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Biosimilar infliximab CPT-13 in inflammatory bowel disease in real clinical setting: pharmacokinetics outcomes, immunogenicity and drug survival

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ABSTRACT

Background

The efficacy and safety after switching to biosimilar infliximab (CPT-13) in patients with inflammatory bowel disease (IBD) has been studied, but, few cohort studies compare the pharmacokinetic profiles, immunogenicity and safety of the reference infliximab (IFX) and CPT-13 in real clinical setting.

Objective

To compare the pharmacokinetic profiles and drug survival on the long-term outcome of reference IFX and CPT-13 at weeks 54 and 104. A secondary objective was to determine the immunogenicity and safety profile on long-term patients with IBD in a real clinical setting.

Methods

A retrospective observational cohort analysis in a single centre was performed of patients with IBD in treatment with reference IFX or CPT-13.

Serum drug concentrations were compared to determine if there were significant differences in pharmacokinetic outcomes between the reference IFX and CPT-13 at 26, 54, 78 and 104 week. The drug survival of reference IFX and CPT-13 was determined at week 54 and 104.

Results

One hundred and six patients were included during the study period. Forty-five (42.5 %) patients received CPT-13 and 61 (57.5 %) reference IFX.

A total of 347 samples of infliximab serum were analysed, no significant differences were observed between reference IFX and CPT-13. The percentage of patients who achieved serum concentrations in the target therapeutic range was similar in both groups (74.1 % reference IFX and 72.5 % CPT-13, $p=0.741$). At week 54, the withdrawal rates for the reference IFX and CPT-13 were 11.5 % and 20.0 %, respectively ($p=0.226$), while at week 104 they were 26.2 % and 28.9 % ($p=0.761$).

Conclusion

In conclusion, the pharmacokinetic characteristics and incidence of immunogenicity of CPT-13, in real clinical setting, are comparable to those of the infliximab originator. The two products also have similar long-term drug survival and the same safety profile.

Abbreviations

IFX: infliximab; IBD: inflammatory bowel diseases; CD: Crohn disease; UC: ulcerative colitis; CT-P13: biosimilar infliximab; IFX: Infliximab; ELISA: enzyme-linked immunosorbent assay; ITL: infliximab trough levels; ATI: antibodies to infliximab; Cl: individual clearance; K_{el} : elimination rate constant; $T_{1/2}$: half-life

Keywords

Infliximab, inflammatory bowel disease, biosimilar, antidrug antibody, pharmacokinetic, drug survival.

INTRODUCTION

The introduction of biological therapy in the past decade has modified the management of patients with inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC). The effectiveness of infliximab (IFX), the first anti-TNF- α (tumor necrosis factor alpha) drug approved for the treatment of CD and UC, has been demonstrated by numerous studies(1,2). Despite the undoubted efficacy of this therapy, the biological drugs are much more expensive than conventional therapy. Nevertheless, the expiration of patents on many biological drugs has allowed for the introduction of biosimilar drugs in the management of these patients. A biosimilar is a biological drug that is very similar to a reference biological drug which has already been approved for use. These molecules are highly similar to reference biologics in terms of quality, efficacy and safety to reference biologics, with the advantage of offering cost savings for healthcare systems(3).

Biosimilar infliximab (CT-P13) the first biosimilar monoclonal antibody that has been approved for use in all indications of the reference product. It received marketing authorisation from the EMA in 2013 and from the FDA in 2016 (3,4). Both CT-P13 and the reference IFX are chimeric immunoglobulin G1 monoclonal antibodies produced in cell lines derived from the same cell type of murine hybridoma. These monoclonal antibodies have an identical amino acid sequence and highly comparable higher-order structures, but they are not exact copies, as the final product is dependent on the manufacturing process, storage and transport(5). Data extrapolation from rheumatic disease clinical trials led to the approval of CT-P13 to treat CD and UC(6,7). However, concerns about the indications of such extrapolation, especially those related to immunogenicity and multiple switching, have been raised by clinicians and patients since the beginning of the CT-P13 biosimilar development program, and continue to exist(8). A meta-analysis investigating the safety and efficacy of CPT-13 for the treatment of IBD indicates that it exhibits the same safety and efficacy profile as the reference IFX(9). In addition, the European Crohn's and Colitis Organisation (ECCO) published its position statement on the use of biosimilars for IBD in December 2016. This states that 'when a biosimilar product is registered in the European Union, it is considered to be as efficacious as the reference product when used in accordance with the information provided in the Summary of Product Characteristics'(10).

Although there are studies(4,8,11–16) that investigate the efficacy and safety after switching to CPT-13, few cohort studies compare the pharmacokinetic profiles, immunogenicity and safety of the reference IFX and CPT-13 in real clinical setting. For this reason, the main objective of the present study was to compare the pharmacokinetic profiles and drug survival on the long-term outcome of reference IFX and CPT-13 at weeks 54 and 104. A secondary objective was to determine the immunogenicity and safety profile of the reference IFX and CPT-13 on long-term patients with IBD in a real clinical setting.

METHODS

A retrospective observational cohort analysis was performed at a single centre in a regional reference hospital which provides medical care to 200,892 patients. Adult patients (> 18 years) with CD or UC treated with reference IFX and CPT-13 between January 2015 and December 2019 were included in the study. Exclusion criteria included patients who were in the induction phase or those without information relating the drug serum concentration (reference IFX or CPT-13) and/or follow-up at other centres. The study was approved by the local research ethics committee.

The study population was identified through electronic prescription records for outpatients at the pharmacy service for the hospital. The biological therapy used was also identified from this database, as was the treatment regimen over time.

The demographic and clinical information collected from the medical records included age, gender, date of diagnosis, disease localisation, disease behaviour, presence of perianal disease, previous surgery, previous exposure to biologic drugs, details of reference IFX or CPT-13 therapy (such as dosage regimen), duration of treatment and reason for withdrawal.

The data about serum drug concentration and the estimated pharmacokinetic parameters of each patient were obtained from a local database of the Clinical Pharmacokinetics Unit (Department of Pharmacy). Serum ITL and antibodies to infliximab (ATI) were measured using an available validated enzyme-linked immunosorbent assay (ELISA) kit (PromonitorR; Grifols, Spain). Estimation of individual pharmacokinetic parameters was performed based on the population pharmacokinetic

model developed by Fasanmade et al(17), using NONMEM software (version 7.3.0; Icon Development Solutions Ellicott City, MD, USA).

PHARMACOKINETIC OUTCOMES

Serum drug concentrations were compared to determine if there were significant differences in pharmacokinetic outcomes between the reference IFX and CPT-13 at 26, 54, 78 and 104 week [\pm 2 weeks]. The percentage of patients with serum concentrations of infliximab who achieved optimal therapeutic range was determined, and comparisons were made between the reference IFX and CPT-13. Infliximab trough levels (ITL) between 3-10 $\mu\text{g/ml}$ and 5-10 $\mu\text{g/ml}$ were considered the optimal therapeutic range values in CD and UC, respectively(18).

DRUG SURVIVAL OUTCOMES

The drug survival of reference IFX and CPT-13 was determined at week 54 and 104. Drug survival was defined as the time interval, in weeks, between initiation and discontinuation of the infliximab (date of last given dose) for any reason(19). The reasons for withdrawal were classified as lack of response, immunogenicity and adverse events.

STATISTICAL ANALYSIS

Categorical data were given as absolute numbers and percentages, whereas continuous variables were expressed as median values and measures of variability as interquartile ranges (IQR). Continuous variables were tested using the Mann–Whitney U test, and categorical variables were analysed using Fisher's exact test.

The Kaplan–Meier estimator was used to generate survival curves with respect to reference IFX and CPT-13 at week 54 and 104. The log-rank test was used to compare survival between reference IFX and CPT-13 at week 54 and 104. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS for

Windows (version 23.0; SPSS Inc., Chicago, IL, USA).

RESULTS

One hundred and six patients were included during the study period. Of these, 66 (62.3 %) were male, with a median age of 42.0 years (IQR: 26.0), and 76 (71.7 %) had a diagnosis of CD. Almost one in four patients had a history of surgery before the initiation of biological treatment. Forty-five (42.5 %) patients received biosimilar IFX and 61 (57.5 %) received the reference IFX; 29 (27.4 %) patients had previously been treated with a biological drug. The baseline characteristics of the study population are shown in Table 1. No significant differences were found between the reference IFX and CPT-13.

A total of 347 samples of infliximab serum were analyzed (59.7 % samples corresponding to the reference IFX and 40.3 % CPT-13). The median of ITL in the maintenance period was 5.8 $\mu\text{g/ml}$ (IQR: 5.5), no differences in the ITL were found between the reference IFX and CPT-13 (5.6 $\mu\text{g/mL}$ (IQR: 5.6) vs 7.1 $\mu\text{g/mL}$ (IQR: 6.6), respectively; $p = 0.419$). The pharmacokinetic parameters obtained from the Bayesian prediction based on a population pharmacokinetic model are shown in Table 2. The median population estimates of individual clearance (Cl), elimination rate constant (K_{el}) and half-life ($t_{1/2}$) were 0.012 l/h (IQR: 0.005), 0.003 hours⁻¹ (IQR: 0.001) and 202.5 hours (IQR: 64.8), respectively. Differences in K_{el} and Cl were observed between reference IFX and CPT-13, although these differences were not clinically relevant.

Regarding serum concentrations at weeks 26, 54, 78 and 104, no significant differences were observed between the reference IFX and CPT-13. Table 3 shows the number of patients that fulfilled the phases of the study and the information related to serum drug concentrations. The percentage of patients who achieved serum concentrations in the target therapeutic range was similar in both groups (74.1 % reference IFX and 72.5 % CPT-13, $p = 0.741$), and no differences were observed at weeks 26, 54, 78 and 104 (figure 1).

More than half of the patients (65.1 %) needed dose escalation. Of these, 63.9 % received reference IFX and 66.7 % received CPT-13 ($p = 0.771$). The most common dose was 5mg/Kg every 6 weeks (48.3 %), every 4 weeks (26.5 %) and every 5 weeks

(12.0 %) (Figure 2).

DRUG SURVIVAL AT 54 AND 104 WEEKS

Drug survival at 54, and 104 weeks was similar in both study cohorts. At week 54, treatment was withdrawn in 15.1 % of patients (11.5 % reference IFX and 20.0 % CPT-13, $p=0.226$), and at week 104, treatment was withdrawn in 27.4 % of patients (26.2 % reference IFX and 28.9 % CPT-13, $p=0.761$) (figure 3). The reasons for treatment withdrawal were immunogenicity (11.3 %), poor response (10.4 %), side effects (4.7 %) and others (0.9 %). The most commonly reported side effects were dermatological causes (2 patients), arthralgia (2 patients), and optic neuritis associated with the use of infliximab (1 patient). The frequency of side effect was similar between the two treatment groups (4 in reference IFX group and 1 in the CPT-13 group, $p=0.220$).

As previously mentioned, we found detectable ATIs in 12 (11.3 %) patients during the study, no significant differences were observed between reference IFX and CPT-13 (9.8 % vs 13.3 % respectively, $p=0.574$). The median ATI concentration in CPT-13-treated patients was 120.0 (IQR: 129.0) AU/ml, whereas that in reference IFX-treated patients was 45.0 (160.7) AU/ml ($p=0.210$).

DISCUSSION

In this retrospective study carried out in patients with IBD in a real clinical setting, we determined the pharmacokinetic characteristics, immunogenicity, safety profile and drug survival during two first years of treatment with the reference IFX and CPT-13. No significant differences were observed between the two cohorts in the study.

Similarities in the pharmacokinetic parameters of reference IFX and CPT-13 were simultaneously evaluated in the patients with IBD on a short-term basis. Smith et al.(20) conducted a non-inferiority, multicentre, phase 4 trial to investigate whether serum concentration of infliximab with CPT-13 were non-inferior to those with reference IFX 16 weeks after switching in patients with IBD. They showed that serum concentrations of infliximab 16 weeks after initiating CPT-13 were non-inferior to those at baseline. Similar studies showed that there were no differences in the long term(13) after the switch to biosimilar. In our study, we also did not observe

differences between the two study cohorts. Our results are similar with other publications that analyze the trough levels between reference IFX and CPT-13 in other authorized indications, such as in the randomized controlled trial carried out by Cohen et al.(21), who analyzed the serum concentrations of both treatments in patients with rheumatoid arthritis, where observed that trough serum concentrations at weeks 2, 4, 6, 14, 22, and 30 and immediate postdose serum concentrations on day 1 and week 14 were similar between both treatments. Regarding the pharmacokinetic parameters, no differences were seen in volume of distribution, clearance and exposure to the IFX (AUC). However, a difference was observed in the median elimination half-life, which was approximately 28 hours, but we do not consider it to be of clinical significance.

Many studies have shown high inter-individual variability in serum infliximab concentrations, which can influence the dose-response relationship (17,22,23) . Therapeutic drug monitoring (TDM) is a tool that allows the individual optimization of dosage regimens of drugs with high inter-individual variability, to ensure adequate exposure to the drug (24–26). In our study, we evaluated the percentage of patients who achieved infliximab trough concentrations in the therapeutic range in the medium and long term (weeks 26, 54, 78 and 104). Our data show that both cohorts were comparable in pharmacokinetic terms, and that the need for dose escalation to achieve the pharmacokinetic outcome was comparable in both groups. To our knowledge, there are no previous studies comparing the percentage of patients who achieve pharmacokinetic outcomes.

The immunogenicity of infliximab has been widely reported(27), but the rate of ATIs varies considerably across studies. This variation can be explained by both patient- and treatment-related factors such as genetics, type of immune response, TNFi characteristics, dosing regimen and co-medication(28,29). In addition, the assay format used for the assessment of ADA affects the results(30). In the majority of these studies, the percentage of patients developing ADA is underestimated, since, in most common standard assays, the measurement of ADA is hampered by the presence of the drug itself (drug-sensitive assay)(28,30). Drug-tolerant assays can, in contrast to drug-sensitive assays, also measure ADA that are bound to the TNFi(30). Our data show that there are no differences between reference IFX and CPT-13. Our data are in line with

those obtained in previous studies(8,13,20), in which no differences were observed between reference IFX and CPT-13.

In our work, we evaluated the drug survival in the first two years from the start of treatment. We observed that the persistence of reference IFX and CPT-13 at week 54 was 88.5 % and 79.8 %, respectively. At week 104, it was approximately 70 % for both study cohorts. Similar results have been shown in other studies during the first (31) and second years of follow-up in a cohort of IBD patients who continued on CPT-13 after switching from originator infliximab.

Despite the available studies, a systematic review by Feagan et al.(32) collected the available evidence about the evaluation of the safety and efficacy of the switch between reference IFX and biosimilar in the different approved indications, the authors concluded that, higher quality data based upon the performance of multiple-switch studies are needed to validate the concept of interchangeability. In the same way, others authors (33) present in a review on patients with psoriasis, where they expose the different studies that demonstrate that CPT-13 is effective in infliximab-naïve patients, with the improvement in PASI score being in line with the reference infliximab, concluding that, more rigorous and normative research studies are necessary. However, there are more and more studies with a greater number of patients that show the similarity of both molecules in terms of safety and efficacy as a the French study(34) that included 5050 patients with CD where, by means of a multivariable analysis, it was observed that did not demonstrate any significant differences between both products in serious infections. It also showed that the effectiveness of CT-P13 is equivalent to that of reference IFX for infliximab naive patients with CD.

This study had some limitations. First, it was retrospective, with a study period between 2015 and 2019, so the time frame of each patient could be different. For this reason, a drug survival study was conducted during the first and second years from the start of treatment. We want to highlight that despite the retrospective nature of the study, the data collected for the TDM were obtained prospectively, which reduced the amount of missing data. Second, the study was performed at a single centre. For this reason, the number of patients receiving CPT-13 was relatively small, and did not allow

for the disaggregation of the data according to the diagnosis of CD and UC. Third, the lack of faecal calprotectin data and activity indices at different study periods did not allow for evaluation of the response to treatment in both study cohorts.

Despite the limitations mentioned above, we consider our study interesting because there are few cohort studies that compare the pharmacokinetic profile, immunogenicity and safety between reference IFX and CPT-13 in real clinical setting and in the long term.

In conclusion, the pharmacokinetic characteristics and incidence of immunogenicity of CPT-13, in real clinical setting, are comparable to those of the reference IFX. The two products also have similar long-term drug survival and the same safety profile. Considering the economic aspect, the use of CPT-13 can lead to important cost savings and greater access to biological products.

CONFLICT OF INTEREST

CIN has received speaker fees from Amgen. RGE has received speaker fees from Amgen, Takeda and Janssen. INP has received speaker fees from Amgen, Takeda and Janssen. The other authors declare no conflict of interests.

AUTHORS' INDIVIDUAL CONTRIBUTIONS

CIN, MGC, INP and RGE performed the research. CIN, ISV, and LRR designed the research study and analysed the data. CIN, MCG, ISV and INP collected the data. CIN and LRR wrote the manuscript, and CIN, INP and RGE performed critical revision. All authors have approved the final version of the manuscript.

REFERENCES

1. Stephen B, Brian G, Gary R, et al. Maintenance infliximab for Crohn ' s disease : The ACCENT I randomised trial. *Lancet*. 2002;359:1451-9.
2. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. *N. Engl. J. Med*. 2005;353:2462-76.
3. Kurti Z, Gonczi L, Lakatos PL. Progress with infliximab biosimilars for

- inflammatory bowel disease. *Expert Opin. Biol. Ther.* 2018;18:633–40.
4. Gonczi L, Gecse KB, Vegh Z, et al. Long-term Efficacy, Safety, and Immunogenicity of Biosimilar Infliximab after One Year in a Prospective Nationwide Cohort. *Inflamm. Bowel Dis.* 2017;23:1908–15.
 5. Papamichael K, Stappen T Van, Jairath V, et al. Review article: Pharmacological aspects of anti-TNF biosimilars in inflammatory bowel diseases. *Aliment. Pharmacol. Ther.* 2015;42:1158–69.
 6. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: The PLANETRA study. *Ann. Rheum. Dis.* 2013;72:1613–20.
 7. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. *Ann. Rheum. Dis.* 2017; 76:346–54.
 8. Arguëlles-Arias F, Guerra Veloz MF, Perea Amarillo R, et al. Switching from reference infliximab to CT-P13 in patients with inflammatory bowel disease: 12 months results. *Eur. J. Gastroenterol. Hepatol.* 2017;29:1290–5.
 9. Komaki Y, Yamada A, Komaki F, et al. Systematic review with meta-analysis: the efficacy and safety of CT-P13, a biosimilar of anti-tumour necrosis factor- α agent (infliximab), in inflammatory bowel diseases. *Aliment. Pharmacol. Ther.* 2017;45:1043–57.
 10. Danese S, Fiorino G, Raine T, et al. ECCO Position statement on the use of biosimilars for inflammatory bowel disease-an update. *J. Crohn's Colitis.* 2017;1:26–34.
 11. Bronswijk M, Moens A, Lenfant M, et al. Evaluating Efficacy, Safety, and Pharmacokinetics after Switching from Infliximab Originator to Biosimilar CT-P13: Experience from a Large Tertiary Referral Center. *Inflamm. Bowel Dis.* 2020;26:628–34.
 12. Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to

- biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 2017;389:2304–16.
13. Smits LJT, Grelack A, Derikx LAAP, et al. Long-Term Clinical Outcomes After Switching from Remicade® to Biosimilar CT-P13 in Inflammatory Bowel Disease. *Dig. Dis. Sci*. 2017;62:3117–22.
 14. Smits LJT, Esch AAJ Van, Derikx LAAP, et al. Drug survival and immunogenicity after switching from remicade to biosimilar CT-P13 in inflammatory bowel disease patients: Two-year follow-up of a prospective observational cohort study. *Inflamm. Bowel Dis*. 2019;25:172–9.
 15. Ye BD, Pesegova M, Alexeeva O, et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. *Lancet*. 2019;393:1699–707.
 16. Berends SE, Strik AS, Selm JC Van, et al. Explaining Interpatient Variability in Adalimumab Pharmacokinetics in Patients with Crohn's Disease. *Ther. Drug Monit*. 2018;40:202–11.
 17. Fasanmade AA, Adedokun OJ, Blank M, et al. Pharmacokinetic Properties of Infliximab in Children and Adults with Crohn's Disease: A Retrospective Analysis of Data from 2 Phase III Clinical Trials. *Clin. Ther*. 2011;33:946–64.
 18. Mitrev N, Castele N Vande, Seow CH, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. *Aliment. Pharmacol. Ther*. 2017;46:1037–53.
 19. Menter A, Papp KA, Gooderham M, et al. Drug survival of biologic therapy in a large, disease-based registry of patients with psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J. Eur. Acad. Dermatology Venereol*. 2016;30:1148-58.
 20. Smits LJT, Derikx LAAP, Jong DJ de, et al. Clinical outcomes following a switch from Remicade® to the biosimilar CT-P13 in inflammatory bowel disease

- patients: A prospective observational cohort study. *J. Crohn's Colitis*. 2016;10:1287–93.
21. Cohen SB, Alten R, Kameda H, et al. A randomized controlled trial comparing PF-06438179/GP1111 (an infliximab biosimilar) and infliximab reference product for treatment of moderate to severe active rheumatoid arthritis despite methotrexate therapy. *Arthritis Res Ther*. 2018;20:1–13.
 22. Santacana E, Rodríguez-Alonso L, Padullés A, et al. *Predictors of Infliximab Trough Concentrations in Inflammatory Bowel Disease Patients Using a Repeated-Measures Design*. 2020; *Ther Drug Monit*. 2020;42:102-10.
 23. Gil Candel M, Gascón Cánovas JJ, Espín RG, et al. Usefulness of population pharmacokinetics to optimize the dosage regimen of infliximab in inflammatory bowel disease patients. *Rev. Esp. Enfermedades Dig*. 2020;112:590–7.
 24. Mitchell RA, Shuster C, Shahidi N, et al. The Utility of Infliximab Therapeutic Drug Monitoring among Patients with Inflammatory Bowel Disease and Concerns for Loss of Response: A Retrospective Analysis of a Real-World Experience. *Can. J. Gastroenterol. Hepatol*. 2016; 2016:5203898.
 25. Papamichael K, Cheifetz AS, Melmed GY, et al. Appropriate Therapeutic Drug Monitoring of Biologic Agents for Patients With Inflammatory Bowel Diseases. *Clin. Gastroenterol. Hepatol*. 2019;17:1655-68.
 26. Sparrow MP, Papamichael K, Ward MG, et al. Therapeutic Drug Monitoring of Biologics During Induction to Prevent Primary Non-Response. *J. Crohn's Colitis*. 2020; 14:542-56.
 27. Strand V, Balsa A, Al-Saleh J, et al. Immunogenicity of Biologics in Chronic Inflammatory Diseases: A Systematic Review. *BioDrugs*. 2017;31:299–316.
 28. Llinares-Tello F, Rosas-Gómez de Salazar J, Senabre-Gallego JM, et al. Practical application of acid dissociation in monitoring patients treated with adalimumab. *Rheumatol. Int*. 2014;34:1701–8.
 29. Thomas SS, Borazan N, Barroso N, et al. Comparative Immunogenicity of TNF Inhibitors: Impact on Clinical Efficacy and Tolerability in the Management of Autoimmune Diseases. A Systematic Review and Meta-Analysis. *BioDrugs*. 2015; 29:241-58.

30. Atiqi S, Hooijberg F, Loeff FC, et al. Immunogenicity of TNF-Inhibitors. *Front. Immunol.* 2020;11:1–13.
31. Razanskaite V, Bettey M, Downey L, et al. Biosimilar Infliximab in Inflammatory Bowel Disease: Outcomes of a Managed Switching Programme. *J. Crohns. Colitis.* 2017;11:690–6.
32. Feagan BG, Lam G, Ma C, Lichtenstein GR. Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. *Aliment Pharmacol Ther.* 2019;49:31–40.
33. Gong Y, Shi Y. In fl iximab and biosimilar in fl iximab in psoriasis : ef fi cacy , loss of ef fi cacy , and adverse events. 2019;2491–502.
34. Meyer A, Rudant J, Drouin J, et al. Effectiveness and safety of reference infliximab and biosimilar in Crohn disease: A French equivalence study. *Ann Intern Med.* 2019;170:99–107.

Table 1. Baseline characteristics of population study

	Reference IFX (N=61)	CPT-13 (N=45)	P value
Male, n (%)	39 (63.9)	27 (60)	0.680
Median age, (IQR) years	40.0 (24.0)	44.5 (36)	0.300
CD, n (%)	42 (68.9)	34 (75.6)	0.449
CD location, n (%)			
L1 (ileal)	21 (50.0)	17 (50.0)	0.849
L2 (colonic)	3 (7.1)	3 (8.8)	
L3 (ileocolonic)	18 (42.9)	14 (41.2)	
CD behaviour, n (%)			
B1 (nonstricturing, nonpenetrating)	19 (48.1)	11 (32.3)	0.153
B2 (stricturing)	14 (33.3)	16 (47.1)	
B3 (penetrating)	9 (21.4)	7 (20.6)	
Perianal disease, n (%)	6 (9.8)	7 (15.6)	0.375
UC location, n (%)			
E1 (proctitis)	1 (5.4)	1 (9.1)	0.548
E2 (left-sided colitis)	9 (47.4)	3 (27.3)	
E3 (pancolitis)	9 (47.4)	7 (63.3)	
Previous biological therapy, n	16 (26.2)	12 (28.0)	0.761

IFX: infliximab; CD: Crohn disease; UC: ulcerative colitis

Table 2. Estimated pharmacokinetic between reference infliximab and CPT-13 at maintenance period of population study

	Reference IFX	CPT-13	P value
C_{min}, µg/mL	5.6 (5.6)	7.1 (6.4)	0.419
IPRED, µg/mL	5.5 (5.1)	7.0 (6.6)	0.203
K_{el}, h⁻¹	0.003 (0.001)	0.004 (0.001)	0.010
V_c, L	3.71 (0.76)	3.82 (0.52)	0.743
V_p, L	1.41 (0.47)	1.42 (1.03)	0.372
Cl, L·h⁻¹	0.012 (0.006)	0.013 (0.003)	0.117
T_{1/2}, h	219.3 (78.5)	191.3 (54.2)	0.012
AUC (mg/h/L)	28310 (7463)	28643 (11766)	0.900

C_{min}: minimum observed concentration; IPRED: individual model predicted concentrations; K_{el}: elimination rate constant; V_c: central distribution volume; V_p: peripheral distribution volume; Cl: clearance; T_{1/2}: half-life; AUC: Area under curve.

Table 3. Patients in active treatment with reference IFX and CPT-13 and serum drug concentration at week 26, 54, 78 and 104.

	Patients N (%)			Infliximab trough concentration		
	Reference IFX (N=61)	CPT-13 (N=45)	p	Reference IFX	CPT-13	p
26-week	58 (95.1)	40 (88.9)	0.233	4.4 (4.8)	5.9 (5.5)	0.363
54-week	54 (88.5)	36 (80.0)	0.226	4.9 (4.7)	5.9 (8.1)	0.158
78-week	50 (82.0)	32 (71.1)	0.187	7.3 (5.8)	5.2 (7.2)	0.157
104-week	45 (73.8)	32 (71.1)	0.761	5.3 (7.1)	5.1 (4.1)	0.408

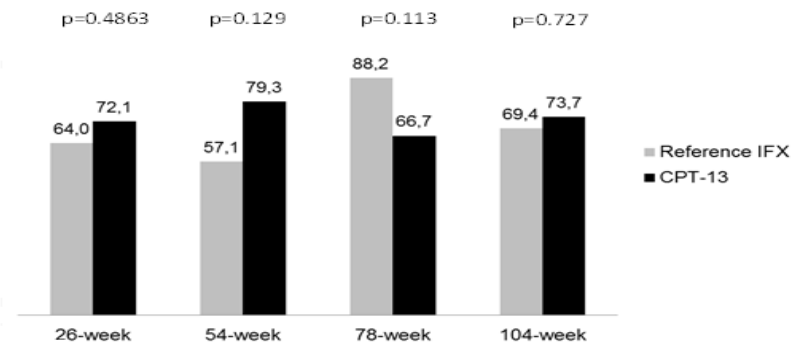


Figure 1. Percentage of patients who achieved pharmacokinetic outcomes at weeks 26, 54, 78 and 104. Infliximab trough levels between 3-10 µg/ml and 5-10 µg/ml were considered the optimal therapeutic range values in CD and UC.

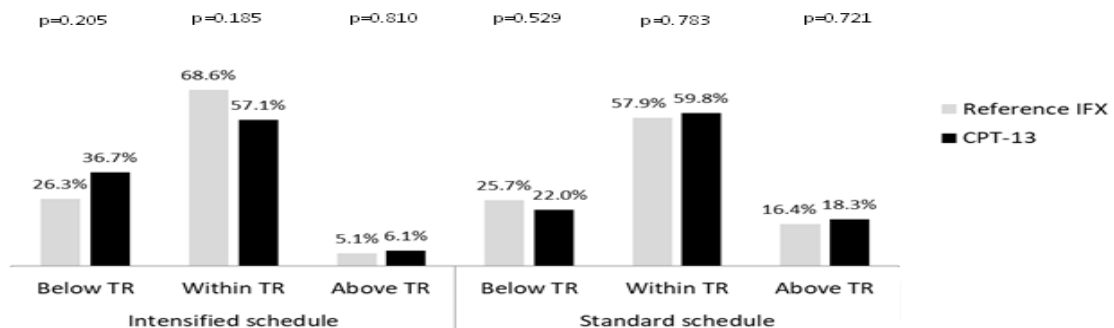


Figure 2. Percentage of patients who achieved pharmacokinetic outcomes according to dosage regimen. TR: therapeutic range. Infliximab trough levels between 3-10 µg/ml and 5-10 µg/ml were considered the optimal therapeutic range values in CD and UC.

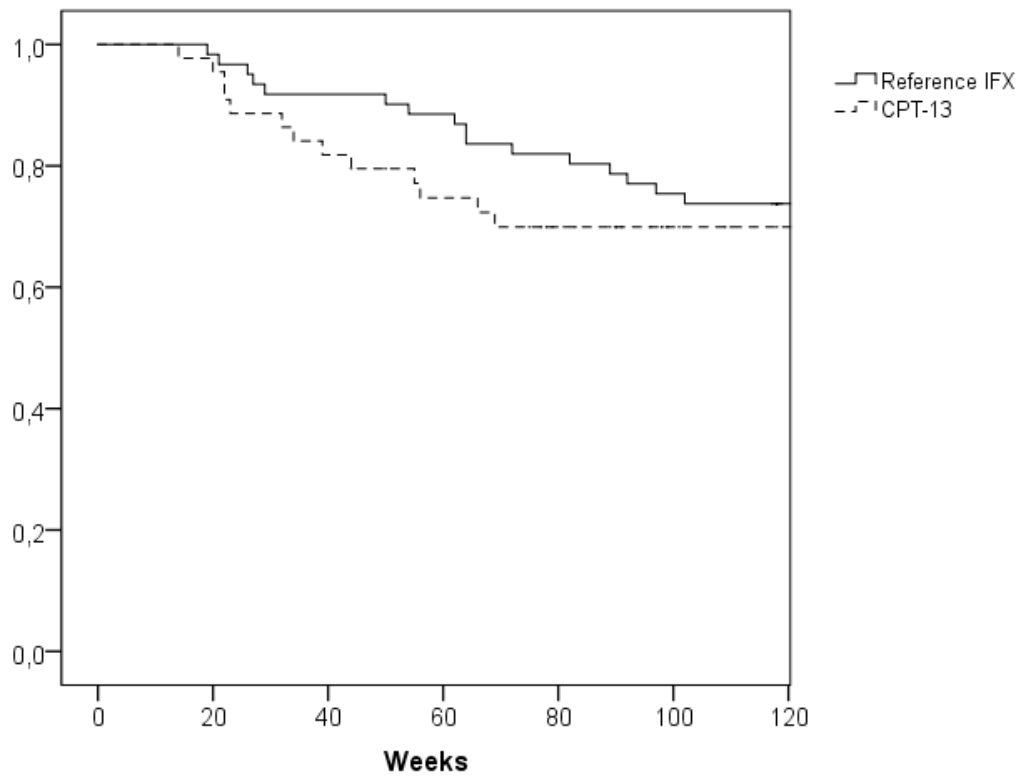


Figure 3. Drug survival of reference IFX and CPT-13 during the 54 week (log Rank $p=0.195$) and 104 weeks (log Rank $p=0.397$) follow period.