Retention rate and long-term safety of biosimilar CT-P13 in patients with ankylosing spondylitis: data from the Korean College of Rheumatology Biologics registry

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Abstract

Objective

To evaluate the long-term drug retention, efficacy, and safety of the infliximab biosimilar CT-P13 in Korean patients with ankylosing spondylitis (AS) in clinical practice. The primary outcome was drug retention (i.e. time to treatment discontinuation or changing to another biologic) in Korean patients with AS. Additional outcomes included efficacy and safety.

Methods

Data were collected through the Korean College of Rheumatology Biologics (KOBIO) registry (ClinicalTrials.gov identifier: NCT01965132). CT-P13 efficacy was assessed using standard disease activity parameters, and safety was evaluated by adverse events (AEs).

Results

Between December 2012 and December 2017, 244 patients with AS treated with CT-P13 were enrolled. Of those, 203 (83.2%) received CT-P13 as first-line therapy. The median duration of treatment was 2.05 years. After 4 years' follow-up, the retention rate of CT-P13 in the overall patient population was 66%. Treatment changes or discontinuations occurred in 38 (15.6%) and 32 (13.1%) patients, respectively. Lack of efficacy was the most common reason for treatment changes, whereas AEs were the most common single cause of discontinuation. Disease activity decreased markedly from baseline following initiation of CT-P13 treatment, and thereafter remained stable. A total of 313 AEs occurred in 118 patients (48.4%); the majority (94.6%) were mild or moderate in severity. The most common treatment-related AEs were infusion or injection-site reactions (4.1% of patients), uveitis (3.7%), and skin rash (3.7%).

Conclusion

In this real-world study, CT-P13 demonstrated encouraging drug retention rates and times, together with reasonable long-term efficacy and safety, in Korean patients with AS.

Key words

ankylosing spondylitis, biosimilar pharmaceuticals, CT-P13, infliximab, registries

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Introduction

Biosimilars have joined the list of biologic therapies and are used for the treatment of active rheumatic diseases (1). These are products that are highly similar to licensed biologic medicines or reference products (RPs) (2-4). CT-P13 is an immunoglobulin gamma 1 chimeric human–murine monoclonal antibody and is the first biosimilar monoclonal antibody to be approved by the European Medicines Agency (5-9). CT-P13 is approved in numerous countries for the same indications as infliximab RP, including ankylosing spondylitis (AS), rheumatoid arthritis (RA), psoriatic arthritis (PsA), plaque psoriasis, and inflammatory bowel diseases (IBDs) (5, 10-13). In the PLANETAS study, a randomised, double-blind trial involving 250 patients with active AS, the pharmacokinetics, efficacy, and safety profile of CT-P13 were comparable with those of infliximab RP (6, 14). Furthermore, the PLANETAS open-label extension study showed that changing from infliximab RP to CT-P13 had no negative effects on either efficacy or safety (8). Similar findings were obtained in patients with active RA in the randomised, double-blind PLANETRA study and the PLANETRA open-label extension study (7, 9). A meta-analysis of 13 randomised controlled trials in patients with AS has confirmed that CT-P13 has comparable efficacy and safety to infliximab and other biologic agents (adalimumab, etanercept, and golimumab) (15).

To date, however, few studies have investigated the long-term efficacy or safety of CT-P13 in patients with AS. In the PLANETAS extension study, patients originally randomised to receive CT-P13 were maintained on treatment for an additional 48 weeks, making a total of 102 weeks of follow-up, while those originally randomised to infliximab RP received CT-P13 from week 54 to 102 (8). In the PLANETAS extension study, the efficacy of CT-P13 in patients treated for 102 weeks was comparable with patients who changed from infliximab RP to CT-P13, and changing treatment had no adverse impact on safety or tolerability (8). The NOR-SWITCH trial, which included patients with spondyloarthritis (SpA), as well as RA, PsA, chronic plaque psoriasis, Crohn's disease, and ulcerative colitis, investigated the efficacy and safety of changing from infliximab RP to CT-P13 with a 52-week follow-up (16). In this trial, drug discontinuation was similar between patients treated with infliximab RP and CT-P13 (16). A recent report of data from the DANBIO registry, which included patients with RA, PsA, and axial SpA, has shown that 1-year retention rates were similar between CT-P13 and infliximab RP (17). A real-world study, which included 109 patients with AS/SpA, found that 2-year drug retention rates were higher among patients receiving CT-P13 as their first infliximab product than in those receiving infliximab RP (18). A total of 30% and 62% of patients treated with CT-P13 or infliximab RP discontinued treatment within 2 years, respectively (18). Although such findings suggest that the efficacy and safety of CT-P13 are maintained during long-term treatment, they are limited by their relatively short follow-up duration.

The Korean College of Rheumatology Biologics (KOBIO) registry is a prospective, observational study established to gather and assess data on patients with RA, AS, and PsA who are receiving treatment with biologic therapies in Korea (19, 20). The original aims of this registry were to monitor the clinical course of the disease and safety issues emerging during treatment with biologic therapies (19); because data are collected during routine clinical practice, the registry provides a "real-world" perspective on these issues. The aim of this analysis from the KOBIO registry was to evaluate the long-term drug retention rate, retention time, efficacy, and safety of CT-P13 in Korean patients with AS who were followed for up to 4 years. In addition, we also investigated the outcomes between patients receiving CT-P13 as first-line or subsequent-line therapy.

Methods

Study population

The KOBIO registry (ClinicalTrials.gov identifier: NCT01965132) is an ongoing multicentre, prospective, obser-

vational study organised by the Korean College of Rheumatology (20, 21). The KOBIO registry includes information about patients with AS, PsA, or RA who are considered eligible for treatment with biologic therapies (etanercept, adalimumab, infliximab, golimumab, tocilizumab, abatacept, rituximab, ustekinumab, secukinumab) (21).

Patients are eligible for inclusion in the KOBIO registry if they are aged ≥18 years, and have a diagnosis of RA, AS, or PsA (21). The KOBIO registry enrols patients with RA, AS, or PsA when the patient initiates or restarts a biologic therapy or when treatment is changed to another biologic agent (21). Patients previously treated with biologic therapies prior to screening may be included, but the efficacy outcome of this previous treatment is not recorded. We assessed data from patients with AS enrolled in the KOBIO registry between December 2012 and December 2017 who had received CT-P13, either as first-line treatment or following a change from another tumour necrosis factor (TNF) inhibitor. CT-P13 was approved by the Korean Ministry of Food and Drug Safety in July 2012 and was commercially available from September 2012. Non-medical switches were not included in this analysis. The present analysis was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all patients prior to the collection of any data, and the data collection form and study protocol were approved by institutional review boards or local ethics committees at each participating centre.

Data collection and outcomes

Data were collected annually from participating hospitals using standardised case report forms and uploaded by the investigators to the KOBIO web server. Baseline demographic data collected in the KOBIO registry included age, gender, body mass index, disease duration and activity, smoking status, human leukocyte antigen-B27 status, and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. The following outcome measures were recorded for the assessment of disease activity at baseline: swollen joint count; tender joint count; Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score (22); Ankylosing Spondylitis Disease Activity Score (ASDAS) (23); and patient's global assessment (GA). The primary outcome of this analysis was drug retention (*i.e.* time to treatment discontinuation or changing to another biologic). Additional outcomes of this analysis included efficacy (disease activity) and safety. Efficacy was assessed by BASDAI; ASDAS-ESR, and ASDAS-CRP scores; and patient's GA. Safety was assessed by adverse events (AEs) categorised according to the Medical Dictionary for Regulatory Activities, version 17.0 (24).

Treatment-related data included details of treatment received (dates, and line of therapy), treatment changes and reasons for changing, and discontinuations and reasons for discontinuation. Discontinuation was defined as permanent discontinuation of biologic agents. Patients who did not have a documented time to discontinuation were included in the analyses of baseline demographics, efficacy, and safety, but were excluded from the analysis of drug retention rates.

Statistical analyses

The sample size was determined by the number of eligible Korean patients at participating centres during the study period. Drug retention was assessed by means of Kaplan-Meier curves. A log-rank test was performed to demonstrate differences in survival function. Confidence bands for the survival function were calculated using the method of Hall and Wellner (25). Secondary outcomes included clinically important improvements or major improvements in ASDAS scores. Clinically important improvement was defined as an improvement of at least 1.1 points between two consecutive values of ASDAS, and an improvement of at least 2 points was defined as a major improvement (26, 27). Descriptive statistics were derived for baseline levels and changes from baseline in BASDAI, ASDAS-ESR, ASDAS-CRP scores, and patient's GA. All statistical analyses were two-sided and were performed using SAS statistical software, v. 9.4 (SAS Institute), and p-values <0.05 were considered statistically significant.

Results

Patients

Between December 2012 and December 2017, 3,424 patients with AS (n=1,658), RA (n=1,711) and PsA (n=55) were enrolled in the KOBIO registry; of these, 244 were patients with AS who were treated with CT-P13. These 244 patients comprised the analysis population reported here. The baseline demographic and clinical characteristics of these patients are summarised in Table I. The mean (standard deviation [SD]) age of patients was 38.8 (12.6) years and 73% of patients were male. All patients had active AS, as shown by baseline BASDAI, ASDAS-CRP, and ASDAS-ESR scores, with a mean (SD) disease duration of 4.2 (5.4) years.

At baseline, most patients (203/244; 83.2%) received CT-P13 as first-line therapy (Table I). Compared with patients treated with CT-P13 in the first-line setting, those receiving CT-P13 in second or subsequent lines had significantly longer disease duration (3.8 years *vs*. 6.1 years, respectively, p=0.010) (Table I). However, there were no significant differences in BASDAI, ASDAS-CRP, or ASDAS-ESR scores between patients receiving CT-P13 as first-line or subsequent therapy (Table I).

Treatment duration and drug retention

Data on treatment duration were available for 208 patients, of whom 173 were receiving CT-P13 as first-line therapy and 35 were receiving second-line or subsequent therapy. The overall median duration of CT-P13 treatment was 2.05 (range 0.04–4.18) years, and the median treatment durations in patients receiving first-line or subsequent CT-P13 therapy were 2.09 (range 0.04–4.18) and 1.11 (range 0.04–4.01) years, respectively. After up to 4 years' follow-up, the retention rate of CT-P13 was 66% in the overall patient population, and 67% in patients receiving CT-P13 as first-line therapy.

Drug retention

Drug retention tended to be longer in patients receiving CT-P13 as first-line

Table I. Baseline demographic and clinical characteristics.*

	CT-P13			*p*-value
	All patients (n=244)	1st-line (n=203)	≥2nd-line (n=41)	
Age, years	38.8 ± 12.6	38.7 ± 12.7	39.4 ± 12.4	0.754
Disease duration, years	4.2 ± 5.4	3.8 ± 5.3	6.1 ± 5.7	0.010
Male, n (%)	178 (73.0)	150 (73.9)	28 (68.3)	0.462
Smoking status, n (%)				0.653
Current smoker	65 (26.6)	52 (25.6)	13 (31.7)	–
Ex-smoker	51 (20.9)	42 (20.7)	9 (22.0)	–
Never	128 (52.5)	109 (53.7)	19 (46.3)	–
BMI, kg/m^2	23.9 ± 3.2	24.1 ± 3.2	23.0 ± 3.2	0.043
Swollen joint count	0.8 ± 3.3	0.9 ± 3.5	0.6 ± 2.1	0.517
Tender joint count	1.4 ± 4.7	1.4 ± 4.7	1.3 ± 4.5	0.962
BASDAI score	6.3 ± 1.9	6.3 ± 1.9	6.4 ± 1.7	0.586
Patient's GA	6.4 ± 2.1	6.3 ± 2.2	6.6 ± 1.7	0.547
ASDAS-ESR	3.7 ± 1.0	3.7 ± 1.0	3.7 ± 1.0	0.89
ASDAS-CRP	3.7 ± 1.2	3.7 ± 1.3	3.5 ± 1.0	0.346
ESR, mm/h	35 ± 30.7	35 ± 30.5	35 ± 31.7	0.999
CRP, mg/dL	2.1 ± 2.9	2.1 ± 2.8	1.9 ± 3.5	0.742
HLA-B27 status, n (%)				0.700
Positive	192 (78.7)	158 (77.8)	34 (82.9)	–
Negative	33 (13.5)	28 (13.8)	5 (12.2)	–
Not determined	19 (7.8)	17 (8.4)	2 (4.9)	–

*Data presented are mean ± standard deviation, unless otherwise indicated. *p*-value comparisons across biologic categories are based on the Chi-squared test of homogeneity for categorical variables; *p*-values for continuous variables are based on the *t*-test for the mean.
ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GA: global assessment; HLA-B27: human leukocyte antigen-B27.

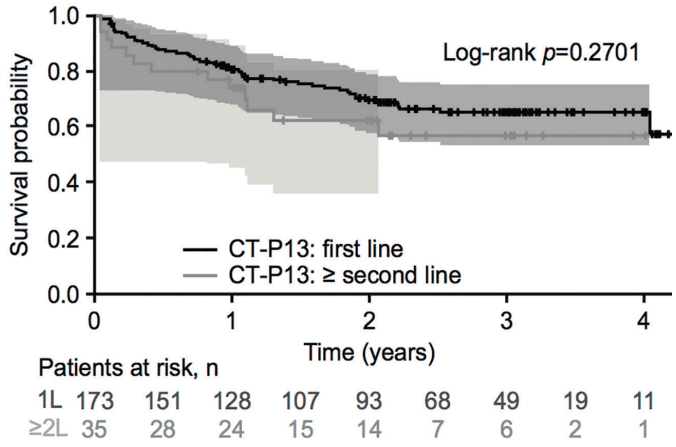


Fig. 1. Kaplan-Meier plot of drug retention in patients with ankylosing spondylitis receiving CT-P13 as first-line or subsequent therapy for up to 4 years. Shaded area represents 95% Hall-Wellner bands, censored data are shown by +.
Drug retention estimates with number of subjects at risk and 95% Hall-Wellner bands. Events defined as CT-P13 discontinued or changed. 1L: first line; 2L: second line.

therapy than in those patients receiving it in subsequent lines from 4-year follow-up, but differences between groups were not statistically significant (log-rank *p*=0.2701; Fig. 1).

Therapy changes and discontinuations

In the study population, 38/244 (15.6%) patients changed from CT-P13 to a different therapy, and 32 (13.1%) patients discontinued CT-P13 without starting another biologic treatment (Table II). Rates of changing treatment and discontinuation were slightly higher in patients receiving CT-P13 as second-line or subsequent therapy than in those receiving as first-line therapy: 17.1% and 14.6%, respectively, in patients receiving second-line or subsequent treatment, compared with 15.3% and 12.8%, respectively, in those receiving first-line therapy (Table II). Overall, the most common reason for changing or discontinuing treatment was lack of efficacy (13.9% [34/244]). Lack of efficacy was the single most common reason for treatment changes. A total of five patients, all of whom were receiving CT-P13 as first-line therapy, discontinued therapy because clinical remission had been achieved.

AEs were the second most common reason for changing treatment or discontinuation, which occurred in 18/244 (7.4%) patients (Table II). AEs were the most common single cause of discontinuation. AEs leading to changing treatment or discontinuation of CT-P13 are listed in Supplementary Table SI. Overall, 10 patients (4.1%) changed from CT-P13 to another treatment because of AEs. The most common AEs resulting in treatment changes were infusion or injection-site reactions (n=8 events), skin rash (n=2 events), and uveitis (n=1 event) (Suppl. Table SI). Treatment discontinuations due to AEs occurred in 8 (3.3%) patients (Table II). The most common of these were infusion or injection-site reactions, *Mycobacterium* tuberculosis infection and headache (n=2 events each); conception, urticaria, and gastrointestinal disturbances each occurred once (Suppl. Table SI). Rates of changing treatment or discontinuation due to AEs were higher among patients receiving CT-P13 as second-line or subsequent therapy than in those receiving first-line therapy (Suppl. Table SI).

Details of the drugs received following CT-P13 are summarised in Table III. Following first-line CT-P13 treatment, the most commonly substituted drugs were golimumab (45.2%) or adalimumab (32.3%), followed by etanercept and infliximab RP; one patient (2.6%) was changed to an etanercept biosimilar (Table III). The same trend was seen in patients changing from second-line or subsequent CT-P13, in whom golimumab and adalimumab were the most commonly substituted products.

Efficacy

Median scores for BASDAI, ASDAS-ESR, ASDAS-CRP, and patient's GA are shown in Fig. 2. Disease activity as-

Table II. Reasons for discontinuing CT-P13 or changing from CT-P13 to another therapy.

	All patients (n=244)	1st-line treatment (n=203)	≥2nd-line treatment (n=41)
Changed, n (%)*	38 (15.6)	31 (15.3)	7 (17.1)
Lack of efficacy	27 (11.1)	23 (11.3)	4 (9.8)
AE	10 (4.1)	7 (3.4)	3 (7.3)
Unspecified	1 (0.4)	1 (0.5)	0
Discontinuation, n (%)	32 (13.1)	26 (12.8)	6 (14.6)
AE	8 (3.3)	6 (3.0)	2 (4.9)
Lack of efficacy	7 (2.9)	6 (3.0)	1 (2.4)
Clinical remission	5 (2.0)	5 (2.5)	0
Other	12 (4.9)	9 (4.4)†	3 (7.3)‡

*Expressed as percentage of total number of patients.
†Reasons include lost to follow-up (n=4), patient's decision (n=2), optionally stopped (n=1), insurance costs (n=1), and unknown (n=1).
‡Reasons include patient's decision (n=2) and planning for pregnancy (n=1).
AE: adverse event.

Table III. Biologics received following change from CT-P13.

n (%)	All patients (n=38)	After 1st-line CT-P13 (n=31)	After ≥ 2nd-line CT-P13 (n=7)
Golimumab	17 (44.7)	14 (45.2)	3 (42.9)
Adalimumab	12 (31.6)	10 (32.3)	2 (28.6)
Etanercept	4 (10.5)	3 (9.7)	1 (14.3)
Infliximab*	4 (10.5)	3 (9.7)	1 (14.3)
Etanercept biosimilar	1 (2.6)	1 (3.2)	0

*Infliximab reference product (Remicade®).

sessed by BASDAI, ASDAS-ESR, ASDAS-CRP, and patient's GA, decreased markedly from baseline following initiation of CT-P13 treatment, and thereafter remained stable during follow-up (Fig. 2).

The proportion of patients showing clinically important or major changes in ASDAS scores (defined as ≥1.1 or ≥2-point improvements, respectively) are shown in Suppl. Table SII. In the overall patient population, 56.5% and 82.2% of patients showed a major or clinically important improvement in ASDAS score, respectively, after 1 year of treatment. These improvements were maintained at 2 years (major improvement: 56.9% of patients, clinically important improvement: 85.4% of patients) (Suppl. Table SII). Similarly, among patients receiving CT-P13 as first-line therapy, 59.9% experienced a major improvement in ASDAS score and 84.1% experienced a clinically important improvement at first follow-up, and similar proportions were seen at 2 years (54.7% and 85.8%, respectively).

Safety

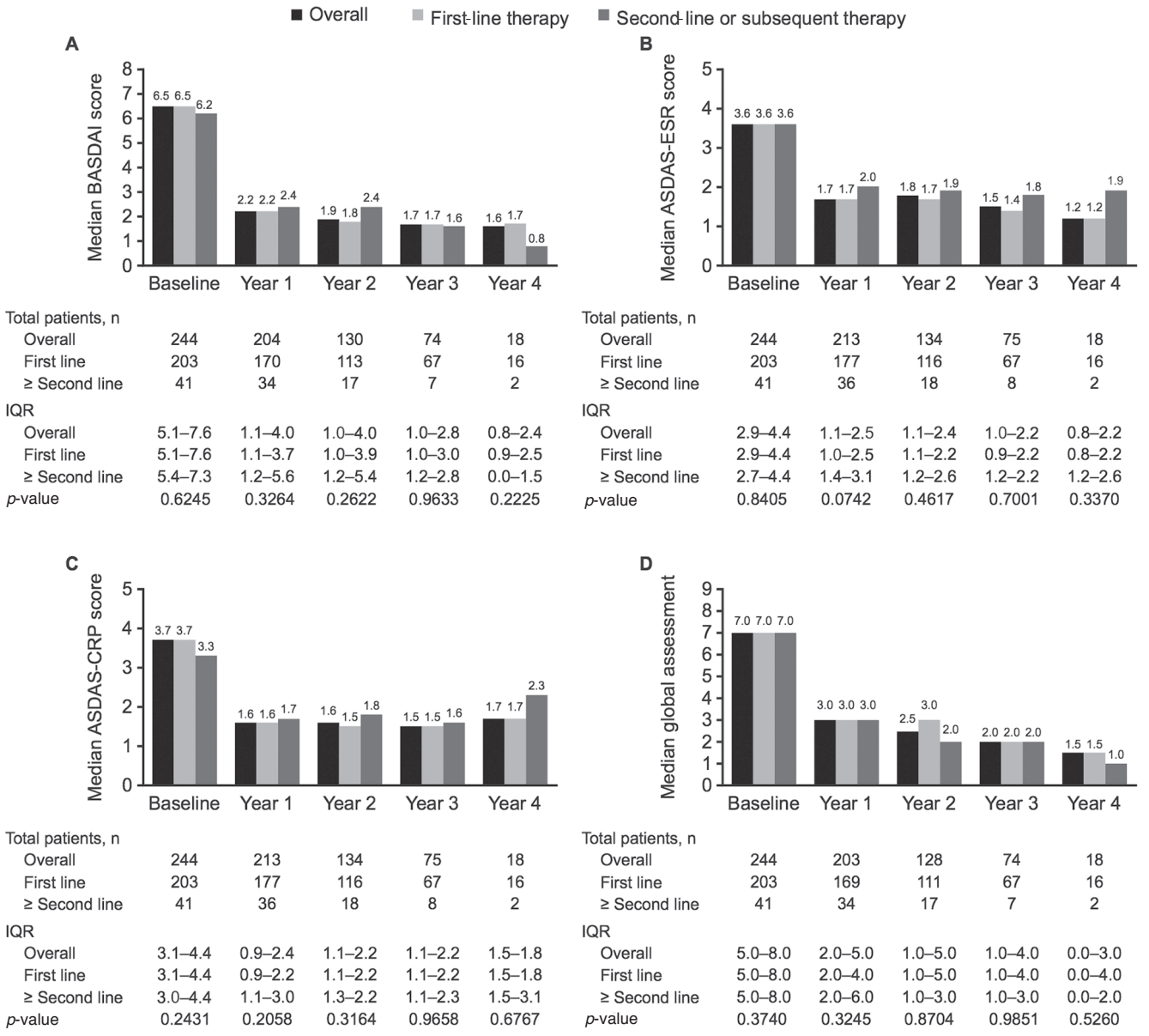
CT-P13 was well tolerated during long-term treatment. Overall, 118 patients (48.4%) reported 313 AEs (Suppl. Table SIII), the majority of which were mild (grade 1) or moderate (grade 2) in severity (62.3% and 32.3%, respectively). A total of 72 AEs in 41 patients (16.8%) were considered by the investigators to be related to CT-P13 treatment (Suppl. Table SIII). Of these, the majority (63/72 events [87.5%]) of events occurred in patients receiving CT-P13 as first-line therapy. Treatment-related AEs occurring in two or more patients, and all grade 3 treatment-related AEs, are summarised in Table IV. The most common CT-P13-related AEs were infusion or injection-site reactions (4.1%), uveitis (3.7%), and skin rash (3.7%). A total of four grade 3 CT-P13-related AEs were reported: uveitis, infusion or injection-site reaction, *Mycobacterium* tuberculosis infection, and itching, which occurred in one patient each.

Discussion

In this prospective, registry-based, observational study, CT-P13 demonstrated encouraging drug retention rates and retention times in Korean patients with AS who were treated with CT-P13 as either first-line or subsequent therapy for a median of 2.05 years. Treatment discontinuations or changes were infrequent (13.1% and 15.6%, respectively): the majority of changes were due to a lack of efficacy (11.1%), whereas AEs were the most common single reason for discontinuation (3.3%).

Our analysis has demonstrated that CT-P13 had reasonable long-term efficacy and was well tolerated in this patient population. Disease activity was markedly improved at 1 year, compared with baseline, and these improvements were sustained over the 4-year follow-up period. Major improvements in ASDAS score were achieved in the majority of patients during the first year of treatment. The majority of AEs were mild or moderate in severity. The most common treatment-related AEs were infusion or injection-site reaction, uveitis, and skin rash, all of which occurred in fewer than 5% of patients.

Our findings with CT-P13 are consistent with previous studies of infliximab (28-32). In a Korean single-centre study involving patients with AS and RA, 79% of patients with AS treated with a first TNF inhibitor remained on treatment at 2 years; median drug retention time with infliximab RP did not differ from etanercept or adalimumab (30). Consistent with our study, AEs were the most common reason for discontinuation of TNF inhibitors in patients with AS, accounting for 39.7% of cases. A slightly higher discontinuation rate was reported in a single-centre study from Spain, in which 26.5% of patients with AS who received infliximab RP discontinued treatment during the 5-year follow-up period (29). In a Spanish single-centre study, the most common reason for discontinuation of TNF inhibitor therapy was lack of efficacy. Registry-based studies conducted in Spain (28) and the Czech Republic (32) have reported drug retention rates of approximately 72–76% after 3 years of follow-up in patients with AS receiving TNF inhibitors. A Swedish registry study demonstrated that comedication with conventional synthetic disease-modifying anti-rheumatic drugs was associated with TNF inhibitor drug



	Baseline	Year 1	Year 2	Year 3	Year 4
A					
Total patients, n					
Overall	244	204	130	74	18
First line	203	170	113	67	16
≥ Second line	41	34	17	7	2
IQR					
Overall	5.1–7.6	1.1–4.0	1.0–4.0	1.0–2.8	0.8–2.4
First line	5.1–7.6	1.1–3.7	1.0–3.9	1.0–3.0	0.9–2.5
≥ Second line	5.4–7.3	1.2–5.6	1.2–5.4	1.2–2.8	0.0–1.5
p-value	0.6245	0.3264	0.2622	0.9633	0.2225
B					
Total patients, n					
Overall	244	213	134	75	18
First line	203	177	116	67	16
≥ Second line	41	36	18	8	2
IQR					
Overall	2.9–4.4	1.1–2.5	1.1–2.4	1.0–2.2	0.8–2.2
First line	2.9–4.4	1.0–2.5	1.1–2.2	0.9–2.2	0.8–2.2
≥ Second line	2.7–4.4	1.4–3.1	1.2–2.6	1.2–2.2	1.2–2.6
p-value	0.8405	0.0742	0.4617	0.7001	0.3370
C					
Total patients, n					
Overall	244	213	134	75	18
First line	203	177	116	67	16
≥ Second line	41	36	18	8	2
IQR					
Overall	3.1–4.4	0.9–2.4	1.1–2.2	1.1–2.2	1.5–1.8
First line	3.1–4.4	0.9–2.2	1.1–2.2	1.1–2.2	1.5–1.8
≥ Second line	3.0–4.4	1.1–3.0	1.3–2.2	1.1–2.3	1.5–3.1
p-value	0.2431	0.2058	0.3164	0.9658	0.6767
D					
Total patients, n					
Overall	244	203	128	74	18
First line	203	169	111	67	16
≥ Second line	41	34	17	7	2
IQR					
Overall	5.0–8.0	2.0–5.0	1.0–5.0	1.0–4.0	0.0–3.0
First line	5.0–8.0	2.0–4.0	1.0–5.0	1.0–4.0	0.0–4.0
≥ Second line	5.0–8.0	2.0–6.0	1.0–3.0	1.0–3.0	0.0–2.0
p-value	0.3740	0.3245	0.8704	0.9851	0.5260

Fig. 2. Median scores for BASDAI (**A**), ASDAS-ESR (**B**), ASDAS-CRP (**C**), and patient's global assessment (**D**) in the overall patient population, and in patients receiving first-line and second-line or subsequent CT-P13.
p-values were calculated using the Wilcoxon rank sum method comparing the medians of the first-line group and ≥ second-line group.
ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range.

retention in patients with AS (31). In these registry studies, the most common reasons for discontinuation of therapy were lack of efficacy (31) or AEs (28, 32). It is noteworthy that the single-centre and registry studies have consistently found that discontinuation rates of TNF inhibitor therapy are higher, and drug retention lower, in patients with RA, compared with AS or other forms of SpA (28, 30, 32).

As briefly mentioned, few studies to date have investigated the long-term drug retention, efficacy, or safety of CT-P13 in patients with AS (8, 16, 33, 34). It is important to note that none of the previously reported studies followed patients for more than 2 years (8, 16, 18). As such, the 4-year follow-up in our analysis offers important insights into the efficacy and tolerability of CT-P13 during long-term treatment.

In general, clinicians may have a number of key concerns about changing patients to a biosimilar, including potential loss of efficacy, changes in immunogenicity, and unanticipated differences in the safety profile compared with the RP (35). These concerns may be addressed by the accumulating real-world experience with CT-P13 in routine clinical practice. Several recent studies have investigated the efficacy and safety of CT-P13 in patients with AS treated under "real-world" conditions, either as first-line infliximab therapy (36), or following a change from infliximab RP (37, 38). In a study from three European countries, which involved 70 patients with AS who were considered to be candidates for biologic therapy, 22 patients (31%) achieved

Table IV. CT-P13-related adverse events (occurring in ≥2 patients overall or ≥1 patient(s) at grade 3–4) in the overall patient population.

	n (%)	
	Grade 1–2	Grade 3
Eye disorder (NOS)	2 (0.8)	–
Uveitis	8 (3.3)	1 (0.4)
Gastrointestinal disorder (NOS)	3 (1.2)	–
Gastritis	2 (0.8)	–
General disorder (NOS)	5 (2.0)	–
Infusion/injection-site reaction	9 (3.7)	1 (0.4)
Mycobacteria tuberculosis infection	1 (0.4)	1 (0.4)
Transaminitis	3 (1.2)	–
Headache	2 (0.8)	–
Respiratory disorder (NOS)	2 (0.8)	–
Common cold*	5 (2.0)	–
Upper respiratory tract infection	3 (1.2)	–
Chronic urticaria	3 (1.2)	–
Itching	–	1 (0.4)
Skin rash	9 (3.7)	–

*Recurrent in one patient.
NOS: not otherwise specified.

remission and 45 (64%) achieved low disease activity at the end of the 24-week treatment period with CT-P13 (36). A total of eight treatment-related AEs, the majority of which were mild or moderate in severity, were reported. Real-world studies in mixed populations of rheumatology patients have shown comparable efficacy and tolerability following a change from infliximab RP to CT-P13 (37, 38), and this experience is supported by studies in patients with IBD (39). It may be anticipated that, as real-world data continue to accrue, the cumulative evidence of the efficacy and safety of CT-P13 in patients with AS will allay concerns and aid clinical decision making.

In addition to offering efficacy and safety comparable with RPs, biosimilars may provide important economic benefits due to their lower cost, compared with the RP (12). While there are currently no cost-analyses specific to the use of CT-P13 in the treatment of patients with AS, several studies assessing the economic impact of changing from infliximab RP to CT-P13 in various indications provide compelling evidence of the cost saving of CT-P13 (40-43). For example, a budget impact analysis investigating the potential savings over 1 year following the introduction of CT-P13 for various indications in five European countries found that annual cost savings ranged from €2.89 million in Belgium to €33.8 million in Germany, depending on the level of discount applied (42). Across the five countries, the cumulative savings in drug costs ranged from €25.79 million to €77.37 million. The modeled population included both infliximab-naïve patients and patients who changed from infliximab RP to CT-P13. Cost savings achieved with CT-P13 may enable more patients to be treated (40, 44, 45). In countries where infliximab is not recommended due to cost constraints, introduction of the lower-priced CT-P13 might alter this situation.

A key strength of this study is that it provides real-world data from Korean patients with AS who are receiving treatment with biologic therapies. Additional strengths of this study include the long duration of follow-up, the prospective nature of the KOBIO registry, and the relatively large patient population studied. Potential limitations include the relatively small number of patients receiving CT-P13 as second-line or subsequent therapy, and the possibility of bias since the registry includes only patients treated at participating centres. Moreover, as the median treatment duration of CT-P13 was 2.05 years and only 12 of 208 patients received treatment for 4 years, rare AEs such as malignancy may not be observed. This limitation may be overcome with longer follow-up or recruitment of additional patients. A further potential limitation is that the study did not investigate efficacy outcomes in patients who changed from infliximab RP to CT-P13, or vice versa.

In conclusion, CT-P13 demonstrated encouraging drug retention rates and retention times, as well as reasonable long-term efficacy and safety, in Korean patients with AS.

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