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ORIGINAL RESEARCH ARTICLE

A 5-year Retrospective Analysis of Drug Survival, Safety, and Effectiveness of the Infliximab Biosimilar CT-P13 in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis

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Abstract

Background The infliximab biosimilar CT-P13 has widely received regulatory approval in all indications of reference infliximab, including rheumatoid arthritis (RA) and ankylosing spondylitis (AS).

Objective This retrospective analysis investigated drug survival and long-term safety and effectiveness of CT-P13 in patients with RA or AS in the Republic of Korea.

Methods This non-interventional, retrospective, multicenter analysis collected medical record data for adult patients with RA or AS who received CT-P13 treatment at five Korean referral hospitals (2012–2017). Drug survival and long-term safety were primary outcomes. The secondary outcome was long-term effectiveness, assessed by disease activity measures.

Results Overall, 491 patients were treated with CT-P13 (154 patients with RA [135 infliximab-naïve; 19 switched from reference infliximab]; 337 patients with AS [219 infliximab-naïve; 118 switched from reference infliximab]). Drug survival was similar in naïve and switched patients. Treatment-emergent adverse events (TEAEs) occurred in 31.8% and 29.4% of patients with RA and AS, respectively; incidence was similar in naïve and switched groups. Upper respiratory tract infection, influenza-like illness, and urticaria were the most common TEAEs. Overall, nine (1.8%) patients experienced serious adverse events (SAEs) deemed potentially drug-related; SAEs led to permanent CT-P13 discontinuation in five (1.0%) patients, including three with tuberculosis. Disease activity decreased over time.

Conclusion Up to 5 years of CT-P13 treatment was safe and effective in patients with RA and AS, based on drug survival, incidence of TEAEs, and disease activity. Drug survival and safety were similar in naïve patients and switched groups, supporting switching from reference infliximab to CT-P13.

1 Introduction

CT-P13, a biosimilar of infliximab, is a chimeric human-murine monoclonal antibody that targets the proinflammatory cytokine tumor necrosis factor (TNF) [1–3]. As of September 2019, CT-P13 has received regulatory approval in 91 countries. It is licensed in all the same indications as reference infliximab by the United States Food and Drug Administration, European Medicines Agency and the Ministry of Food and Drug Safety in the Republic of Korea [1–6]. These comprise rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis, psoriatic arthritis (PsA), and inflammatory bowel diseases.

Compared with reference products, biosimilars offer the potential for cost savings and expanded patient access to biologic treatments [7]. However, the complexity and inherent variability of biologics may contribute to physician concerns about loss of efficacy and unanticipated differences in safety, tolerability and immunogenicity between biosimilars and their reference products [8, 9]. Clinical trial and real-world data are crucial to boost physician and patient confidence in biosimilars. Crucially, in patients, reticence about switching to a biosimilar can significantly affect acceptance and retention rates [10], leading to reduced therapeutic efficacy

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Key Points

Five-year analysis showed that long-term treatment with the infliximab biosimilar CT-P13 was safe and effective in patients with rheumatoid arthritis (RA) or ankylosing spondylitis (AS) treated under routine medical care in the Republic of Korea. This study provides the longest-term evidence available to date regarding the safety and effectiveness of CT-P13 in patients with RA or AS.

Drug survival and safety were similar in infliximab-naïve patients and those who switched from reference infliximab to CT-P13.

Five patients experienced potentially drug-related serious adverse events which led to permanent discontinuation of CT-P13: tuberculosis (three patients), hypersensitivity vasculitis (one patient), serum sickness-like reaction (one patient) and splenic abscess (one patient who also experienced tuberculosis).

– the 'nocebo' effect [11]. To date, long-term experience with biosimilar biologic disease-modifying antirheumatic drugs (bDMARDs) remains fairly limited [8].

Clinical studies have demonstrated the comparable efficacy and safety of CT-P13 and reference infliximab in patients with RA [12–14] and AS [15, 16]. In addition, a meta-analysis of biologic treatments for AS found that CT-P13 had similar efficacy and safety to reference infliximab and other biologics licensed for the treatment of AS [17]. Subsequent open-label extensions to the clinical studies in patients with RA and AS showed CT-P13 to be well tolerated, with its comparable efficacy and safety to reference infliximab maintained over 102–110 weeks [18–20]. In addition, no adverse impact of switching therapy from reference infliximab to CT-P13 was identified [18–20]. Data from the open-label extension to the NOR-SWITCH study concur: in a study population comprising patients with rheumatic diseases (including spondyloarthritis and RA), chronic plaque psoriasis and inflammatory bowel disease, the efficacy and safety of CT-P13 18 months after switching from reference infliximab was similar to that observed after 12 months' treatment with either reference infliximab or CT-P13 [21]. To date, no clinical studies have looked at the comparable effects of CT-P13 and reference infliximab in RA and AS beyond 2 years.

Long-term real-world evidence of the drug survival and safety of CT-P13 exists. In a single-center analysis of routine medical care data from 395 patients with rheumatological diagnoses conducted over a 2-year period, the safety profiles of CT-P13 and reference infliximab were similar; drug survival was better for patients initiating CT-P13 compared with reference infliximab [22]. Further, an interim 2-year analysis of the ongoing, observational PERSIST study, which is evaluating CT-P13 treatment in 329 patients with RA, AS and PsA, reported a safety profile of CT-P13 consistent with the known profile for reference infliximab [23]. A pooled analysis combining data for 1579 patients with RA, AS, PsA or psoriasis from PERSIST and three other global post-marketing studies (KOREA PMS, CT-P13 4.2 and CT-P13 4.4) also found CT-P13 to be well tolerated, with a comparable incidence of adverse events (AEs) to previous reports for reference infliximab [24]. To date, the longest-term real-world evaluation of the effectiveness and safety of CT-P13 and infliximab in RA and AS comes from analyses of the Korean College of Rheumatology Biologics (KOBIO) registry: an ongoing, multicenter, prospective, observational study collecting real-world data for patients with RA, AS or PsA treated with biologics in the Republic of Korea [25, 26]. Data from 199 patients with RA [26] and 244 patients with AS [25] included in the KOBIO registry showed comparable CT-P13 drug survival rates and long-term effectiveness and safety to previous studies of reference infliximab, with up to 4 years of follow-up.

Here we report the findings of a retrospective analysis to determine drug survival and long-term (up to 5-year) safety and effectiveness of CT-P13 treatment in patients with RA or AS receiving routine medical care in the Republic of Korea, including patients who switched from reference infliximab to CT-P13.

2 Methods

2.1 Study Design

This was a non-interventional, retrospective, multicenter analysis conducted at five referral university hospitals in the Republic of Korea. Data were collected from the medical records of patients at each participating hospital using case record forms and were anonymized using an alphanumeric code.

2.2 Study Population

Eligible patients were aged ≥ 18 years with a previous diagnosis of RA or AS and had received ≥ 1 dose of CT-P13 between September 1, 2012 and December 31, 2017. The study population included patients who were naïve to infliximab treatment at the start of CT-P13 treatment ('naïve' patients) and those who underwent non-medical switching from reference infliximab to CT-P13 ('switched' patients). Patients were excluded if CT-P13 treatment had not been administered in line with the approved label.

2.3 Assessments

Demographic data (including age, sex, height and body weight) were assessed at baseline (Week 0) immediately prior to CT-P13 dosing. Disease characteristics, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and disease activity were assessed before CT-P13 dosing at every clinical visit. Due to the differences in measurement schedule between groups, analysis time points were selected as Weeks 0, 27, 54, 102, 156, 210 and 264. For patients with RA, disease activity was assessed using the Disease Activity Score in 28 joints (DAS28)-ESR and DAS28-CRP. Remission per DAS28-ESR and DAS28-CRP was defined as a score < 2.6, low disease activity as a score ≥ 2.6– < 3.2, moderate disease activity as a score ≥ 3.2– ≤ 5.1, and high disease activity as a score > 5.1 [27]. For patients with AS, disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [28]. For each patient, data were also collected on CT-P13 treatment classification (i.e. whether naïve or switched) and dosing (i.e. weekly date of CT-P13 administration, body weight at each dose, designated and actual doses, any treatment changes and reasons for changing, discontinuations and reasons for discontinuation), as well as prior and concomitant therapy. For patients switched to CT-P13 from infliximab, the number of doses and start and end dates of reference infliximab treatment were also recorded. Safety data included the incidence, severity, duration, relation to CT-P13 treatment and outcome of AEs, including infusion-related reactions, adverse drug reactions (ADRs) and serious adverse events (SAEs). Severity of AEs was determined by investigators.

2.4 Outcomes

The primary outcomes of the study were drug survival (i.e. time to treatment discontinuation) and long-term safety of CT-P13 treatment in patients with RA and AS. Discontinuation included switching to another bDMARD or stopping treatment, including for a drug holiday. The secondary outcome was the long-term effectiveness of CT-P13 treatment, assessed by the effect on disease activity according to DAS28-ESR, DAS28-CRP and BASDAI scores.

2.5 Statistical Analyses

All patients who received ≥ 1 dose of CT-P13 were included in the safety analysis group. All patients who received CT-P13 and underwent effectiveness evaluation were included in the effectiveness analysis group. Descriptive summary statistics were derived for patient demographics, safety and disease activity changes (changes from baseline in DAS28-ESR, DAS28-CRP and BASDAI scores). Disease activity outcomes were analyzed using modified intention-to-treat analysis. Drug survival was determined by Kaplan–Meier survival analysis, based on the time period from the first dose of CT-P13 to the last dose. Time to discontinuation was censored at the last tracking date for patients lost to follow-up or who discontinued treatment due to pregnancy, symptom improvement, or insurance exclusion. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3 Results

3.1 Patients

Overall, data from 491 patients treated with CT-P13 between September 1, 2012 and December 31, 2017 were included in the analysis, comprising 154 patients with RA and 337 patients with AS. Of the patients with RA, 135 (87.7%) were naïve to infliximab treatment and 19 (12.3%) had switched from reference infliximab. Among the 337 patients with AS, 219 (65.0%) and 118 (35.0%) were in the naïve and switched groups, respectively. For both RA and AS, baseline patient characteristics were broadly similar between naïve and switched groups, with two anticipated exceptions. First, duration of disease was longer in the switched versus naïve group for both RA and AS. Second, at baseline, patients with AS who switched from reference infliximab to CT-P13 had more stable disease than those in the naïve group (Table 1).

Most of the patients with RA were female (87.7%). Median (range) baseline DAS28-ESR and DAS28-CRP scores were 5.8 (1.9–8.4) and 5.2 (2.5–8.1), respectively (Table 1), reflecting an RA population with established moderate-to-severe active disease. Overall, 37 (24.0%) patients with RA had received a bDMARD prior to CT-P13 treatment. With the exception of reference infliximab, by definition the most commonly used bDMARD for switched patients, adalimumab ($n = 10$) and etanercept ($n = 8$) had been used most frequently (Table S1 in Online Resource 1). The majority of patients with RA (94.8%) had received concomitant therapy: 139 (95.2%) and 40 (27.4%) patients had received methotrexate and prednisolone, respectively (Table 1).

The majority of the 337 AS patients included in the study population were male (76.6%). The median (range) baseline BASDAI score was 6.6 (0–10.0), indicative of active AS. Overall, 141 (41.8%) patients with AS had received treatment with a bDMARD before treatment with CT-P13 (Table 1). Most commonly, this consisted of prior treatment with adalimumab ($n = 22$) or etanercept ($n = 20$), excluding reference infliximab for switched patients (Table S1 in Online Resource 1). In total, 64.1% of AS patients had received concomitant therapy (Table 1).

3.2 Treatment Duration

For switched patients with RA, the median (range) number of prior reference infliximab treatments was 11 (2–31), administered over a median (range) duration of 13.3 (0.4–48.6) months (Table 2). Switched patients with AS had received a median (range) of 16 (1–56) reference infliximab treatments over a median (range) duration of 30.0 (0.0–104.0) months.

The median number of CT-P13 treatments was similar between naïve and switched groups for patients with RA (8 and 9, respectively) and AS (12 and 16) (Table 2). For patients with RA, the median (range) duration of CT-P13 treatment was longer for switched patients (19.5 [0.0–56.7]

Table 1 Baseline patient and disease characteristics (safety analysis group)

	RA			AS		
	Total $n=154$	Naïve $n=135$	Switched $n=19$	Total $n=337$	Naïve $n=219$	Switched $n=118$
Male, *n* (%)	19 (12.3)	16 (11.9)	3 (15.8)	258 (76.6)	163 (74.4)	95 (80.5)
Age, years	50.0 (11.6)	49.5 (11.2)	53.9 (13.9)	40.0 (13.3)	39.5 (13.8)	41.1 (12.2)
Body weight						
n	101	89	12	272	177	95
kg	58.0 (12.4)	57.9 (12.4)	58.8 (12.7)	67.1 (11.8)	67.5 (12.2)	66.3 (11.1)
BMI						
n	95	83	12	231	142	89
kg/m^2	23.2 (4.3)	23.2 (4.2)	23.2 (5.1)	23.7 (3.6)	23.7 (3.7)	23.6 (3.3)
Disease duration						
n	119	108	11	266	171	95
Months; median (range)	62.7 (4.7–262.2)	58.9 (4.7–262.2)	85.8 (15.7–194.2)	54.3 (3.0–216.7)	37.6 (3.0–195.0)	85.2 (3.4–216.7)
ESR						
n	133	115	18	310	200	110
mm/h; median (range)	40.0 (0.3–125.0)	43.0 (0.3–125.0)	24.0 (3.0–64.0)	21.5 (0.0–126.0)	32.0 (2.0–126.0)	11.0 (0.0–93.0)
CRP						
n	132	114	18	310	200	110
mg/L; median (range)	1.2 (0.0–114.0)	1.4 (0.0–114.0)	0.3 (0.0–7.5)	0.8 (0.0–20.3)	1.4 (0.0–20.3)	0.2 (0.0–4.7)
DAS28-ESR						
n	103	100	3	–	–	–
Median (range)	5.8 (1.9–8.4)	5.8 (1.9–8.4)	6.3 (2.6–6.9)	–	–	–
DAS28-CRP						
n	79	77	2	–	–	–
Median (range)	5.2 (2.5–8.1)	5.1 (2.5–8.1)	5.9 (5.6–6.1)	–	–	–
BASDAI						
n	–	–	–	265	168	97
Median (range)	–	–	–	6.6 (0.0–10.0)	7.5 (1.4–10.0)	1.6 (0.0–9.7)
Previous bDMARDs use						
Patients, *n* (%)	37 (24.0)	18 (13.3)	19 (100.0)	141 (41.8)	23 (10.5)	118 (100.0)
Number of bDMARDs	1.2 (0.5)	1.2 (0.4)	1.2 (0.5)	1.2 (0.4)	1.3 (0.5)	1.1 (0.4)
Concomitant therapy						
Patients, *n* (%)	146 (94.8)	130 (96.3)	16 (84.2)	216 (64.1)	151 (68.9)	65 (55.1)
Methotrexate[a]	139 (95.2)	123 (94.6)	16 (100.0)	61 (28.2)	43 (28.5)	18 (27.7)
Prednisolone[a]	40 (27.4)	39 (30.0)	1 (6.3)	24 (11.1)	19 (12.6)	5 (7.7)

Values are mean (SD) unless otherwise stated. The *n* is shown for variables where data were missing for any patient

AS ankylosing spondylitis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *bDMARD* biologic disease-modifying antirheumatic drug, *BMI* body mass index, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 joints, *ESR* erythrocyte sedimentation rate, *RA*, rheumatoid arthritis, *SD* standard deviation

[a]The denominator for percentages was the number of patients receiving concomitant therapy

months) versus naïve patients (10.7 [0–58.5] months). Similar findings were observed for patients with AS: the median (range) duration of CT-P13 treatment was 31.4 (0–56.8) and 17.5 (0.0–57.4) months for switched and naïve patients, respectively.

3.3 Drug Survival

Long-term (5-year) drug survival was 43.3% for the overall RA population and 67.2% for the overall AS population. Drug survival was similar in naïve and switched groups for patients with RA (log-rank $p = 0.61$; Fig. 1a) and AS (log-rank $p = 0.68$; Fig. 1b). For patients with RA, 5-year drug survival rates were 41.2% and 52.9% for naïve and switched patients, respectively. For patients with AS, 5-year drug survival rates were 63.5% and 72.1% for naïve and switched patients, respectively.

3.4 CT-P13 Treatment Discontinuation

Overall, 239 (48.7%) patients discontinued CT-P13 treatment, with a greater proportion of patients with RA discontinuing treatment compared to those with AS (66.9% vs 40.4%, respectively). Lack of effectiveness was the single most common reason for discontinuation, accounting for the discontinuation of 97 (40.6%) patients overall (Table 3). Rates of discontinuation due to lack of effectiveness were higher in naïve versus switched patients in both the RA (53.3% vs 36.4%, respectively) and AS (36.9% vs 25.0%, respectively) populations. Loss to follow-up and drug holidays both accounted for treatment discontinuation in 35 (14.6%) patients, while AEs accounted for discontinuation in a further 25 (10.5%) patients. No patient discontinued due to remission, although two patients discontinued due to improvement in symptoms. Reasons for discontinuation differed somewhat between RA and AS patients: a lower proportion of patients with AS compared to those with RA discontinued due to lack of effectiveness (32.4% and 51.5%, respectively), while a greater proportion of patients with AS compared to those with RA discontinued due to loss to follow-up (19.1% and 8.7%, respectively).

3.5 Safety

In total, 31.8% of patients with RA and 29.4% of patients with AS experienced at least one treatment-emergent AE (TEAE) (Table 4). The incidence of TEAEs was similar between naïve and switched patients. The most frequent TEAEs in both RA and AS patient populations were upper respiratory tract infection (3.9% and 4.2%, respectively), influenza-like illness (2.6% and 1.5%, respectively), and urticaria (1.3% and 2.1%, respectively) (Table 5). Infusion-related reactions occurred in three (1.9%) and two (0.6%) patients with RA and AS, respectively. ADRs occurred in a similar proportion of patients with RA and AS (approximately 18%; Table 4); incidence rates were slightly lower in naïve versus switched patients. There were no cases of malignancy.

In total, 22 SAEs occurred in 17 (3.5%) patients; the vast majority occurring in naïve patients (19 events in 14 [4.0%] patients) (Table 4). Overall, 11 SAEs (in 9 [1.8%] patients) were considered to be potentially drug related. Of these, six SAEs led to permanent discontinuation of CT-P13 treatment, in five patients. These SAEs were severe hypersensitivity vasculitis, life-threatening serum sickness-like reaction, moderate splenic abscess, and three cases of tuberculosis. Of the tuberculosis cases, two were due to reactivation and one was new-onset tuberculosis. The cases comprised: a severe reactivation case of pulmonary tuberculosis in a patient with AS who had previously tested negative on screening for *Mycobacterium* infection; a life-threatening reactivation case of tuberculosis pericarditis in a patient with RA for whom the *Mycobacterium* infection screening history was unknown; and new-onset pulmonary tuberculosis in a patient with AS who had previously tested negative on screening for *Mycobacterium* infection. In addition, an SAE of moderate

Table 2 Median (range) number and duration of CT-P13 and prior reference infliximab treatment (safety analysis group)

	RA			AS		
	Total $n = 154$	Naïve $n = 135$	Switched $n = 19$	Total $n = 337$	Naïve $n = 219$	Switched $n = 118$
Reference infliximab						
Number of prior treatments	11 (2–31)	–	11 (2–31)	16 (1–56)	–	16 (1–56)[a]
Duration, months	13.3 (0.4–48.6)	–	13.3 (0.4–48.6)	30.0 (0.0–104.0)	–	30.0 (0.0–104.0)[a]
CT-P13						
Number of treatments	8 (1–34)	8 (1–34)	9 (1–30)	13 (1–40)	12 (1–40)	16 (1–39)
Duration, months	10.9 (0.0–58.5)	10.7 (0.0–58.5)	19.5 (0.0–56.7)	22.0 (0.0–57.4)	17.5 (0.0–57.4)	31.4 (0.0–56.8)

AS ankylosing spondylitis, *RA* rheumatoid arthritis

[a]Three patients with missing reference infliximab treatment data were excluded from the statistical analysis

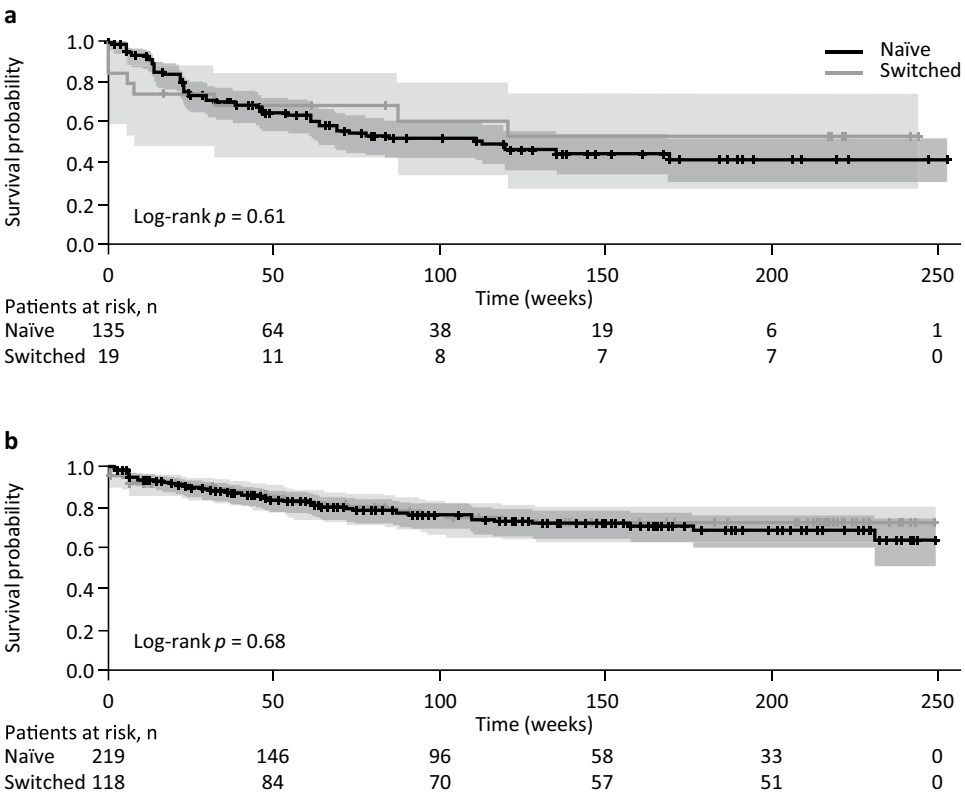

Fig. 1 Drug survival, according to previous infliximab treatment (naïve vs switched; safety analysis group). **a** Drug survival in patients with RA. **b** Drug survival in patients with AS. The numbers of patients still receiving each drug at different time points are shown. + Indicates censored patients. Shaded areas show the 95% confidence interval. *AS* ankylosing spondylitis, *RA* rheumatoid arthritis

Table 3 Reasons for discontinuation of CT-P13 (safety analysis group)

n (%)	Overall population *n* = 491	RA			AS		
		Total *n* = 154	Naïve *n* = 135	Switched *n* = 19	Total *n* = 337	Naïve *n* = 219	Switched *n* = 118
Patients who discontinued CT-P13	239 (48.7)	103 (66.9)	92 (68.1)	11 (57.9)	136 (40.4)	84 (38.4)	52 (44.1)
Reason for discontinuation							
Lack of effectiveness	97 (40.6)	53 (51.5)	49 (53.3)	4 (36.4)	44 (32.4)	31 (36.9)	13 (25.0)
AE	25 (10.5)	12 (11.7)	10 (10.9)	2 (18.2)	13 (9.6)	11 (13.1)	2 (3.9)
Loss of follow-up	35 (14.6)	9 (8.7)	8 (8.7)	1 (9.1)	26 (19.1)	17 (20.2)	9 (17.3)
Pregnancy	8 (3.4)	4 (3.9)	3 (3.3)	1 (9.1)	4 (2.9)	3 (3.6)	1 (1.9)
Remission	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drug holiday[a]	35 (14.6)	16 (15.5)	16 (17.4)	0 (0.0)	19 (14.0)	8 (9.5)	11 (21.2)
Other[b]	39 (16.3)	9 (8.7)	6 (6.5)	3 (27.3)	30 (22.1)	14 (16.7)	16 (30.8)

AE adverse event, *AS* ankylosing spondylitis, *bDMARD* biologic disease-modifying antirheumatic drug, *RA* rheumatoid arthritis

[a]Defined as a delay in drug administration for at least 12 weeks after the last infusion

[b]Other reasons for discontinuation ($n = 39$) were: change in therapy to infliximab or other bDMARD ($n = 19$), patient wanted to discontinue ($n = 8$), investigator judgment ($n = 3$), surgery ($n = 3$), patient switched to another clinical study ($n = 2$), improvement in symptoms ($n = 2$), insurance criteria not fulfilled ($n = 1$), trial ended ($n = 1$)

lung infection led to temporary discontinuation of CT-P13 treatment in another patient. The life-threatening SAE of serum sickness-like reaction occurred during the induction period in a 41-year-old, treatment-naïve, male patient with AS and was judged to be definitely related to study treatment. The patient had received three previous CT-P13 infusions and was being treated with concomitant sulfasalazine. CT-P13 was discontinued permanently and the SAE resolved. Four additional potentially treatment-related SAEs occurred in three patients (moderate pneumonia and severe influenza in one patient, moderate pyelonephritis in one patient and severe infectious colitis in one patient), but none

Table 4 Incidence of AEs (safety analysis group)

	Overall population			RA			AS		
	Total $n=491$	Naïve $n=354$	Switched $n=137$	Total $n=154$	Naïve $n=135$	Switched $n=19$	Total $n=337$	Naïve $n=219$	Switched $n=118$
AE, *n* (%)	148 (30.1)	105 (29.7)	43 (31.4)	49 (31.8)	44 (32.6)	5 (26.3)	99 (29.4)	61 (27.9)	38 (32.2)
Events, *n*	294	220	74	112	99	13	182	121	61
ADR, *n* (%)	91 (18.5)	62 (17.5)	29 (21.2)	28 (18.2)	24 (17.8)	4 (21.1)	63 (18.7)	38 (17.4)	25 (21.2)
Events, *n*	149	110	39	46	40	6	103	70	33
SAE, *n* (%)	17 (3.5)	14 (4.0)	3 (2.2)	5 (3.3)	4 (3.0)	1 (5.3)	12 (3.6)	10 (4.6)	2 (1.7)
Events, *n*	22	19	3	9	8	1	13	11	2
Drug-related SAE, *n* (%)	9 (1.8)	6 (1.7)	3 (2.2)	3 (2.0)	2 (1.5)	1 (5.3)	6 (1.8)	4 (1.8)	2 (1.7)
Events, *n*	11	8	3	4	3	1	7	5	2

ADR adverse drug reaction, *AE* adverse event, *AS* ankylosing spondylitis, *RA* rheumatoid arthritis, *SAE* serious adverse event

Table 5 TEAEs experienced by ≥ 1% of patients in the total RA and AS population (safety analysis group)

Preferred term, *n* (%)	RA $n=154$	AS $n=337$
Upper respiratory tract infection	6 (3.9)	14 (4.2)
Influenza-like illness	4 (2.6)	5 (1.5)
Urticaria	2 (1.3)	7 (2.1)
Alanine aminotransferase increased	1 (0.6)	6 (1.8)
Pruritus	2 (1.3)	5 (1.5)
Rash	2 (1.3)	5 (1.5)
Infusion-related reaction	3 (1.9)	2 (0.6)
Nasopharyngitis	3 (1.9)	2 (0.6)
Aspartate aminotransferase increased	0 (0.0)	4 (1.2)
Urinary tract infection	2 (1.3)	1 (0.3)
Dyspnea	2 (1.3)	0 (0.0)

Values are expressed as *n* (%)

AS ankylosing spondylitis, *RA* rheumatoid arthritis, *TEAE* treatment-emergent adverse event

of these events resulted in changes to CT-P13 treatment. All of the 11 SAEs that were considered potentially related to treatment resolved. One patient permanently discontinued CT-P13 following moderate pyrexia, which was considered unlikely to be drug-related. There were no deaths.

3.6 Effectiveness

In the total RA population, disease activity, assessed by DAS28-ESR and DAS28-CRP, decreased markedly from baseline following treatment initiation, and thereafter remained relatively stable during follow-up (Fig. 2a, b). The number of switched patients with available DAS28 data was too low for meaningful comparison between naïve and switched patients. In patients with AS, median BASDAI score decreased from baseline following initiation of CT-P13 treatment (Fig. 2c). Disease activity score was well maintained in patients with AS switched from reference infliximab to CT-P13.

4 Discussion

This study provides the longest-term evidence available to date regarding the safety and effectiveness of the infliximab biosimilar CT-P13 in patients with RA or AS. Analysis of medical records over 5 years demonstrated that long-term CT-P13 treatment was safe and effective in patients with either long-established moderate-to-severe RA or active AS treated under routine medical care in the Republic of Korea. Drug survival and safety of CT-P13 were similar in patients who were infliximab-naïve at the start of CT-P13 treatment and those who switched from reference infliximab to CT-P13.

The similarity in drug survival rates between naïve and switched patients is in line with previous reports. Previous analyses of long-term data from the KOBIO registry demonstrated an overall 4-year drug survival rate of 66% in Korean patients with AS treated with CT-P13 in routine clinical practice [25]. Drug survival tended to be longer in naïve patients compared with switched patients, but the difference between groups was not significant. In addition, our findings with CT-P13 were similar to previous reports of long-term drug survival for reference infliximab. In our analysis, the 5-year drug survival rate for the subset of infliximab-naïve RA patients was 41.2%, which is similar to the 44.3% reported for reference infliximab treatment in 222 TNF-inhibitor-naïve RA patients in an Italian single-center study [29], and slightly higher than the 4-year retention rate (37.6%) reported for patients with longstanding RA included in an Italian national registry [30]. This similarity between

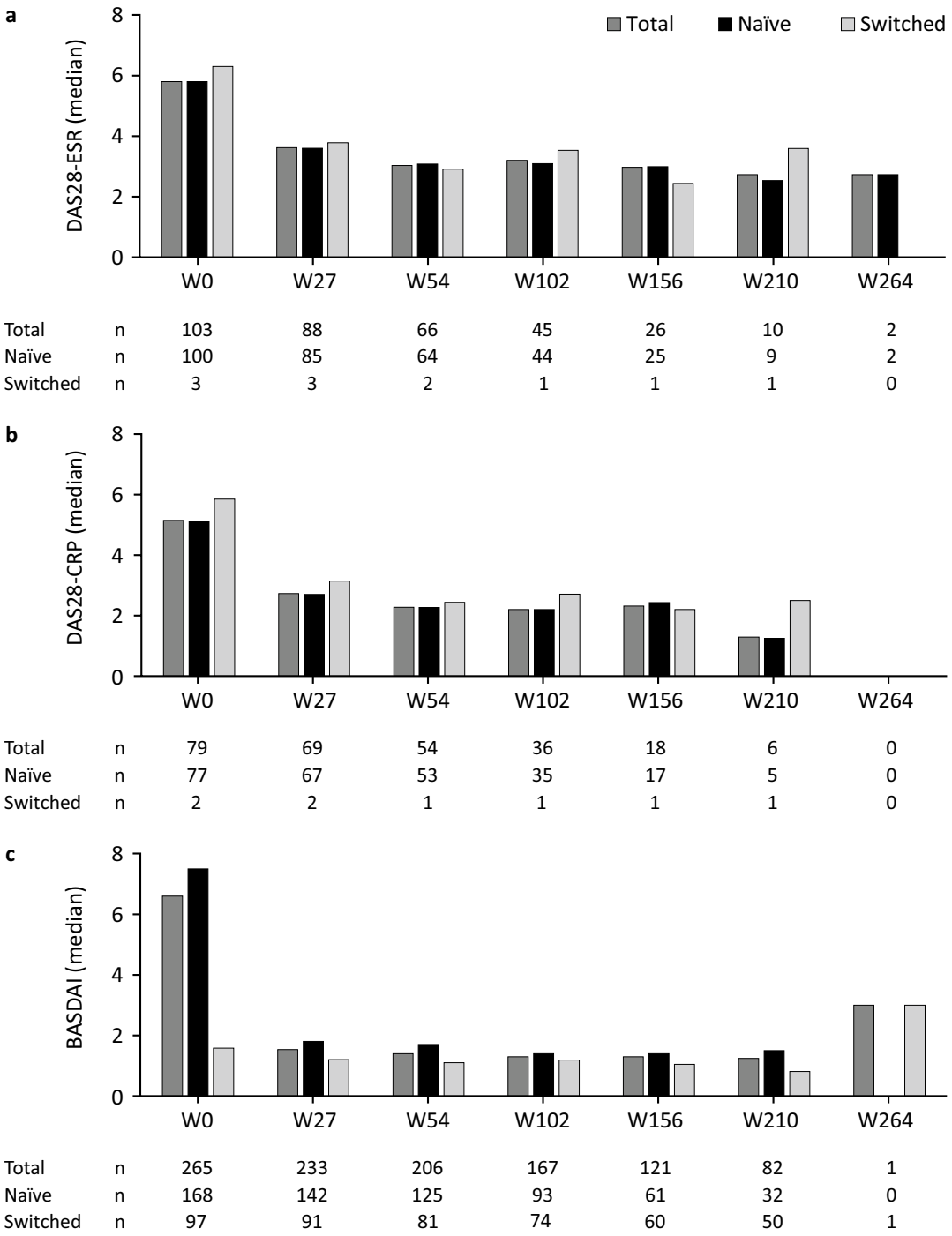

Fig. 2 Median disease activity in the total, naïve and switched RA and AS patient populations (effectiveness analysis group). **a** DAS28-ESR in patients with RA. **b** DAS28-CRP in patients with RA. **c** BASDAI score in patients with AS. *AS* ankylosing spondylitis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 joints, *ESR* erythrocyte sedimentation rate, *RA* rheumatoid arthritis, *W* week

CT-P13 and reference infliximab is in keeping with previous findings for patients with RA enrolled in the KOBIO registry: long-term drug survival was comparable between agents for the overall population, and for naïve and switched patients [26]. In our analysis, the 5-year drug survival in the overall AS population (67.2%) and in the naïve group (63.5%) is similar to that reported for 179 patients with axial spondyloarthritis receiving reference infliximab as a first-line biologic (64%) [31].

We observed that the probability of drug survival at Year 5 for patients with AS was numerically higher than for those with RA, for both naïve and switched groups. This is in line with previous observations with infliximab and other TNF inhibitors from registry and single-center studies [32–34]. The drug survival rate in 310 patients with AS in the Czech National Registry ATTRA was greater than in 958 patients with RA (72% vs 49%, respectively) after 3 years' treatment with TNF inhibitors [34]. Similarly, analysis of the Spanish BIOBADASER registry revealed significantly greater drug survival in spondyloarthritis patients ($n = 1524$; including 657 with AS) treated with TNF inhibitors compared with RA patients ($n = 4006$) over 3 years; the difference was attributed in part to a better safety profile in spondyloarthritis [32].

Drug survival is a composite measure of safety, tolerability and effectiveness [35]. Previous studies with infliximab and other TNF inhibitors have identified lack of effectiveness and AEs as the most common reasons for discontinuation [29, 32–38]. In our analysis, we did not detect any differences in the frequency of AEs or the proportion of patients discontinuing due to AEs between RA and AS patients; however, markedly more RA than AS patients discontinued due to lack of effectiveness (51.5% vs 32.4%, respectively). Similar findings regarding discontinuations due to lack of effectiveness were observed in a Korean single-center analysis of patients with RA ($n = 114$) and AS ($n = 310$) with at least 1 year of follow-up [33]. In that analysis, 21.0% of AS patients discontinued first-line TNF inhibitor treatment (comprising infliximab, etanercept or adalimumab), compared with 56.1% of RA patients. In common with our study, lack of effectiveness was the most common reason for treatment discontinuation for patients with RA, accounting for 43/64 (67.2%) discontinuations compared with 21/65 (32.3%) discontinuations for patients with AS. In addition, AEs were the most common reason for TNF inhibitor discontinuation in patients with AS, accounting for 27/65 (41.5%) discontinuations.

Infliximab has a well-established long-term safety profile in rheumatologic disease, characterized by increased rates of infection, in common with other TNF inhibitors [39, 40]. The safety profile of CT-P13 observed in this study was similar in patients with RA and AS and did not differ between naïve and switched patients. In addition, the safety profile was in accordance with the established safety profile of infliximab [39, 40]. The incidence of AEs (31.8% and 29.4% in patients with RA and AS, respectively) was similar or slightly lower than that reported in previous real-world studies with CT-P13 [23–25]. In our analysis, the most commonly reported TEAEs were related to infection: upper respiratory tract infection and influenza-like illness were the two most frequent TEAEs overall. Many of the most frequent TEAEs identified in our analysis have also been reported among the most common TEAEs or study drug-related TEAEs in clinical trials [12–16] and real-world studies [23, 25] of CT-P13 treatment in RA and AS.

Reference infliximab and CT-P13 treatment are known to be associated with acute infusion-related reactions, including anaphylactic shock, and delayed hypersensitivity [1–3, 5, 6]. In our retrospective analysis, infusion-related reactions occurred in 1.9% and 0.6% of patients with RA and AS, respectively, a slightly lower rate than observed with CT-P13 for patients with AS reported in a prospective analysis of the KOBIO registry (4.1%) [25] and in the interim analysis of the PERSIST study (2.5%) [23]. In our study, one life-threatening serum sickness-like reaction occurred in a treatment-naïve patient with AS who had received three CT-P13 infusions. This SAE was considered to be related to CT-P13 and led to permanent discontinuation of the study drug. Serum sickness or serum sickness-like reaction is listed as an uncommon ADR in the EU product information for reference infliximab and CT-P13 [1, 2, 5]; the product information notes that serum sickness-like reactions (or delayed hypersensitivity) have been reported to occur early in the treatment course in clinical studies, as observed in this case, as well as with infliximab re-treatment after an extended infliximab-free interval [1–3, 5, 6]. In the literature, rare reports of serum sickness-like reactions after initial infliximab therapy exist, with one case occurring after the first infliximab infusion potentially linked to presensitization to murine antigens [41]. In addition, anti-drug antibody formation has been postulated as a risk factor for serum sickness-like reactions to infliximab [42]; however, since immunogenicity data were not collected during our analysis, we cannot make any inferences about our case. Such cases underscore the need for continuous pharmacovigilance in patients beginning treatment with, or switching to, CT-P13.

In addition to the SAE of serum sickness-like reaction, potentially drug-related SAEs leading to permanent discontinuation of CT-P13 treatment were experienced by a further four patients. One of these patients, who had switched from reference infliximab to CT-P13, experienced hypersensitivity vasculitis. Vasculitis is listed as a rare ADR in the EU product information for reference infliximab and CT-P13 [1, 2, 5], with several reports describing multiple cases of hypersensitivity vasculitis (or leukocytoclastic vasculitis) related to infliximab treatment in patients with rheumatic diseases [43–47]. Although the pathogenesis of TNF inhibitor-associated vasculitis remains unclear and may be heterogeneous, associations with anti-drug antibody development, TNF/TNF inhibitor complex deposition and skewing of cytokine responses have been suggested [43, 44, 46, 48, 49]. Immunogenicity data were not collected for this analysis, precluding further analysis of this proposed risk

factor for the patient described here. The remaining three patients with potentially drug-related SAEs leading to permanent discontinuation of CT-P13 treatment experienced pulmonary tuberculosis, tuberculosis pericarditis, and (in the same patient) splenic abscess and pulmonary tuberculosis. Tuberculosis is listed as an uncommon ADR in the EU product information for reference infliximab and CT-P13 [1, 2, 5], while EU and US product information both state the importance of evaluating patients for active and latent tuberculosis prior to treatment initiation [1–3, 5, 6]. In our analysis, one of these cases of tuberculosis arose in a patient for whom the *Mycobacterium* infection screening history was unknown.

Considering the similarity in safety profiles between naïve and switched patients in our analysis, this is in keeping with a recent systematic review of 70 studies (largely observational in nature) that did not identify any significant risks associated with a single switch between reference and biosimilar infliximab [40]. However, the systematic review found that there were insufficient data to perform a meta-analysis [40], highlighting the importance of continued data collection. As our study included patients who had switched from reference infliximab to CT-P13, the similarity in overall safety profiles between switched and naïve patients provides further support for the safety of switching from reference infliximab to CT-P13.

Our study had several limitations. It was a retrospective, observational study conducted at five university hospitals in the Republic of Korea, which relied on medical records for data collection. It is possible that data may not have been recorded correctly, and some information of interest may not have been captured. Indeed, the number of RA patients who switched treatment was low ($n = 19$), limiting the conclusions that can be drawn from these patients. In particular, baseline DAS28-ESR and DAS28-CRP were available for only three and two switched patients with RA, respectively (Table 1), meaning that reliable conclusions about long-term disease activity could not be made for this patient group and statistical analyses were not appropriate. The low number of switched patients with RA may reflect the greater number of treatment options available to patients with RA versus AS [50], and the increased drug survival in patients with AS compared to RA, as discussed previously. By contrast, disease activity, assessed by respective DAS28 and BASDAI measures, decreased markedly from baseline in naïve patients with RA and AS, and was maintained in switched patients with AS, over the initial 27 weeks. Improvements were sustained to Week 210, demonstrating the long-term effectiveness of CT-P13. Indeed, one of the key strengths of this analysis is the long (up to 5-year) follow-up period. Despite this, even longer-term follow-up might still be required to detect some AEs, such as malignancy.

An additional strength of our study is the relatively large patient population, which included all patients with RA or AS who received CT-P13 at each participating center during the study period. This provides real-world data for Korean patients with RA or AS receiving bDMARD therapy, with heterogeneity in prior bDMARD treatment reflected in the study population (overall, 13.3% and 10.5% of infliximab-naïve patients with RA and AS, respectively, had received prior bDMARDs other than infliximab). Prior bDMARD treatment has been demonstrated to affect drug survival: for example, data from 563 patients with RA included in the Korean National Health Insurance database showed 1-year persistence after infliximab initiation was higher in patients who were receiving their first bDMARD compared with patients switched from another bDMARD (52.6% and 43.0%, respectively) [51]. Therefore, bDMARD treatment history could affect the drug survival reported in our study.

5 Conclusion

This analysis of patients with RA and AS provides the longest-term evidence available to date about the safety and effectiveness of CT-P13 treatment. CT-P13 treatment (for up to 5 years) was safe and effective, based on the incidence of AEs, drug survival and disease activity measures. Drug survival and safety were similar in infliximab-naïve patients and those who switched from reference infliximab to CT-P13, supporting switching to CT-P13 in patients receiving reference infliximab.

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Author Contributions T-HK made a substantial contribution to the acquisition of data. S-SL, WP, YWS, SKK, YNL and DHY made a substantial contribution to the conception or design of the study and the acquisition/interpretation of data. CHS made a substantial contribution to the conception or design of the study. All authors made a substantial contribution to manuscript development, gave final approval of the manuscript for submission and agree to be accountable for all aspects of the work. DHY is the guarantor for the overall content of the manuscript.

Data Availability Statement All data generated during the current analysis are included in this published article and its supplementary information file.

Compliance with Ethical Standards

Funding This study was supported by Celltrion Healthcare Co., Ltd. (Incheon, Republic of Korea).

Research Involving Human Participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ajou University Hospital Institutional Review Board, AJIRB-MED-MDB-17-449; Chonnam National University Hospital Institutional Review Board, CNUH-2018-030; Hanyang University Hospital Institutional Review Board, HYU 2017-12-037; Inha University Hospital Institutional Review Board, INHAUH201712010; Seoul National University College of Medicine/Seoul National University Hospital Institutional Review Board, H-1801-047-914) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent For this type of retrospective analysis, formal informed consent was not required, in accordance with Article 16 of the Bioethics and Safety Act of the Republic of Korea.

Conflict of interest T-HK, S-SL and YWS report no conflicts of interest. WP received consulting fees from Celltrion Healthcare. C-HS received consulting fees (< $10,000) from CELLTRION. SKK and YNL are employees of Celltrion Healthcare and own stock/stock options for Celltrion Healthcare. DHY received fees from Celltrion for grants, consulting, advisory board meetings, speakers' bureau and lectures.

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