, 11.1% of patients with CD, and 6.3% of patients with UC. There were no statistically significant differences in the incidence of AEs depending on sex, age or diagnosis.

Nine AEs (1 case each) that were not reflected in the Korean product information (i.e., unexpected AEs) were reported for 8 (4.4%) patients, and comprised anal fissure, colitis, duodenal ulcer, tinnitus, biliary cirrhosis, encephalitis, decreased appetite, polyarthritis, and productive cough.

Effectiveness Evaluation

Overall, SB2 was effective in 93.0% of patients including both naïve and switched based on the investigator's overall effectiveness assessment. Disease activity was improved in 94.6% of IFX-naïve and improved or remained stable in 82.4% of switched patients (64.7% improved and 17.7% remained stable) (Table 3). Across indications, SB2 was effective in 98.0% of patients with RA, 93.5% of patients with AS,

75.0% of patients with CD and 92.9% of patients with UC (Table 3).

Among IFX-naïve patients, mean (SD) changes of disease activity scores from baseline were − 1.9 (0.79; $p < 0.0001$) in DAS28 for RA patients (Week 30), − 3.8 (1.68; $p < 0.0001$) in KBASDAI for AS patients (Week 24), − 200.4 (112.47; $p = 0.0015$) in CDAI for CD patients (Week 30), and − 6.6 (2.92; $p = 0.0001$) in Full Mayo Score for UC patients (Week 30) (Fig. 2). In IFX-naïve patients with IBD, 7/8 (87.5%) of CD and 8/9 (88.9%) of UC patients achieved clinical response within the 30-week study period. All (100%) patients with CD and 7/9 (77.8%) patients with UC were in remission.

Persistence Rate Evaluation

Of 180 patients, 101 completed the study and 58 patients did not complete the study due to study termination. Overall, the persistence rate of SB2 treatments was 88.3% (159/180) and median treatment duration was 30.1 weeks (Table 4) (Fig. 3). Reported Week 32 study persistence rates across all indication were 87.1% and 84.9%, 89.4%, 50%, 85.2%, and 100% in patients with RA, AS, PsA, CD, and UC, respectively.

DISCUSSION

This prospective, multi-center, observational PMS study in a Korean population confirmed the safety and effectiveness of the IFX-biosimilar SB2 in routine clinical practice across indications.

The proportions of patients with AEs (12.8%), ADRs (7.8%), and SAEs (1.7%) in this observational study were lower than those among SB2-treated patients in the pivotal phase III study in patients with severe RA receiving concomitant methotrexate (57.6%, 21.4%, and 9.0%, respectively) [10]. This difference may be attributed to the different patient populations as this PMS study included patients with other indications. Furthermore, patients in interventional clinical studies are in general more closely monitored than in real-world practice, which may result in higher rates of reported AEs. Compared to available RWE data of SB2 in different populations and different switching schemes reporting up to 27.8% with AEs and up to 20.7% with SAEs, the proportions in this study are well within and below the range reported in RWE [11–15].

This PMS study reported 4.4% incidence of infusion-related reaction or hypersensitivity, which is lower compared to other reference infliximab RWE while the design of the study was different. RWE of IFX reference product mainly originate from registries that have been initiated in relation to the manufacturer's post-marketing commitments [5]. Among those with comparable patient populations and reported outcomes, RemiTRAC, a Canadian registry of 1632 patients with different indications (40.1% RA, 17.5% AS, 5.5% PsA, 25.5% IBD; 65.5% infliximab-naïve), reported one or more infusion reaction in 13.5% of infliximab-naïve and 10.2% infliximab-experienced patients [16]. BIOBADASER, a registry of patients with chronic inflammatory rheumatic diseases in Spain that included 2504 infliximab-naïve patients, reported 13 infusion or injection site reactions per 1000 patient years [17]. Two other registries, ENCORE and TREAT, included only CD patients. ENCORE reported infusion-related reaction or hypersensitivity for 11.2% of infliximab-naïve and 9.4% of switched patients [18]. TREAT reported infusion reactions for 3.0% of all infusions [19].

Overall, this study showed 93.0% effectiveness of SB2 in IFX-naïve and switched patients, ranging from 75.0% in patients with CD to 98.0% in patients with RA. Even among patients who had already received another IFX product, disease activity scores improved in 64.7% of patients and remained stable in 17.7% of patients after the switch to SB2. Among IFX-naïve patients, disease activity scores significantly improved across indications from baseline to Week 30 (RA, CD, UC) or Week 24 (AS). Among the small samples of naïve patients with CD ($n = 8$) or UC ($n = 9$), almost all achieved clinical response and were in remission at Week 30 of SB2 treatment.

The effectiveness results among patients with different indications in this study are comparable to reference IFX and other SB2 RWE

while limited number of patients in some indications are evaluated. The 1.9-point reduction of the DAS28 score at Week 30 among naïve patients with RA in this study compares well with 2.0-point reduction (baseline to Week 30) in an observational study of reference IFX in 50 patients with RA [20]. An ongoing non-interventional study of SB2 (PERFUSE) reported a 1.1-point decrease among 22 naïve patients with RA at its 12-month analysis [13].

Among naïve patients with AS, the decrease in the Korean BASDAI (− 3.1 at Week 6) is comparable to the 3.4-point reduction of BASDAI at Week 14 in an observational study of reference IFX in 21 patients with AS [21].The 3.8-point reduction of Korean BASDAI at Week 30 in this study is similar to the results in 81 SB2-treated naïve patients with AS in the PERFUSE study, a 2.3-point reduction at its 12-months analysis [13].

The response and remission rates of this study at Week 30 among naïve patients with CD and UC are comparable to that of reference IFX and other SB2 RWE. In this study, the response rates were 87.5% in CD patients and 88.9% in UC patients. All (100%) patients with CD and 77.8% patients with UC were in remission. A meta-analysis of nine observational studies of patients with IBD who were retreated with reference IFX due to relapse after treatment discontinuation reported a pooled clinical remission rate of 85% for induction treatment and 73% for maintenance treatment [22]. A retrospective study of 18 patients with moderate to severe UC who were treated with reference IFX reported response and remission rates of 94.4% and 77.8% at Week 12 and 76.5% and 70.6% at Week 52 [23]. An observational study of 363 CD patients who received induction therapy with reference IFX in Hungary reported overall response and remission rates of 86.2% and 46.0%, respectively [24]. In the SPOSIB study, 66.1% of IBD patients who were naïve to SB2 and anti-TNFs were in steroid-free remission after 8 weeks.

The study presented here provides the first RWE on treatment outcomes of SB2 in Korea. However, it still has limitations due to the open-label, observational nature of the study and clinical practice being different across countries. Furthermore, differences between indications and SB2 naïve and switch patients could not be detected because of the low number of patients, the unequal distribution of the patients for those subgroups, and the short follow-up period.

CONCLUSIONS

This is the first RWE data on the safety and effectiveness of the IFX-biosimilar SB2 in Korea. SB2 was well tolerated throughout the study. The study results establish that SB2 is an effective treatment in clinical practice in Korea and are comparable to RWE of reference IFX and other SB2 RWE data.

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Compliance with Ethics Guidelines. The final study protocol and the informed consent form were approved by the local Institutional Review Boards (IRBs) of all study sites (supplemental Table S1). This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (1996) and that are consistent with the latest International Council for Harmonization Good Clinical Practice guidelines (ICH E6) and applicable local regulatory requirements and laws. The nature and purpose of the study was fully explained to each subject and written informed consent was obtained from each subject before the subject was entered into the study. The consent documents for the study were reviewed and approved by the appropriate Independent Ethics Committee prior to use.

Data Availability. Upon request, and subject to certain criteria, conditions, and exceptions, Samsung Bioepis will provide access to individual de-identified participant data to researchers whose proposals meet the research criteria and other conditions and for which an exception does not apply. Proposals should be directed to the corresponding author. For access, data requestors must enter into a data access agreement with Samsung Bioepis.

REFERENCES

1. Macaluso FS, Cummings JF, Atreya R, Choi J, Orlando A. A systematic review on infliximab biosimilar SB2: from pre-clinical data to real-world evidence. Expert Opin Biol Ther. 2022;22:203–23.

2. Valle E, Gross M, Bickston SJ. Infliximab. Expert Opin Pharmacother. 2001;2:1015–25.

3. Janssen Biologics. Remicade - Prescribing information 1998 [Available from: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf.

4. Janssen Biologics. Remicade - Summary of Product Characterisitcs 1999 [Available from: https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information_en.pdf.

5. Melsheimer R, Geldhof A, Apaolaza I, Schaible T. Remicade(®) (infliximab): 20 years of contributions to science and medicine. Biologics. 2019;13:139–78.

6. European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies—non-clinical and clinical issues 2012 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similarbiological-medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf.

7. US Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product 2015 https://www.fda.gov/media/82647/download.

8. Kim H, Alten R, Avedano L, et al. The future of biosimilars: maximizing benefits across immune-mediated inflammatory diseases. Drugs. 2020;80:99–113.

9. Ministry of Food and Drug Safety. Safety Control after Releasing Medicinal Products etc. - Guideline on re-examination affairs of new drugs etc. 2018 https://www.mfds.go.kr/eng/brd/m_18/down.do?brd_id=eng0003&seq=71469&data_tp=A&file_seq=1.

10. Choe JY, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76:58–64.

11. Macaluso FS, Fries W, Viola A, et al. The SPOSIB SB2 sicilian cohort: safety and effectiveness of infliximab biosimilar sb2 in inflammatory bowel diseases. Including Multiple Switches Inflamm Bowel Dis. 2021;27:182–9.

12. Mazza S, Piazza OSN, Conforti FS, et al. Safety and clinical efficacy of the double switch from originator infliximab to biosimilars CT-P13 and SB2 in patients with inflammatory bowel diseases (SCESICS): A multicenter cohort study. Clin Transl Sci. 2022;15:172–81.

13. Fautrel B, Bouhnik Y, Dougados M, Freudensprung U, Addison J. PERFUSE: A French prospective/retrospective noninterventional cohort study of infliximab-naïve and transitioned patients receiving infliximab biosimilar SB2; 12-month analysis. Ann Rheum Dis. 2021;80:544.

14. Lovero R, Losurdo G, La Fortezza RF, et al. Safety and efficacy of switching from infliximab biosimilar CT-P13 to infliximab biosimilar SB2 in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2021;32:201–7.

15. Fischer S, Cohnen S, Klenske E, et al. Long-term effectiveness, safety and immunogenicity of the biosimilar SB2 in inflammatory bowel disease patients after switching from originator infliximab. Therap Adv Gastroenterol. 2021;14:1756284820982802.

16. Choquette D, Faraawi R, Chow A, Rodrigues J, Bensen WJ, Nantel F. Incidence and management of infusion reactions to infliximab in a prospective real-world community registry. J Rheumatol. 2015;42:1105–11.

17. Hernández MV, Sanmartí R, Cañete JD, et al. Cutaneous adverse events during treatment of chronic inflammatory rheumatic conditions with tumor necrosis factor antagonists: study using the Spanish registry of adverse events of biological therapies in rheumatic diseases. Arthritis Care Res (Hoboken). 2013;65:2024–31.

18. D'Haens G, Reinisch W, Colombel JF, et al. Five-year safety data from ENCORE, a European observational safety registry for adults with Crohn's Disease treated with infliximab [Remicade®] or conventional therapy. J Crohns Colitis. 2017;11:680–9.

19. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT^{TM} registry. Am J Gastroenterol. 2012;107:1409–22.

20. Ducoulombier V, Solau E, Coquerelle P, et al. Long-term results of infliximab therapy in rheumatoid arthritis: experience acquired by the North-Pas-de-Calais hospital network. Joint Bone Spine. 2007;74:56–9.

21. Maksymowych WP, Jhangri GS, Lambert RG, et al. Infliximab in ankylosing spondylitis: a prospective observational inception cohort analysis of efficacy and safety. J Rheumatol. 2002;29:959–65.

22. Yang S, Yang S, Kwon Jo Y, et al. Efficacy and tolerability of infliximab retreatment in patients with inflammatory bowel disease: a systematic review and meta-analysis. Ther Adv Chronic Dis. 2021;12:20406223211041930.

23. Otsuka T, Ooi M, Tobimatsu K, et al. Short-term and long-term outcomes of infliximab and tacrolimus treatment for moderate to severe ulcerative colitis: retrospective observational study. Kobe J Med Sci. 2018;64:E140–8.

24. Miheller P, Lakatos PL, Horváth G, et al. Efficacy and safety of infliximab induction therapy in Crohn's Disease in Central Europe–a Hungarian nationwide observational study. BMC Gastroenterol. 2009;9:66.