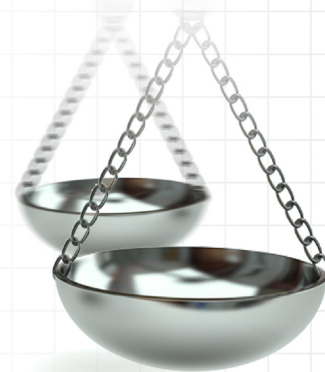




Comparative effectiveness of the biosimilar CT-P13

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The first biosimilar infliximab, CT-P13 (infliximab-dyyb) has been used for the treatment of inflammatory diseases for 4 years. CT-P13 has highly similar efficacy and safety profiles with a lower price than the originator infliximab and has been approved in 81 countries. Despite approval for clinical use, some knowledge gaps still limit the widespread and pertinent use of biosimilar CT-P13. One of the most important factors for proper utilization of CT-P13 for the treatment of immune-mediated inflammatory diseases is confidence in CT-P13, which could be enhanced by scientific evidence supporting the biosimilarity of CT-P13. Overall, five randomized controlled studies have been performed. For the other extrapolated indications, many observational induction and switching studies also support the utility of CT-P13 in the treatment of inflammatory diseases. Here, we review profiles of CT-P13 including physicochemical properties, clinical efficacy and safety data in all indications and current status.

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CT P-13, infliximab-dyyb, is the first biosimilar infliximab (INX), which was approved in 2012 by the Ministry of Food and Drug Safety of Korea [1], 2013 by the EMA [2] and 2016 by the US FDA [3], and is on the market as three brand names with Remsima, Inflectra and Flammegis (in Russia and CIS; Commonwealth of Independent States). Approval from regulatory agencies have been based on the totality of evidences supporting biosimilarity between CT-P13 and originator INX by various comparability exercises. Comparability exercises include biosimilarity on the physicochemical property, equivalence of pharmacokinetics (PK), clinical efficacy and safety including immunogenicity [4–6]. Clinical trials conducted for an approval of CT-P13 were large randomized clinical studies of PLANETAS with 250 ankylosing spondylitis (AS) patients [7] and PLANETRA with 606 active rheumatoid arthritis (RA) patients [8]. To date, CT-P13 has been approved in at least 81 countries worldwide, and currently on the market in at least 63 countries including all European countries, USA, Canada and Mexico. In Asia-Pacific region, it is available in Australia, Korea, Japan, Malaysia, The Philippines, Singapore and Thailand. Clinical indications for CT-P13 include RA, AS, psoriasis, psoriatic arthropathy (PsA), inflammatory bowel diseases (IBDs) including Crohn's disease (CD), ulcerative colitis (UC) and pediatric Crohn's disease (PCD) [2]. Although some countries were reluctant to accept indication extrapolation to IBDs, but Health Canada also recently has approved indication extrapolation to IBDs including fistulizing CD (FCD) [9].

Even after regulatory bodies approved CT-P13 for clinical application, some concerns and knowledge gaps against widespread use of biosimilars still exist [10–12]. The most important factor for increasing uptake of biosimilars is confidence in those biosimilars, which can be increased through scientific evidence from randomized clinical trials and real world data from both pharmacovigilance and investigator-led academic studies. Here, we review physicochemical properties, pharmacologic characteristics, randomized controlled studies for an approval by regulatory authorities and real world experiences of CT-P13 to increase confidence in CT-P13 for the treatment of immune-mediated inflammatory diseases. All valuable published literatures for INX biosimilar, CT-P13 were searched from pub-med at regular interval of 1 week, rather than searching literatures through systematic review

process. Additionally, important abstracts presented at academic congress were assessed through communication with manufacturing company and Google search.

Physicochemical property

CT-P13 is an IgG1 chimeric human-murine monoclonal antibody biosimilar to INX. CT-P13 is produced in the same type of cell-line (Sp2/0-AG14 – purchased from ATCC, Cat. CRL-1581) and has an identical amino acid sequence to INX [13]. CT-P13 and INX have demonstrated comparable *in vitro* primary pharmacodynamics in a range of studies. Studies for the mechanisms of action include binding to tumor necrosis factor (TNF), TNF neutralization, binding to Fc receptors and *in vitro* cytotoxicity study [13,14]. CT-P13 and INX showed comparable binding affinities to monomeric and trimeric human TNF- α (hTNF- α), and transgenic mouse hTNF- α (tmhTNF- α) expressed by Jurkat cells. Comparable hTNF- α neutralizing activity against a TNF- α -sensitive mouse sarcoma cell line (WEHI-164) has also been demonstrated. CT-P13 and INX are also comparable in terms of lack of binding activity to human TNF β and TNF- α from a range of different species known not to bind INX [13]. CT-P13 also demonstrated comparable and dose-dependent suppression of cytokine secretion and suppression of apoptosis by blocking sTNF in an IBD model (epithelial cells) [15]. CT-P13 and INX are also comparable in binding affinities to Fc γ RI, Fc γ RIIa, Fc γ RIIb and FcRn, and to neutrophils from healthy donors or CD patients [13]. Although CT-P13 showed relatively reduced binding affinities to Fc γ RIIIa and Fc γ RIIIb and natural killer cells of healthy donors and CD patients, the difference was genotype specific (V/V and V/F) and disappeared in presence of diluted human serum from CD patient. CT-P13 and INX showed comparable C1q binding and complement-dependent cytotoxicity effects and apoptotic effects against a Jurkat T-cell-line expressing tmhTNF- α , peripheral blood mononuclear cells (PBMC) from healthy donors and CD patients. And there was a comparable blockade of proinflammatory cytokine production by reverse signaling by using a cell-based assay, for example PBMC from healthy donors and CD patients. In terms of cytotoxicity assay, two drugs showed comparable antibody-dependent cellular cytotoxicity activity by using tmTNF-expressing Jurkat cells as target cells and various effector cells: PBMC or natural killer cells from healthy donors; whole blood from healthy donors or CD patients. When lipopolysaccharide-stimulated monocytes from healthy donors or CD patients were used as target cells, PBMC showed comparable antibody-dependent cellular cytotoxicity activity as effector cells. Additionally, highly comparable human tissue cross-reactivity results have been observed for biotinylated CT-P13 and INX [13,15]. All these data strongly demonstrated biosimilarity of CT-P13 and INX [13–16]. Through all these experiments, INX and CT-P13 demonstrated similarity in physicochemical properties.

PK profile

PK equivalence of CT-P13 to INX was demonstrated by three independent studies (Table 1). The first study was the PLANETAS study to demonstrate PK equivalence of steady state between week 22 and week 30 after infusion of CT-P13 and INX in patients with AS. The primary end points were area under the concentration-time curve (AUC) and the observed maximum serum concentration ($C_{\max}$). Equivalence was demonstrated if the 90% confidence interval (CI) for the ratio of the mean of each agent was within the margin of 80–125%. Steady state PKs (AUC and $C_{\max}$) were equivalent for CT-P13 (32,765.8 μ gh/ml and 147.0 μ g/ml) and INX (31,359.3 μ gh/ml and 144.8 μ g/ml) in the overall PK population. The ratio of geometric means was 104.5 for AUC (90% CI: 94.3–115.8) and 101.5 for $C_{\max}$ (90% CI: 94.7–108.9). In the antidrug antibody (ADA)-negative patients ($n = 171$), geometric means of AUC and $C_{\max}$ were higher than in the overall PK population, but the ratios of geometric means in this subgroup were 103.4, 104.7 for AUC and $C_{\max}$, ss (90% CI: AUC, 94.6–113.1; $C_{\max}$, ss, 97.2–112.9), respectively. The mean secondary PK end points were also highly similar between CT-P13 and INX [7].

The second study was to demonstrate PK equivalence of CT-P13 and INX in Japanese patients with RA. The primary end points were the area under the curve (AUC τ) between week 6 and week 14 and $C_{\max}$ at week 6 of these two drugs. The CT-P13 to INX ratios (90% CI) of the geometric mean AUC τ and $C_{\max}$ in patients negative for antibodies to INX at week 14 were 111.62% (100.24–124.29%) and 104.09% (92.12–117.61%), respectively, demonstrating the pharmacokinetic equivalence of these drugs. CT-P13 and INX, administered at a dose of 3 mg/kg in combination with methotrexate (MTX) to active Japanese RA patients, were pharmacokinetically equivalent [17].

According to the guideline for approval from US FDA, PK, safety and tolerability of CT-P13 with two formulations of the INX from either Europe (EU-INX) or the USA (US-INX) were observed by a double-blind, three-arm, parallel-group study (EudraCT number: 2013–003173–10) [18]. Healthy subjects received single doses (5 mg/kg)

Table 1. Summary of results for randomized controlled studies of CT-P13 for the treatment of arthritis.

Study (year)	Study characteristics	Target disease	Number of patients	Primary end point	Main findings	Ref.
Park <i>et al.</i> (2013, 2016)	PLANETAS Phase I RCT	AS	Week 0: 250 (CT-P13 125, RP 125)	Equivalence of PK profile: AUC and $C_{max, ss}$ between weeks 22 and 30	PK profiles were equivalent between groups ASAS20 and ASAS40 responses at week 30 were similar Safety including ADAs were comparable	[7,22]
			Week 54: 210 (CT-P13 106, RP104)	Week 54: comparability of PK profile, efficacy and safety	ASAS20, ASAS40 response and ASAS partial remission were comparable Change from baseline in PROs, ADA positive rate and Safety profile were comparable	
Yoo <i>et al.</i> (2013, 2016)	PLANETRA Phase III RCT	RA	Week 0: 606 (CT-P13 302, RP 304)	Equivalence of ACR 20 response at week 30	ACR20 responses were 60.9% for CT-P13 and 58.6% for INX (95% CI: -6–10%) Secondary disease activity measures were highly similar Incidence of drug-related adverse events and detection of ADAs were highly similar	[8,20]
			Week 54: 455 (CT-P13 233, RP 222)	Comparability of efficacy and safety	ACR20, ACR50 and ACR70 response rates were comparable DAS28, SDAI and CDAI decreased to a similar extent Radiographic progression was also comparable ADA positive rate at week 54 was similar	
Takeuchi <i>et al.</i> (2015)	CT-P13 study in Japan: Phase I/II RCT	RA	101 (CT-P13 50, EU-IFX 51)	PK equivalence (AUC τ at weeks 6–14 and C_{max} at week 6)	Pharmacokinetic equivalence of CT-P13 and INX was demonstrated Comparable therapeutic efficacy at weeks 14 and 30: the ACR response, DAS28, the EULAR response and other efficacy criteria The incidence of adverse events was similar	[17]
Park <i>et al.</i> (2015)	Phase I PK study	Healthy normal	CT-P13:71 US-INX:71 EU-INX:71	PK profile (C_{max} , AUC_{last} and AUC_{inf}) among US-INX, EU-INX and CT-P13	PKs were equivalent between all formulations (CT-P13 vs EU-INX; CT-P13 vs US-INX; EU-INX vs US-INX) All other PK end points supported the high similarity of the three treatments	[18]

ACR: American College of Rheumatology; ADA: Antidrug antibody; AS: Ankylosing spondylitis; ASAS: Assessment in spondyloarthritis international society; AUC: Area under the curve; CDAI: Clinical disease activity index; $C_{max, ss}$: Maximal concentration at steady state; DAS: Disease activity score; EU: European Union; EULAR: European League Against Rheumatism; INX: Infliximab; ITT: Intention to treat; LDA: Low disease activity; PK: Pharmacokinetic; PRO: Patient reported outcome; RA: Rheumatoid arthritis; RCT: Randomized controlled trial; SDAI: Simple Disease Activity Index; US: United States.

of CT-P13 ($n = 71$), EU-INX ($n = 71$) or US-INX ($n = 71$). Primary end points (C_{max} , AUC_{last} and AUC_{inf}) were equivalence between all formulations (CT-P13 vs EU-INX; CT-P13 vs US-INX; EU-INX vs US-INX). All other PK end points supported the high similarity of the three comparators. In terms of PK profiles, CT-P13 is equivalent to originator INX regardless of its source of manufacture (Table 1) [18].

Recently, a randomized controlled Phase III study to compare CT-P13 and INX in patients with active CD has been performed, and demonstrated therapeutic noninferiority (NI) of CT-P13 to INX. In addition, C_{max} and C_{trough} levels from week 0 to week 14 were highly equivalent between CT-P13 and INX in CD patients [19]. Through these randomized controlled studies in normal controls, AS, RA and CD patients, PK profiles of INX and CT-P13 were proved as equivalent.

Clinical efficacy & safety

Induction therapy or randomized controlled study with CT-P13

Rheumatoid arthritis

PLANETRA was a Phase III randomized, double-blind, parallel group study to demonstrate the equivalence of efficacy and comparability of safety between CT-P13 and INX with MTX in patients with active RA. Patients with active disease despite MTX (12.5–25 mg/week) were randomized to receive 3 mg/kg of CT-P13 ($n = 302$) or INX ($n = 304$). The primary end point, American College of Rheumatology 20% (ACR20) responses at week 30 were 60.9% for CT-P13 and 58.6% for INX (95% CI: -6–10%) in the intention-to-treat population. Thus primary end point was completely within predefined equivalence margin of $\pm 15\%$. The proportions in CT-P13 and INX groups achieving good or moderate European League Against Rheumatism responses-C-reactive protein (EULAR-CRP) at week 30 were 85.8 and 87.1%, respectively. Low disease activity or remission according to DAS28-CRP, ACR-EULAR remission rates, ACR50/ACR70 responses and all other PK and PD end points were highly similar at week 30. This study proved that CT-P13 was equivalent in efficacy to INX at week 30 [8].

Among 606 RA patients participated into the PLANETRA study, 455 patients (CT-P13 233, INX 222), were treated up to week 54. At week 54, ACR20 response rate was highly similar between groups (CT-P13 74.7%, INX 71.3%). ACR50 and ACR70 response rates were also comparable between groups (CT-P13 43.6 and 21.3%, respectively; INX 43.1 and 19.9%, respectively). DAS28, Simple Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) decreased from baseline to week 54 to a similar extent with CT-P13 and INX. Radiographic progression measured by Sharp scores modified by van der Heijde was also comparable. With both treatments, patient assessments of pain, disease activity and physical ability, as well as mean scores on the Medical Outcomes Study Short Form Health Survey (SF-36) improved markedly at week 14 and remained stable thereafter up to week 54 [20].

In a randomized, double-blind, parallel-group, multicenter study performed in Japan, 3 mg/kg of CT-P13 or INX, in combination with MTX (6–16 mg/week), was administered for 54 weeks to active RA patients with an inadequate response to MTX, to compare their efficacy and safety. In full analysis set, 50 and 51 patients were randomized to receive CT-P13, or INX respectively, and CT-P13 and INX showed comparable therapeutic efficacy at weeks 14 and 30 by the ACR response, DAS28, the EULAR response and other efficacy criteria (Table 2) [17].

Very recently, the real world experience data observed the characteristics of RA patients receiving either biosimilar CT-P13 or INX and identified the effectiveness and safety of CT-P13 in RA patients in South Korea [21]. A total of 100 RA patients from a prospective biologic disease modifying antirheumatic drugs (bDMARDs) registry, 55 CT-P13 and 45 INX users were analyzed. Baseline characteristics were similar in the two groups, but baseline DAS28-erythrocyte sedimentation rate (ESR) was higher in the originator INX group (6.3 ± 1.1 vs 5.8 ± 1.1 , $p = 0.02$). The early DAS28-ESR remission was observed 7.9 months after starting CT-P13 whereas 15.0 months with originator INX respectively ($p = 0.47$).

Ankylosing spondylitis

PLANETAS study was a Phase I randomized, double-blind, multicentre, parallel-group, prospective study comparing the PK, safety and efficacy of CT-P13 and INX in patients with AS. Patients were randomized to receive 5 mg/kg of CT-P13 ($n = 125$) or INX ($n = 125$). Assessment of spondyloarthritis international society (ASAS20) and ASAS40 responses at week 30 were 70.5 and 51.8% for CT-P13 and 72.4 and 47.4% for INX, respectively [7]. In addition, 54 week data of PLANETAS showed comparable efficacy, immunogenicity and safety of CT-P13 with INX in patients with AS. Of 250 randomized patients, 210 (84.0%) completed 54 weeks of treatment. At week 54, ASAS20, ASAS40 response and ASAS partial remission were comparable between treatment groups. Changes from baseline in mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and SF-36 scores were similar between treatment groups (Table 1) [22].

Inflammatory bowel diseases

Although randomized controlled study in patients with IBD has not yet been published, a randomized controlled Phase III study to compare CT-P13 and INX in patients with active CD has been performed. This study was set to demonstrate therapeutic noninferiority (NI) of CT-P13 to INX, and primary end point was CDAI-70 response at week 6. Overall 220 patients were enrolled and 111 patients were randomized to CT-P13 group, and 109 to INX. Among them, 92 and 88 patients respectively completed 30 weeks of trial. CDAI-70 response rates at week 6

Table 2. Summary of controlled studies and real world experiences of switching from infliximab originator to CT-P13 in rheumatic diseases.

Study (year)	Study characteristics	Enrolled patients	Main findings	Ref.
Yoo <i>et al.</i> (2017)	Extension study of PLANETRA	302 RA patients: maintained on CT-P13 group 158 (maintenance), switched to CT-P13 group 144 (switch)	ACR20/50/70 rates at week 102 were 71.7/48.0/24.3 vs 71.8/51.4/26.1% in the maintenance vs switch groups, respectively ADA positive rate was comparable between groups TEAEs occurred in similar proportions of patients in the two groups	[48]
Park <i>et al.</i> (2017)	Extension study of PLANETAS	174 AS patients: maintained on CT-P13 group 88, switched to CT-P13 group 86	ASAS20 response rates at week 102 were 80.7 and 76.9%. ASAS40 and ASAS partial remission were also similar between groups ADA positivity rates were comparable Adverse events led to treatment discontinuation were similar	[50]
Tanaka <i>et al.</i> (2017)	Extension study of Japan study	71 RA patients: maintained on CT-P13 group 38, switched to on CT-P13 group 33	TEAE incidence was comparable between groups Safety profiles in both groups were similar to those in the Phase I/II study. 11 of 28 patients who were positive for ADA at week 62 discontinued 10 of 28 ADA-positive patients became negative during the study	[49]
Nikiphorou <i>et al.</i> (2015)	Prospective observational study in Finland	39 rheumatic disease patients: RA 15, AS 14, psoriatic arthritis 7, JIA 2, chronic reactive arthritis 1	Disease activity and patient reported outcomes were similar after switching to CT-P13 for 11 months Discontinued CT-P13 in 11: ADAs against INX before switching (3); LTBI (1); other (1); subjective reasons without flare (6) Six patients back to originator infliximab treatment again	[53]
Jorgensen <i>et al.</i> (2017)	NOR-SWITCH: randomized, double-blind, noninferiority, Phase IV trial	481 patients under treatment with INX at least for 6 months: RA 77, SpA 91, CD 155, UC 93, PsA 30, chronic plaque psoriasis INX 241; CT-P13 240	Flare according to predefined criteria of flare up at 52 weeks was 26.2% in the INX and 29.6% of the CT-P13 group. 95% confidence interval of the adjusted treatment difference was -12.7~3.9%, meeting noninferiority margin of 15% The secondary end points of remission rate, change in composite score, immunogenicity, or safety were comparable	[55]
Glintborg <i>et al.</i> (2017)	DANBIO registry: a nationwide observational study for switch from INX to CT-P13	802 patients under INX therapy: RA 403, AxSpA 279, PsA 120	Disease activity and flares 3 months before and after the switch were similar for the three diseases Flare rate in RA and PsA (Δ DAS28 ≥ 1.2): 10% in each of pre- and postswitch Crude 1 year retention rate to CT-P13 was 84.1%, compared with 86.2% of historic INX cohort. Adjusted absolute retention rate was 3.4% lower after switching compared with historic data due to placebo effect	[56]
Benucci <i>et al.</i> (2017)	Italian spondyloarthropathy cohort study	41 SpA treated with INX for more than 6 months with activity: AS 22, enteropathic arthritis 5, PsA 10, undifferentiated SpA 4	After 6 months of CT-P13 therapy, there were no statistical differences in their median BASDAI, BASFI, ASDAS-CRP, DAS28-CRP, VAS pain scores, whereas the median duration of morning stiffness had significantly decreased There was no change in drug levels or ADA levels	[51]

ACR: American College of Rheumatology; ADA: Antidrug antibody; AS: Ankylosing spondylitis; ASAS: Assessment in spondyloarthritis international society; ASDAS-CRP: Ankylosing spondylitis disease activity score-C reactive protein; AxSpA: Axial spondyloarthritis; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; CD: Crohn's disease; INX: Infliximab; JIA: Juvenile idiopathic arthritis; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; SpA: Spondyloarthropathy; TEAE: Treatment emergent adverse event; UC: Ulcerative colitis; VAS: Visual analog scale.

were 71.4% (75/105) in CT-P13 group and 75.2% (76/101) in INX group, and treatment difference was 3.8%, thus 95% CI was -15.9~9.0, which was completely within the predefined NI margin of 20% in per protocol analysis. CDAI-70 response rates at week 30 were 78.1% (82/105) in CT-P13 group and 77.2% (78/101) in INX group, and treatment difference was 0.9%, thus 95% CI was -10.6~12.4. In addition, CDAI-100 response and remission rate were highly similar between two groups. PK profile, ADA-positive rate and adverse events were highly comparable [19].

To date, 17 uncontrolled prospective or retrospective studies with CT-P13 have been conducted in South Korea and European countries. In these studies, CT-P13 showed favorable clinical responses in patients with IBD; however, there were some differences in the outcome measures between studies (Table 3 & 4). To date, 13 prospective studies have been reported for the treatment of IBD with CT-P13. Out of the 13 prospective studies, 6 studies were pure induction therapeutic trials with CT-P13 for IBD patients [23–28] and other three studies were switching trials from INX to CT-P13 [29–31]. The other four studies contained both induction population and switching population

Table 3. Clinical study results of induction therapy with CT-P13 in patients with inflammatory bowel disease.

Study (year)	Characteristics	Country	Number of patients	Primary end point	Clinical response and safety	Ref.
Kim <i>et al.</i> (2017)	Randomized controlled double blinded study	Korea, Europe, Russia, Israel	CD 220; CT-P13 111, INX 109	CDAI-70 response rate at week 6	CDAI-70 response rates at week 6: 71.4% (75/105) in CT-P13 group and 75.2% (76/101) in INX group 95% CI: -15.9~9.0% (NI margin = 20%)	[19]
Kang <i>et al.</i> (2015)	Retrospective open label study	Korea	CD 3, UC 5	CDAI, MSS	Clinical response at week 8: 7/8(87.5%); 5/5 UC, 2/3 CD One UC patient discontinued CT-P13 and had arthralgia	[39]
Jung <i>et al.</i> (2015)	Retrospective study	Korea	CD 32 (LCD 31, FCD 1), UC 42	CDAI MSS, PMSS	Clinical response/remission rates in CD: 90.6% /84.4% at week 8, 87.5% /75.0% at week 54 Clinical response/remission rates in UC: 81.0% /38.1% at week 8, 100% /50.0% at week 54	[36]
Farkas <i>et al.</i> (2015)	Prospective induction therapy	Hungary	CD 18, UC 21; 16 CD and 15 UC patients completed induction	CDAI, MSS	Clinical response/remission in LCD: 37.5% / 50% at week 8 2/3 FCD responded, and 1 in remission Clinical response/remission in UC: 20% /66.7% at week 8	[24]
Park <i>et al.</i> (2015)	Postmarketing study	Korea	CD43, FCD 8, UC 62	TEAEs and disease-specific clinical response and remission	TEAEs of total cohort: 18.1% (15/83 CD; Naive n = 43, switch n = 40), 16.7% (2/12 FCD; naive n = 8, switch n = 4), 26.9% (21/78 CD; Naive n = 62, switch n = 16), 10% related to treatment Response/remission at week 30: 79.5% /59.0%, 66.7% /50.0%, 72.2% /37.0% in CD, FCD, UC	[37]
Jahnsen <i>et al.</i> (2015)	Prospective observational study	Norway	CD 46, UC 32	Remission at week 14, CRP and FCP	Remission: 79% in CD, 56% in UC Significant reductions of CRP and FCP after treatment	[23]
Gecse <i>et al.</i> (2016)	Prospective, multicenter, nationwide cohort study	Hungary	CD 126, UC 84	Clinical remission at week 14 Clinical response, remission at week 30	Clinical response/remission at week 14: 81.4/53.6% in CD, 77.6/58.6% in UC At week 30, 67.2/80% of week 14 responder CD/UC patients maintained clinical response TEAE 17.1%, infusion reactions 6.7% and infection 5.7%	[25]
Keil <i>et al.</i> (2016)	Prospective induction study	Czech	CD 30, UC 22	CDAI, MSS before and after 14 weeks	In CD, remission in 50.0%, and partial response in 50.0%. In UC, remission in 40.9%, partial response in 54.5% and no response in 4.5%	[26]
Farkas <i>et al.</i> (2016)	Prospective induction therapy	Hungary and Czech	UC 63	MSS at week 14 Sigmoidoscopy at week 14 TL	Clinical response/steroid-free remission at week 14: 82.5% /47.6% complete mucosal healing: 27%	[27]
Fiorino <i>et al.</i> (2017)	A prospective, multicenter, cohort studyPROSIT-BIO Study	Italy	Group A: 311 anti-TNF naive; CD 156, UC155 Group B: 139 pre-exposed to anti-TNFs; CD 103, UC 36	Clinical remission or response and treatment persistency; the immunogenicity predictive factors of safety and efficacy	After 8/16/24 weeks, efficacy estimations: 95.7% /86.4% /73.7% for naive, 97.2% /85.2% /62.2% for pre-exposed Serious adverse events of total cohort(n = 547): 66 (12.1%), infusion-related reactions 38 (6.9%)	[32]

ADA: Antidrug antibody; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CRP: C reactive protein; FCD: Fistulating CD; FCP: Fecal calprotectin; HBI: Harvey-Bradshaw Index for Crohn's disease; Hgb: Hemoglobin; INX: Infliximab; LCD: Luminal CD; MES: Mayo endoscopic subscore; MSS: Mayo Scoring System; NI: Noninferiority; PCDAI: Pediatric Crohn's Disease Activity Index; PMSS: Partial Mayo Scoring System; PUCAI: Pediatric Ulcerative Colitis Activity Index; SCCAI: Simple Clinical Colitis Activity Index for ulcerative colitis; TL: Trough level of infliximab; UC: Ulcerative colitis; VAS: Visual analog.

Table 3. Clinical study results of induction therapy with CT-P13 in patients with inflammatory bowel disease (cont.).

Study (year)	Characteristics	Country	Number of patients	Primary end point	Clinical response and safety	Ref.
Jahnsen <i>et al.</i> (2015)	Induction study	Norway	CD 46, UC 32	HBI, PMSS, SCCAI, CRP, FCP, TL of INX at week 14	Significant improvement of all parameters in CD and UC after 14 weeks 79% of CD and 56% of UC patients were in clinical remission at week 14	[23]
Kolar <i>et al.</i> (2017)	Prospective study	Czech	CD 90, UC 29	HBI, SCCAI endoscopy laboratory parameters, TL, ADA	Response at week 14: CD 92%, UC 83% At week 46: CD 86% UC 64% No increase in immunogenicity Comparable type and frequency of AE	[34]
Argulles-Arias <i>et al.</i> (2017)	Prospective observational study	Spain	CD 13, UC 9	HBI, PMSS, CRP	Remission rate at months 3 and 6: CD (66.7 & 50.0%), UC (44.4 & 66.7%) Adverse events in 7.5% of patients	[35]
Kolar <i>et al.</i> (2017)	Observational study	Czech	CD 107, UC 33	Clinical, endoscopic, laboratory parameter (CRP, FCP, ATI, TL)	Response rate: week 14(CD 94%, UC 82%), week 54(CD 87%, UC 60%), Remission at week 54 (CD 47%, UC 36%)	[34]

ADA: Antidrug antibody; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CRP: C reactive protein; FCD: Fistulating CD; FCP: Fecal calprotectin; HBI: Harvey-Bradshaw Index for Crohn's disease; Hgb: Hemoglobin; INX: Infliximab; LCD: Luminal CD; MES: Mayo endoscopic subscore; MSS: Mayo Scoring System; NI: Noninferiority; PCDAI: Pediatric Crohn's Disease Activity Index; PMSS: Partial Mayo Scoring System; PUCAI: Pediatric Ulcerative Colitis Activity Index; SCCAI: Simple Clinical Colitis Activity Index for ulcerative colitis; TL: Trough level of infliximab; UC: Ulcerative colitis; VAS: Visual analog.

from INX to CT-P13 [32–35]. Additionally, four retrospective or postmarketing studies recruited 504 patients from South Korea: 287 biologic naive patients and 217 patients for switching trials (330 CD, 36 fistulizing CD [FCD] and 138 UC patients) [36–39]. As a total, 2459 patients with IBD have participated in the CT-P13 studies: 904 CD, 639 UC and 19 FCD patients for induction studies, whereas 648 CD, 227 UC and 22 other IBD patients including FCD for switching studies. Therefore, there have been clinical study data for 1552 CD, 866 UC and 41 other IBD patients.

The first study was conducted in South Korea, and was a retrospective open label observational study with a total of 17 patients, consisted of 8 CD and 9 UC. Eight patients were naive to biologics, and 5 CD and 4 UC patients were switched from INX to CT-P13. Among eight naive cases, clinical responses at week 8 were achieved in seven patients (5/5 UC and 2/3 CD), and one UC patient discontinued CT-P13 due to arthralgia [39].

The first pure induction study with CT-P13 was performed in Hungary with 39 biologic naive patients. Reduction of more than 100 point in Crohn's Disease Activity Index (CDAI) was used as clinical response in CD, and remission was defined as CDAI <150 for luminal CD(LCD). UC response was defined as >30% decrease in Mayo scoring system and a decrease in the rectal bleeding and endoscopy subscores. Remission was classified as a partial Mayo score ≤ 2 , with no individual subscores >1. Additionally, mucosal healing was defined as Mayo endoscopy subscore of 0 or 1. Induction treatment was completed in 16 (13 with luminal CD, 3 with FCD) CD and 15 UC patients. In those with luminal CD, clinical response and remission was achieved in 6/16 (37.5%) and 8/16 (50%) of the patients respectively at week 8. Among three FCD patients, two patients reached clinical response and one patient achieved a remission. In 15 UC cases, clinical response and remission was achieved in 3(20%) and 10 (66.7%) patients at week 8. Two UC patients discontinued treatment due hypersensitivity in one patient and toxic megacolon in another case [24].

Prosit-Bio study was a prospective, multicenter, cohort study using a structured database from 31 Italian referral centers. Among enrolled 547 patients (313 CD and 234 UC), 311 patients were naive to anti-TNF agent, 139 had a previous exposure to biologics (INX 34, adalimumab 105, and golimumab 3), and the remaining 97 were switched to CT-P13 after a mean of 18 ± 14 infusions of INX. The anti-TNF agents were stopped in these patients for any reasons except intolerance 6–23 months before starting CT-P13. Main reasons for stopping therapy were loss of response (63%) or adverse events (23%). The mean follow-up was 4.3 ± 2.8 months, and the total follow-up time was 195 patient-years. The efficacy of the biosimilar was evaluated in 434 patients who received treatment for at least 8 weeks, using time-to-event methods for censored observations. After further 8, 16 and 24 weeks, the efficacy estimations were 95.7, 86.4 and 73.7% for naive, 97.2, 85.2 and 62.2% for pre-exposed patients and 94.5,

Table 4. Summary of clinical studies on the switching from INX to CT-P13 in patients with inflammatory bowel disease.

Study (year)	Study characteristics	Country	Number of patients	Primary end point	Main findings	Ref.
Kang <i>et al.</i> (2015)	Retrospective open label study	South Korea	CD 5, UC 4	CDAI, MSS	8/9 maintained clinical efficacy One CD patient experienced loss of response	[39]
Jung <i>et al.</i> (2015)	Retrospective study	South Korea	CD 27, UC 9	CDAI, MSS, PMSS for UC	Maintenance of efficacy: 92.6% in CD, 66.7% in UC Adverse events: 11.8% of UC patients	[36]
Park <i>et al.</i> (2015)	Postmarketing study	Korea	CD 40, FCD 4, UC 16	TEAEs and disease-specific clinical response and remission	Stable disease in 87.1% of CD None UC patients worsened 75.0% of FCD maintained disease control	[37]
Smits <i>et al.</i> (2016)	Prospective observational cohort study	Netherlands	CD 57, UC 24, IBD-unclassified 2	HBI, SCCAI, CRP, FCP, TL, ADAs Averse events Clinical remission	No change of disease activity in CD and UC No change in median CRP and FCP levels Median TL was increased ADA positive: 7, 2 new ADA, 5/7 ADA positive: discontinued CT-P13	[29]
Buer <i>et al.</i> (2016)	Prospective open label study	Norway	CD 99, UC 44	Maintenance of CT-P13 at 6 months after switching HBI, PMSS, CRP Hgb, FCP, ADA	97% remained on the medication at 6 months No change in disease activity, CRP, Hgb, FCP, infliximab dose and interval or p-infliximab Three patients developed new detectable ADAs	[30]
Fiorino <i>et al.</i> (2017)	A prospective, multicenter, cohort study PROSIT-BIO Study	Italy	CD 53, UC 44	Clinical remission or response and treatment persistency	After 8/16/24 weeks, response rate 94.5%/90.8%/78.9%	[32]
Razanskaite <i>et al.</i> (2017)	Managed switching study	UK	CD 118, UC 23, IBD unclassified 2	Adverse event laboratory data	Patients reported a similar incidence of side effects before and after switch No clinically significant differences in drug persistence, laboratory finding after the switch to CT-P13 No increase in immunogenicity	[31]
Jahnsen <i>et al.</i> (2017)	Prospective study	Norway	CD 37, UC 19	HBI, PMSS, SCCAI, CRP, FCP, TL of IFX at week 14	No differences in disease activity, and biomarkers, but increase of TL after switching in CD patients. UC patient – no significant differences in PMSS, CRP, FCP, TL	[33]
Kolar <i>et al.</i> (2017)	Prospective study	Czech	CD56, UC 18	HBI, PMSS, SCCAI laboratory parameter	Remission at week 0: 72.2%, week 56, 77.8% HBI, SCCAI difference between week 0 and 56 = 0 Mean change between week 0 and 56 in CRP and FC: not significant	[34]
Argulles-Arias <i>et al.</i> (2017)	Prospective observational study	Spain	CD 67, UC 31	HBI, PMSS, CRP	Among patients in remission at baseline, remission was maintained at months 3 and 6: CD (87.5 and 83.9%); UC (92.0 and 91.3%)	[35]

ADA: Antidrug antibody; CD: Crohn's disease; CDAI: Crohn's Disease Activity Index; CRP: C reactive protein; FCP: Fecal calprotectin; HBI: Harvey-Bradshaw Index for Crohn's disease; Hgb: Hemoglobin; IFX: Infliximab; MES: Mayo Endoscopic Subscore; MSS: Mayo Scoring System; PCDAI: Pediatric Crohn's Disease Activity Index; PMSS: Partial Mayo Scoring System; PUCAI: Pediatric Ulcerative Colitis Activity Index; SCCAI: Simple Clinical Colitis Activity Index for ulcerative colitis; TL: Trough level of infliximab; UC: Ulcerative colitis; VAS: Visual analog.

90.8 and 78.9% for switched patients, respectively. Thus, preliminary data on efficacy and safety of CT-P13 were in line with those of INX [32]. CT-P13 had to be stopped in 29 (5.3%) cases for severe infusion reactions (8 naive, 19 previous exposed, and 2 switch), and in further 16 patients (2.9%) for other serious adverse events. Infusion reactions were significantly more frequent in patients pre-exposed to INX than to other anti-TNF- α (incidence rate ratio = 2.82; 95% CI: 1.05–7.9).

A prospective, multicenter, nationwide cohort study conducted in Hungary recruited 210 patients, who were consisted of 126 CD and 84 UC patients. Among them, anti-TNF agents were pre-exposed in 26.2% of CD, and 19.3% of UC patients. At Week 14, 81.4% of CD and 77.6% of UC patients showed clinical response and 53.6% of CD and 58.6% of UC patients were in clinical remission. Clinical remission rates at week 14 were significantly higher in CD and UC patients who were INX naive (60.9% in CD, 65.1% in UC), compared with those with previous exposure to the originator compound (35.7% in CD, 33.3% in UC) [25]. However this statistical difference disappeared at week 30. At week 30, 67.2% of CD and 80% of UC responders at week 14 maintained clinical response to CT-P13. Up to week 30, adverse events had occurred in 17.1% of all patients. Infusion reactions occurred in 14 patients (6.7%) among CT-P13 treated patients. Ten of the 14 patients had previously received the originator INX. Infusion reactions occurred in a significantly higher proportion of patients with previous INX exposure compared with naive patients (27 vs 2.5%, $p < 0.001$). In another study, 140 IBD patients (CD, 107; UC, 33) were treated with CT-P13, and were assessed based on clinical, endoscopic and laboratory parameters. Overall, 94% of CD and 82% of UC patients responded to induction therapy (week 14). At week 54, the response rates were 87% in CD and 60% in UC, and 47 and 36% of patients were in remission, respectively. Fifty-two percent of UC patients experienced mucosal healing at week 14 and improvement of perianal disease occurred in 96% of CD patients at week 54. Treatment was continued in 83% of patients at the end of the follow-up (89% CD and 64% UC). These findings suggest that INX after 1 year in naive patients with IBD patients seems to be effective and safe, with no additional safety issues comparing to the originator [28].

Two additional retrospective study data with Korean patients with IBD, who were 187 INX naive patients and 114 patients switched from originator INX to CT-P13. In one study, 32 CD (LCD 31, FCD 1), 42 UC patients, who were INX naive, showed following response: clinical response and remission rates in CD were 90.6% (29/32) and 84.4% (27/32) at week 8, and 87.5% (7/8) and 75.0% (6/8) at week 54, respectively. In UC, clinical response and remission rates were 81.0% (34/42) and 38.1% (16/42) at week 8, and 100% (12/12) and 50.0% (6/12) at week 54, respectively [36]. One postmarketing study recruited 113 biologic naive patients [37]. Treatment emergent adverse events (TEAEs) occurred in 18.1, 16.7 and 26.9% of CD, FCD and UC patients, respectively. Treatment-related TEAEs occurred in 10% of patients and were mostly mild-moderate in severity. Response/remission rates at week 30 were 79.5%(31/39) /59.0%(23/39), 66.7%(4/6) /50.0%(3/6), 72.2%(39/54) /37.0%(20/54), in CD, FCD, UC respectively, regardless of whether patients had received prior INX or not. At week 14 response/remission rates were 87.2%(34/39) /69.2%(27/39), 66.7%(4/6) /33.3%(2/6), 75.5%(40/53) /49.1%(26/53). Very recently, one multicenter observational study enrolled 204 patients consisted of 24 FCD and 180 moderate to severe active CD patients in South Korea. Among 10 anti-TNF naive FCD patients, remission rates at week 14 and week 30 were 40.0% (4/10) and 60.0% (6/10), respectively. In anti-TNF naive CD patients, remission rates at week 14 and 30 were 72.0 and 82.4%, respectively. Switched patients from INX to CT-P13 achieved remission in 87.5 and 80.0%, respectively, among FCD and CD patients during postbaseline visits. The overall safety profile up to week 30 was comparable to historical data [38]. A recent meta-analysis identified 11 observational studies reporting outcomes in 829 patients treated with CT-P13 [40]. The pooled rates of clinical response among CD and UC at 8–14 weeks were 0.79 (95% CI: 0.65–0.88) and 0.74 (95% CI: 0.65–0.82), respectively, and at 24–30 weeks were 0.77 (95% CI: 0.63–0.86) and 0.77 (95% CI: 0.67–0.85), respectively. Adverse events were rare (CD, 0.08 (95% CI: 0.02–0.26); UC, 0.08 (95% CI: 0.03–0.17).

Taken together, one randomized controlled study demonstrated the NI of efficacy and comparability of safety between CT-P13 and INX in CD patients. Additionally, sufficient numbers of observational induction studies also supported real world experiences of CT-P13 in terms of efficacy and safety compared with historical data of INX in the management of IBD patients.

Pediatric IBD

Most of clinical study results in pediatric IBD patients have not been published yet. The first experience of the efficacy and safety of the CT-P13 in the induction therapy of pediatric UC was derived with six patients. Three patients completed the induction therapy and showed a decrease in the Pediatric Ulcerative Colitis Activity Index

Scores (PUCAI) [41]. The efficacy of induction therapy with the biosimilar IFX has been assessed in 12 pediatric patients with CD. 10/12 patients (83%) showed a significant decrease in Pediatric Crohn's Disease Activity Index (PCDAI) Scores and a drop off in the inflammatory marker levels. AEs were recorded in only two subjects [42].

One of the largest induction study in the treatment of patients with pediatric IBD compared the efficacy and safety of INX and CT-P13. CT-P13 was used for 24 patients (18 CD and 6 UC), whereas INX in 17 patients (15 CD and 2 UC). Median number of infusions per patient was 3 and 6, respectively, for CT-P13 and INX. Clinical remission was achieved in 7/11 (64%) CD patients receiving CT-P13, whereas 8/15 (53%) receiving INX. Remission rate was the same with both treatments [43].

Another prospective observational study recruited 36 pediatric CD patients from three Polish academic centers. Patients received three induction doses (5 mg/kg) of CT-P13 at weeks 0, 2, 6 and 34/36 (94.4%) patients completed induction therapy. A clinical response or remission after three initial doses was achieved in 31/36 (86%) and 24/36 (67%) of patients, respectively. Clinically and statistically significant decreases in PCDAI, CRP and ESR were observed in the responders' group [44]. To date, CT-P13 was tried to children with IBD in less than 100 patients, but was very useful with similar safety and efficacy profile to INX in this disease.

Psoriasis

The first and positive case series was reported from an institute in Czech. CT-P13 was initiated in three men and a woman who suffered from severe chronic plaque psoriasis, and three patients were associated with psoriatic arthritis. They were treated with 5 mg/kg of CT-P13 at weeks 0, 2, 6 and then every 8 weeks. The effect of therapy was evaluated at weeks 14 and 30 after therapy initiation. All four patients reached in clinical remission according to Psoriasis Area Severity Index (PASI) Score and clinical presentation of three patients with arthritis [45]. There was another observational study with five psoriasis patients who were naive to INX, and presented moderate to severe disease activity. PASI and visual analog pain scale for subjective improvement were used as outcome measures. Four of five INX naive patients treated with CT-P13 achieved 75% improvement or better from baseline [46]. Recent report from the Psobiosimilars registry in Italy showed that 82 patients who were naive to INX responded well to CT-P13. PASI score was significantly reduced from 20.8 ± 12.1 at baseline to 7.2 ± 7.1 after 6 months ($p = 0.001$). PASI75 response was achieved by 80% of patients at 6 months [47]. Thus more clinical experiences need to be accumulated in patients with psoriasis and PsA.

Study results for switching from originator to CT-P13

A particularly common question is whether patients currently treated with a biologic can be switched to a biosimilar without affecting treatment efficacy or safety. With the introduction of CT-P13, it is possible to treat biologic naive patients with CT-P13 earlier than current recommendation, but also to switch from originator INX to biosimilar CT-P13 taking advantage of reducing healthcare cost. Switching can be carried out either under consent of healthcare provider or without such consent but following payer's policy or decision.

Rheumatoid arthritis

To date, there have been several studies on the efficacy and safety of switching from originator INX to CT-P13 in various indications. The first open-label extension study recruited 302 RA patients who had completed PLANETRA study. Data were analyzed for 158 patients who received CT-P13 for 102 weeks (maintenance group) and for 144 patients who received INX for 54 weeks and then switched to CT-P13 (switch group). Response rates at week 102 for maintenance versus switch groups, were 71.7 versus 71.8% for ACR20, 48.0 versus 51.4% for ACR50 and 24.3 versus 26.1% for ACR70, respectively. Conclusively, efficacy was well maintained in patients who switched from INX to its biosimilar CT-P13 for an additional year [48].

The Japanese extension study aimed to evaluate the efficacy and safety of CT-P13 in patients with RA after switching from INX supported additional evidence. Patients who completed 54 weeks of treatment in a Phase I/II study received CT-P13 at an initial dose of 3 mg/kg at week 62, with dose increase permitted up to 10 mg/kg. A total of 71 patients, who were consisted of 38 patients in the maintenance group and 33 in the switch group reported similar safety profiles. Eleven of 28 patients who were positive for ADA at week 62 discontinued the study before week 110. Forty-one of 43 ADA-negative patients remained negative, and 10 of 28 ADA-positive patients became negative during the study. This study added data that switching was not delivering a detrimental effect. Unfortunately, all extension studies did not have a group of patients continued on originator INX treatment for 2 years as a control group [49].

AS & spondyloarthritis

The PLANETAS extension study was conducted to investigate the efficacy and safety of switching from INX to CT-P13 or maintaining CT-P13 treatment in patients with AS. This study recruited 174 patients with AS, and 88 versus 86 were allocated to each group, respectively. In these maintenance and switch groups, respectively, ASAS20 response rates at week 102 were 80.7 and 76.9%. ASAS40 and ASAS partial remission were also similar between groups. This study also provided that switching from INX to its biosimilar CT-P13 is possible without negative effects on safety or efficacy in patients with AS [50].

Recently, an Italian study to investigate the real-life efficacy, safety and immunogenicity of switching from INX to CT-P13 in patients with spondyloarthritis (SpA) was reported. Forty-one patients from three Italian rheumatology centers with a previous diagnosis of SpA and clinically inactive or moderate disease activity (AS 22, enteropathic arthritis 5, PsA 10, undifferentiated SpA 4), who had been treated for more than 6 months with INX, were switched to CT-P13 and followed up for 6 months. At the time of the switch, the patients had a median duration of treatment with INX of 73.7 months (range 6–144). After switching, there were no statistical differences in their median BASDAI, BASFI, ASDAS-CRP, DAS28-CRP, VAS pain scores, whereas the median duration of morning stiffness had significantly decreased. Furthermore, there was no change in drug levels or ADA levels. Thus, the switch from innovator to CT-P13 in that Italian multicenter SpA cohort supported an additional efficacy and safety experience of switching to CT-P13 [51].

Inflammatory bowel diseases

To date, six prospective and three retrospective studies in South Korea and European countries have been performed in patients with IBD, consisted of 483 CD patients, 196 UC patients and 8 other and undifferentiated IBD patients.

The first experience of switching in IBD patients was conducted in South Korea, and was a retrospective open label observational study with five CD and four UC patients. Eight patient among nine switched patients maintained their clinical efficacy, but one patient experienced loss of response during the study period [39].

A Prosit-Bio study from Italy recruited 97 patients who were switched from INX to CT-P13 after a mean of 18 infusions of INX. After 8, 16, and 24 weeks of treatment, the efficacy estimations were 94.5, 90.8 and 78.9% for switched patients, which were highly similar to the efficacies of CT-P13 in biologic naive patients and biologic pre-exposed patients [32].

In a managed switching study performed in UK, a total of 143 patients – consisting of 118 CD, 23 UC and 2 unclassified IBD – agreed to switch from INX to CT-P13. However, two patients were switched back to originator INX at the patients' request. They compared clinical efficacy, drug persistence, immunogenicity between 120 patients treated with INX before and 143 switched patients. That UK study noticed following results: similar incidence of side effects before and after switch; no clinically significant differences in laboratory findings after the switch to CT-P13; mean IBD-control-8 score rather improved from 10.4 to 11.2, which was statistically significant; no significant difference in drug persistence and no increase in immunogenicity. By this trial, hospital was able to achieve drug at reduced costs by £40,000–60,000 per month. This study demonstrated that a managed switching program from originator INX to biosimilar CT-P13 in IBD, using a gain-share agreement, delivers significant cost savings and investment in clinical services while maintaining similar patient-reported outcomes, biochemical response, drug persistence and adverse event profile [31].

A recent meta-analysis identified 11 observational studies reporting outcomes in 829 patients treated with CT-P13. The pooled rates of sustained clinical response among CD and UC after switching from INX to CT-P13 at 30–32 weeks were 0.85 (95% CI: 0.71–0.93) and 0.96 (95% CI: 0.58–1.00), respectively, and at 48–63 weeks were 0.75 (95% CI: 0.44–0.92) and 0.83 (95% CI: 0.19–0.99), respectively. Adverse events were rare (CD, 0.10; 95% CI: 0.02–0.31; UC, 0.22; 95% CI: 0.04–0.63). The conclusion of that meta-analysis is the fact that CT-P13 was associated with excellent clinical efficacy and safety profile, supporting its use in the treatment of IBD [40].

Pediatric IBD

A prospective switching study in pediatric patients with IBD was performed in Poland. Thirty-nine pediatric patients, consisting of 32 CD and 7 UC, were recruited. Among 32 CD patients, 26 (81%) patients were anti-TNF-naïve, but 5 CD patients were previously treated with INX and 1 patient received adalimumab before. One patient with UC had an 11-month history of INX therapy. Remission of CD was defined as PDAI <10 or <7.5 without the height item. In UC, a PUCAI <10 indicated remission. Efficacy of last CT-P13 doses of all patients

revealed rates of clinical remission in 88% for CD and 57% for UC patients, respectively. Among 20 patients who continued with CT-P13 therapy until last follow-up, 16/20 (80%) CD patients and all 4 UC individuals were in remission. One infusion reaction to CT-P13 was observed in a CD patient. The incidence of sporadic mild adverse events before and after switching did not differ significantly and was consistent with the safety profile of the INX [52].

Psoriasis

A small observational study was conducted with 30 psoriasis patients, who were under INX treatment. The median time on INX was 237 weeks before switching, and the median follow-up after switching was 23 weeks. After switching, PASI and visual analog scale scores were not significantly different before and after switching. Usually, about 50% of patients with psoriasis who start INX have to discontinue treatment within the first year because of loss of efficacy. However, when patients had a long-lasting response to the INX before switch, the adverse events and new immunogenicity may not develop in these patients [46].

Psobiosimilars is an observational registry of psoriasis patients from Italy, and identified 122 patients who switched from INX to CT-P13. The mean PASI score remained unchanged for 6 months from the time of switching (2.05 ± 2.8 vs 2.2 ± 3.2 , mean $\pm$ SD, $p = 0.3$). Among 204 psoriasis patients from Psobiosimilars registry, a total of 16 adverse events were observed, including infusion reactions and viral infections without any significant difference between the switch and naive group. The principal findings of these studies are that CT-P13 is effective as an induction therapy of psoriasis, and patients with chronic plaque psoriasis who respond to the INX originator can be switched to the biosimilar CT-P13 without experiencing a significant change in clinical response or additional adverse events including infusion reactions [47].

Switching data for patient groups with various diseases

The first real world switching experience in patients with various diagnosis was reported from Finland [53]. The study was focused on the clinical efficacy and safety of switching from INX to CT-P13 in 39 patients with established rheumatic diseases (RA 15, AS 14, PsA 7, juvenile idiopathic arthritis 2, chronic reactive arthritis 1). Patients were switched to CT-P13 after a mean of 4.1 years on INX. Disease activity and patient reported outcomes were similar after switching to CT-P13 for 11 months (median). Eleven patients (28.2%) discontinued CT-P13 due to ADAs against INX detected prior to CT-P13 infusion ($n = 3$); latent tuberculosis ($n = 1$); new-onset neurofibromatosis ($n = 1$); subjective reasons with no objective deterioration of disease ($n = 6$). Thus, the clinical effectiveness of CT-P13 was comparable to prior INX therapy during the first year after switching, and did not elaborate immediate safety signals. Although 11 patients discontinued CT-P13 after switching, ADA to INX was found in 3 patients, and for subjective reasons, probably negative expectations by patients may play a role among discontinuations of biosimilars. Therefore, increasing confidence in biosimilar medicine through education by related stakeholders is really important in accepting and continuing biosimilar therapy by patients. Authors worried about ADA to INX can induce immune-mediated adverse events, but PLANETRA already presented ADA to originator may cross react with CT-P13, as two drugs might be aiming the same target antigen [8,54]. Also switching did not increase adverse reaction including infusion reaction. An interesting finding from this report was the fact that 6 of the 11 discontinued patients switched back to INX treatment again. Although this observational study was not planned to look at the efficacy and safety of back and forth switching, eventually back and forth switching occurred without reporting significant adverse events [53].

The Norwegian NOR-SWITCH study is a 52-week randomized double blinded NI Phase IV trial, which was funded by Norwegian government. This study recruited 498 patients, and 482 patients were randomized (91 SpA, 77 RA, 30 PsA, 155 CD, 93 UC and 35 chronic plaque psoriasis). Patients should be on stable treatment with INX for at least 6 months, but had been treated with INX for 6.7 years (mean) and were randomized to continue INX or to switch to the CT-P13. For full analysis set, 241 and 240, a total of 481 patients were allocated to INX or CT-P13 treated group respectively. The primary end point was disease worsening during follow-up as revealed by worsening in disease-specific composite measures. The rate of disease flare up to 52 weeks was 26.2% in the INX group and 29.6% in the CT-P13 group. The adjusted treatment difference was -4.4%, and 95% CI was -12.7~3.9%, which was completely within the predefined NI margin of 15%. Although flare rates were different between diseases, but the number of patients was not sufficient to show NI in individual diseases. There were no differences between groups in the secondary end points of remission rate, change in composite score, immunogenicity or safety [55].

DANBIO registry, which is a nationwide registry holding almost all of patients with inflammatory arthritis under medical care in Denmark, reported observational results after switching. All Danish patients under treatment with INX for almost 7 years were switched to CT-P13 since 2015 according to the decision by healthcare authority. The DANBIO registry found 802 patients with different diagnosis (403 RA, 279 SpA and 120 PsA) who were infused CT-P13 as a nationwide nonmedical switch. Flare was defined as change in DAS28 ≥ 1.2 (RA/PsA) or Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥ 1.3 (AxSpA). Prior INX treatment duration was 6.8 (4.3–9.5) years. Disease activity and flares 3 months before and 3 months after the switch were similar for the three diseases. Crude 1-year CT-P13 retention rate (84.1 [95% CI: 81.3–86.5]) was similar to the historic IFX cohort (86.2 [95% CI: 84.0–88.0]; $p = 0.22$). The adjusted absolute retention rates were 83.4 (95% CI: 80.8–86.2) and 86.8% (95% CI: 84.8–88.8), respectively ($p = 0.03$), probably due to placebo effect. Patients with previous INX treatment duration >5 years had longer CT-P13 retention compared with shorter INX treatment duration. In total 132 patients withdrew due to lack of efficacy in 71 (54%), and adverse events in 37 (28%). As a conclusion, a nationwide nonmedical switch to CT-P13 had no negative impact on disease activity [56].

When NOR-SWITCH and DANBIO switching trial were performed as a nationwide nonmedical switch, both physicians and patients might be anxious in those switching studies because there had been no published data at that time. With growing evidences from real world experiences, physicians and patients may be confident in the safety and efficacy of CT-P13 gradually, and these positive findings support the widespread uptake of this particular biosimilar agent. But physicians need to understand that these results for the CT-P13 switching should not be extrapolated to the other biosimilars.

Immunogenicity data & related adverse events

The potential for immunogenicity is an important concern with biosimilars, especially since immune responses with biologics may be linked to safety issue. As bio-originators and biosimilars, are immunogenic protein molecules, they might be recognized by the patient's immune system as foreign antigens. The presence of ADA may produce a range of immunologic responses, including loss of efficacy, the potential for anaphylaxis and infusion reactions. The incidence of ADAs depends upon a number of factors, including disease type, combined DMARDs, type of assay, assay sensitivity and interference by free drug [57,58].

In PLANETRA study, the incidence of ADAs at week 30 was 48.4 versus 48.2%, and was highly similar for CT-P13 and INX-treated patients with RA, respectively [8]. The proportion of patients positive for ADAs at week 54 was similar between the two groups: 41.1 and 36.0% with CT-P13 and INX, respectively [20]. In PLANETAS study, ADA positive rate at week 30 was 27.4 and 22.5% for CT-P13 and INX, respectively [7]. At 54 weeks, 19.5 and 23.0% of patients receiving CT-P13 and INX, respectively, had ADAs [22]. During extension studies of PLANETAS and PLANETRA, patients were compared between a group maintained with CT-P13 for 2 years (maintenance group), and another group who switched from INX to CT-P13 (switch group). ADA positivity at week 102 in RA patients was comparable between groups (40.3 and 44.8%), respectively [48]. In PLANETAS extension study, ADA positivity rates at week 102 were 23.3 versus 27.4%, respectively [50].

In the real world experience with 232 patients in the DANBIO switch study, presence of medium-high ADA was unchanged over time and 94% of patients had similar ADA levels at baseline and at 3 months after switch. In the highly selected group of patients treated with INX for >5 years, a nonmedical switch to CT-P13 had no negative impact on drug concentration or presence of ADA at 3 and 6 months following switch. These findings are very consistent with each other study and provide additional support for efficacy, safety and immunogenicity issues related to switching to CT-P13 [59].

Even in real world switching experience studies, new appearance of ADAs was very rare, and mostly did not affect serum levels of effective drug and clinical efficacy. However, ADA and adverse reactions including infusion reaction were seemingly higher in patients who had been exposed to INX, and discontinued for a while [32]. Therefore, switching from INX to CT-P13 must be effective and safe if patients were switched to CT-P13 without interrupting period after INX treatment.

Since first biosimilar guideline was launched in 2005 by the EMA, 38 biosimilar agents have been approved [60]. To date, none of biosimilars approved in Europe have been removed from the market for safety or efficacy concerns. Also some switching data from real world experiences and extension studies of controlled trials demonstrated that switching from INX to biosimilar CT-P13 did not show any detrimental effects on their efficacy and safety including immunogenicity [48,50]. Therefore, concerns on immunogenicity have not been supported by real evidence from

clinical and scientific data, but have been raised by a theoretical point of view [61]. This immunogenicity issue must be answered more clearly by real data from long-term pharmacovigilance programs.

Recently, a study was conducted to identify whether antibodies to INX in 250 patients treated with INX (Remicade) cross-react with the CT-P13. Three different bridge ELISA using Remicade, CT-P13 with two brand names (Remsima, Inflectra) as detecting tagged antigens were used to detect ADAs. Among 250 patients, 50.4% of patients were positive to ELISA with tagged Remicade. In addition, ELISA with either Inflectra or Remsima as tagged antigen also found similar rate of ADA positivity [62]. They used a commercial ELISA for INX ADA detection (Promonitor-ANTI-IFX kit, Progenika Grifols, Spain) and concluded that this could be used to monitor ADAs in patients who would be switched to biosimilar CT-P13; however, this cannot be generalized to other INX biosimilars.

In addition to that result, an ad hoc analysis was conducted to assess the comparability of Remicade- and CT-P13-tagged immunoassays for the detection of ADAs and neutralizing antibodies (Nabs) using data from PLANETAS and PLANETRA trials. Sera from patients were analyzed using an electrochemiluminescence (ECL) bridging assay or Gyros immunoassay, tagged with Remicade or CT-P13 at various time points. In PLANETAS, 93.1% (94/101) of INX ADA-positive samples and 93.0% (93/100) of INX NAb-positive samples cross-reacted with CT-P13; 99.0% (103/104) of CT-P13 ADA-positive and 98.0% (98/100) of CT-P13 NAb-positive samples cross-reacted with the INX. In PLANETRA, 94.7% (426/450) of INX ADA-positive samples and 94.3% (415/440) of INX NAb-positive samples cross-reacted with CT-P13, and 96.6% (458/474) of CT-P13 ADA-positive and 96.4% (452/469) of CT-P13 NAb-positive samples cross-reacted with the INX. In both studies, there was strong agreement in outcome between assays at all postscreening time points, and significant concordance between assays was observed for NAb titer. Thus, these data have demonstrated that ADAs and NAb against CT-P13 and INX are cross-reactive, indicating that CT-P13 and INX may be sharing immunodominant epitopes [7,8,54].

Cross-reactivity of ADAs has also been demonstrated in patients with IBD treated with INX. Gils *et al.* developed three bridging ELISAs to compare cross-reactivity of ADAs to INX with Remsima and Inflectra in 36 serum samples from patients with IBD. The study showed excellent correlation of ADA titers between assays although small but significant differences were observed between the titers obtained by the three ELISAs [63]. An additional study was tested in 125 sera from IBD patients and control for their cross-reactivity. All 56 ADA to Remicade-negative controls were also negative for anti-Remsima ADA. All 69 positive anti-Remicade IBD sera were cross-reactive with Remsima. Thus all these results suggest that epitopes influencing the immune response to Remicade may be shared with the biosimilar CT-P13 [64].

Adverse events

In general, the adverse events including infection, serious infection, infusion reaction and serious adverse events have been not different significantly in biologic naive patients and in patients who were switched from INX to CT-P13.

The rates of TEAEs of special interest seen with CT-P13 in PLANETRA and PLANETAS are highly similar to those of historical clinical studies treated with INX [7,8,20,22]. Infections and infusion-related reactions (IRRs) were the TEAEs occurring most frequently with both CT-P13 and INX in direct comparisons and in historical studies [65]. Moreover, the incidence of TEAEs of special interest (infection, serious infection, IRR, lymphoma and malignancy) was generally comparable between CT-P13 and INX both in PLANETRA and PLANETAS and in other historical studies [7,8,20,22,65].

PLANETRA study reported that incidence of drug-related adverse events at week 30 (35.2 vs 35.9%) was highly similar for CT-P13 and INX, respectively [8]. The incidence of adverse events was also similar for these drugs in Japanese study [17]. In PLANETAS study, more than one adverse event occurred in 64.8 and 63.9% of patients, infusion reactions occurred in 3.9 and 4.9% of patients in the CT-P13 and INX groups, respectively [7]. There was no notable difference between treatment groups in the incidence of adverse events, serious adverse events, infections and IRRs, and CT-P13 was well tolerated and displayed a safety profile comparable to INX in AS and RA patients up to week 54 [22].

During extension study of PLANETRA, TEAEs occurred in similar proportions of patients in the two groups during the extension study (53.5% in maintenance and 53.8% in switch group, respectively). In addition, the occurrence of TEAEs was similar before and after switching to CT-P13 in switched group. Rates of TEAEs related to study treatment (22.0 and 18.9%), serious adverse events (7.5 and 9.1%) and TEAEs leading to discontinuation (10.1 and 5.6%) were also similar between the maintenance and switch groups' patients. IRRs were reported in 6.9

and 2.8% of patients in the maintenance and switch groups, whereas in 5.0 and 9.1% of patients during the main study, in the maintenance and switch groups, respectively [48].

AS extension study also showed that the proportion of patients who experienced at least one TEAE was 48.9% in the maintenance group and 71.4% in the switch group during the extension study, and 70.0 and 61.9% during the main study. Rates of TEAEs in both groups during the main and extension studies were within the range reported in historical studies with originator INX. Treatment-related TEAEs (22.2 and 39.3%), IRRs (7.8 and 7.1%), abnormal liver function tests (4.4 and 4.8%) and upper respiratory tract infection (3.3 and 2.4%) were reported in the maintenance and switch groups during the extension study, respectively. Most treatment-related TEAEs were mild-to-moderate in severity (45.6–65.5%), and TEAEs led to discontinuation of treatment during the extension study were noted in 3 (3.3%) and 4 (4.8%) patients in the maintenance and switch groups, respectively [50].

Additionally, there were no significant differences in the TEAEs in patients with IBDs, but IRRs and mild TEAEs were reported higher in IBD patients who previously had exposed to INX, and then discontinued INX prior to treatment with CT-P13 or who had ADA positivity in some observational studies [25,32,66], but not in other studies [24,27,34].

Pharmacovigilance data

After an approval of clinical use in the treatment of indicated diseases, multiple pharmacovigilance studies are still ongoing. Pharmacovigilance studies for inception cohorts of RA, AS and IBD are underway in South Korea and Europe. Postmarketing surveillance studies for all indication were also performed in South Korea or are ongoing in particular areas. In addition, Celltrion is conducting a multinational randomized controlled NI study to see the efficacy and safety of CT-P13 and INX in patients with CD. And also they communicate with big European registries and utilize CT-P13 exposure data of Germany and the UK. Total number of patients exposed to CT-P13 from official data needs to be at least 3100 according to EMA recommendation [67].

The utilization patterns of TNF inhibitors including CT-P13 in South Korea before and after the introduction of CT-P13 was assessed by using claims data from April 2009 to March 2014 from the Korean Health Insurance Review and Assessment Service database, which includes the entire South Korean population, including 983 with a prescription claim for CT-P13. Among all of the claims for INX, the proportion of CT-P13 among all INX claims increased to 19% through March 2014. After launching of CT-P13 at November 2012, there were significant changes in the slopes for trend in usage, with additional increases in the use of branded INX and CT-P13 (9 more claims per month, 95% CI: 2, 17) and decreases in the use of etanercept and adalimumab. Thus, during the first 15 months since its introduction in South Korea, one-fifth of all INX claims were for CT-P13. This real data showed that introduction of CT-P13 may affect the use of other TNF inhibitors [68].

Additional data from South Korea was a registry data from the prospective observational Korean nationwide Biologics (KOBIO) registry, which involved patient with RA who had started on a biologic agent for the first time or had switched to another biologic agent [69]. The KOBIO registry contained 1184 patients with RA from December 2013 to November 2015. Of the enrolled patients, 801 started with their first biologic agent, 228 were first-time switchers and 89 were second-time or more switchers. Among total population, 125 (11.2%) patients were treated with CT-P13, whereas 43 (3.8%) patients were treated with originator INX. Among 801 patients starting biologic therapy, anti-TNF agents are the first choice mechanism of action, and CT-P13 was used in 107 (13.4%) patients whereas INX in 37(4.6%) patients. Therefore, CT-P13 use was found to be three-times higher in the treatment of RA patients, who were biologic naive. The first and second switching with CT-P13 was rather small, in fact 7% of first switchers [69].

According to IMS health database, total exposure to CT-P13 by pharmacovigilance activities was 36,086 patient-year up to the end of 2015, and became 107,716 patient-year at the last day of 2016. By the expansion of CT-P13 invasion afterward in many countries, the exposure will be increasing rapidly, and we can get a newly updated data every year.

Current status of CT-P13 in Europe & cost saving

CT-P13 has been offered at a lower price to the market than the INX, therefore its use could reduce the whole economic burden associated with biologic therapy and increase access to biologic treatment. However, the magnitude of healthcare cost reduction by selecting CT-P13 instead of INX must be different according to health care policy of each countries, for example policy of determining drug price, gap of drug price between originator and its biosimilar, guidance or recommendation suggested by the healthcare authorities for the use of biosimilars.

Norwegian government utilizes tender system for all biologic use, and has expanded clinical use of CT-P13 in the treatment of approved diseases significantly. According to IMS Health data, total cost saving in Norway after using CT-P13 reached US\$48,023,139 from the fourth quarter of 2013 to at the end of 2016. Thus the number of additional patient available for CT-P13 therapy for 1 year became 7705. Recently total number of INX vials including originator INX and CT-P13 in clinical use became almost double compared with the number of vials in later half of 2013, but the fraction of originator INX among total INX usage in 2016 decreased to <10% of total INX usage [33].

A recent analysis showed the real-world effects of CT-P13 use in five European countries for 1.5 years from the starting point of marketing, 2015 [70]. Market share of CT-P13 was surveyed by IMS Health in France, Germany, Spain, Italy and the UK. Public prices for CT-P13 and INX in France, Spain, Italy and the UK were used to evaluate costs, but IMS Health sales data were used in Germany. Market share of CT-P13 in the first quarter of 2015 in France, Germany, Spain, Italy and the UK was 0, 2.0, 4.4, 0.3 and 0.1%, respectively, but this had risen to 19.6, 25.3, 36.8, 55.2 and 72.6%, respectively. Total cost savings by CT-P13 use in four countries reached €32,436,120 (Germany €2,791,405, Spain €12,233,004, Italy €9,958,223 and UK €7,453,488 respectively). Use of CT-P13 in place of INX could enable an additional 5428 (369, 2222, 1699 or 1138) patients per year to be treated with CT-P13 therapy in Germany, Spain, Italy and the UK, respectively.

Public prices for CT-P13 and originator INX are the same in France, but the prices of both originator INX and CT-P13 were reduced significantly. Thus, this reduction significantly decreased total cost for INX use in France, and use of the CT-P13 has gradually increased to 19.6% in one and half years. Competition between CT-P13 and INX could decrease costs of both drugs. It is anticipated that as the market share of CT-P13 increases, the economic burden in each country will decrease, and finally increasing access to biologic therapy with CT-P13 or other agents. The clinical use of CT-P13 for the treatment of inflammatory diseases in the USA initiated since the fourth quarter of 2016 at 15% reduced cost than INX. It is expected to increase the proportion of CT-P13 among all INX usage in the USA, and it must be dependent to the policy of determining price, and communication between related stakeholders.

By the highly similar efficacy and safety profile with lower price, CT-P13 in the treatment of inflammatory diseases will be used by earlier application to biologic naive patients, switching from originator INX, switching from other biologics. To improve implantation of CT-P13, future educational initiatives are important to overcome misunderstanding about biosimilars.

Conclusion

CT-P13, INX-dyyb is the first INX biosimilar approved in 81 countries including all European countries, the USA, Canada, Japan and Korea. Its biosimilarity has been approved by physicochemical properties, clinical efficacy and safety by controlled trials. In addition, many real world experiences also have enhanced the validity of biosimilar CT-P13 in the treatment of patients with inflammatory diseases.

One of the important advantages of biosimilar CT-P13 is lower price compared with originator, but highly similar efficacy and safety profiles. By the implantation of CT-P13 in clinical practice, significant cost savings can increase the number of patients eligible with treatment with biosimilar CT-P13, and also decrease more the price of originator biologic agent, thus decrease significantly healthcare budget. To improve implantation of CT-P13, all related stakeholders have to provide available information of biosimilar CT-P13 to patients, and physicians to increase awareness and confidence in biosimilar CT-P13.

Financial & competing interests disclosure

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Executive summary

- CT-P13 is the first biosimilar infliximab (INX) approved in 81 countries and has highly similar efficacy and safety profiles but lower price compared with INX.
- Physicochemical similarities between CT-P13 and INX were demonstrated by many experimental evidences including on the mechanisms of action.
- PK profiles were proved as equivalent in normal controls, RA, AS and CD patients.
- Five randomized controlled studies in normal controls, patients with AS, RA and CD demonstrated equivalence of PK, efficacy and comparability of safety with ADA positive rate.
- Observational clinical studies were performed in patients with RA, spondyloarthritis, IBD and Psoriasis, and supported comparable efficacy and safety of CT-P13 compared with the historical data of INX.
- Extension studies of PLANETAS and PLANETRA studies also demonstrated maintenance of clinical efficacy and safety up to week 102 after switching from INX to CT-P13.
- NOR-SWITCH study, which is a randomized double blinded controlled study of switching, demonstrated that switching from INX to CT-P13 was not inferior to maintaining INX in terms of worsening of disease and safety.
- Nonmedical switching study in Denmark also supported the feasibility of switching from INX to CT-P13, by looking at the similar flare rate during 3 months before and after switching, and similar 1-year retention rate, but there was a minor possibility of nocebo effect after switching. Thus, educational exercises to improve awareness on the biosimilars must be beneficial for all related stakeholders.
- Immunogenicity has been one of major concerns raised by some stakeholders, but no biosimilar has been removed from market by safety issue to date.
- Interchangeability is an important concern especially in the USA, but it is somewhat difficult to obtain an approval as interchangeable biosimilar, because a new clinical trial of back and forth and multiple switching should be conducted.

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