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

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ABSTRACT

Background: efficacy and safety were evaluated after switching to a biosimilar infliximab (CPT-13) in patients with inflammatory bowel disease (IBD). However, few cohort studies compare the pharmacokinetic profiles, immunogenicity, and safety of the reference infliximab (IFX) and CPT-13 in a real clinical setting.

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

Methods: a retrospective, observational cohort analysis was performed in a single center, including patients with IBD under treatment with reference IFX or CPT-13. Serum drug concentrations were compared to determine if there were any significant differences in pharmacokinetic outcomes between reference IFX and CPT-13 at 26, 54, 78, and 104 weeks. The drug survival of reference IFX and CPT-13 was determined at weeks 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 %) received reference IFX. A total of 347 serum samples were analyzed and no significant differences were observed between reference IFX and CPT-13. The percentage of patients who achieved serum concentrations within the target therapeutic range was similar in both groups (74.1 % for reference IFX and 72.5 % for CPT-13, p = 0.741). At week 54, withdrawal rates for reference IFX and CPT-13 were 11.5 % and 20.0 %, respectively (p = 0.226), whereas at week 104 they were 26.2 % and 28.9 %, respectively (p = 0.761).

Conclusion: the pharmacokinetic characteristics and incidence of immunogenicity of CPT-13 in a 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.

Keywords: Infliximab. Inflammatory bowel disease. Biosimilar. Anti-drug antibody. Pharmacokinetics. Drug survival.

INTRODUCTION

The introduction of biological therapy in the past decade has modified the management of patients with inflammatory bowel disease (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 in numerous studies (1,2). Despite the undoubted efficacy of this therapy, biological drugs are much more expensive than conventional therapy. Nevertheless, the expiration of patents on many biological drugs has allowed 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 with the advantage of cost savings for healthcare systems (3).

The biosimilar infliximab (CT-P13) was the first biosimilar monoclonal antibody approved for use in all indications of the reference product. It received marketing authorization 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 are highly comparable higher-order structures, although 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 have been raised by clinicians and patients about the indications of such extrapolation, especially those related to immunogenicity and multiple switching, since the beginning of the CT-P13 biosimilar development program, and continue to exist (8). A meta-analysis that investigated the safety and efficacy of CPT-13 for the treatment of IBD indicated that the biosimilar exhibits the same safety and efficacy profile as the reference IFX (9). In addition, the European Crohn's and Colitis Organization (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 the real clinical setting. For this reason, the main objective of this study was to compare the pharmacokinetic profiles and drug survival on long-term outcomes 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 in the long term in patients with IBD in a real clinical setting.

METHODS

A retrospective observational cohort analysis was performed at a single center in a regional reference hospital that 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, those without information relating the drug's serum concentration (reference IFX or CPT-13), and/or follow-up at other centers. The study was approved by the local research ethics committee.

The study population was identified via electronic prescription records for outpatients at the pharmacy service of the hospital. The biological therapy used was also identified from this database, as well as the treatment regimen over time. The demographic and clinical information collected from the medical records included age, gender, date of diagnosis, disease localization, disease behavior, 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 concentrations 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). The estimation of

individual pharmacokinetic parameters was performed based on the population's pharmacokinetic model developed by Fasanmade et al. (17), using the 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 any significant differences in pharmacokinetic outcomes between the reference IFX and CPT-13 at 26, 54, 78, and 104 weeks (± 2 weeks). The percentage of patients with serum concentrations of infliximab achieving an optimal therapeutic range was determined, and comparisons were made between the reference IFX and CPT-13. Infliximab trough levels (ITL) between 3 and 10 µg/mL, and between 5 and 10 µg/mL were considered as the optimal therapeutic range values for CD and UC, respectively (18).

Drug survival outcomes

The drug survival of reference IFX and CPT-13 was determined at weeks 54 and 104. Drug survival was defined as the time interval, in weeks, between initiation and discontinuation of 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 are shown 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 analyzed using Fisher's exact test.

The Kaplan-Meier estimator was used to generate survival curves with respect to reference IFX and CPT-13 at weeks 54 and 104. The log-rank test was used to compare survival between reference IFX and CPT-13 at weeks 54 and 104. A value of $p < 0.05$ was considered statistically significant. The statistical analysis was performed using the SPSS for Windows package (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 serum samples were analyzed (59.7 % samples corresponding to the reference IFX and 40.3 % to CPT-13). The median ITL in the maintenance period was 5.8 μg/mLl (IQR: 5.5), and no differences in ITL were found between the reference IFX and CPT-13 (5.6 μg/mL (IQR: 5.6) vs 7.1 μ/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/h (IQR: 0.001), and 202.5 hours (IQR: 64.8), respectively. Differences in K_{el} and Cl were observed between the 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 % for the reference IFX and 72.5 % for CPT-13, p = 0.741), and no differences were observed at weeks 26, 54, 78, and 104 (Fig. 1).

More than half of the patients (65.1 %) required dose escalation. Of these, 63.9 % received reference IFX and 66.7 % received CPT-13 (p = 0.771). The most common dose was 5 mg/kg every 6 weeks (48.3 %), every 4 weeks (26.5 %), and every 5 weeks (12.0 %) (Fig. 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 % for the reference IFX and 20.0 % for CPT-13, p = 0.226), and in 27.4 % of patients at week 104 (26.2 % for the reference IFX and 28.9 % for CPT-13, p = 0.761) (Fig. 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 conditions (2 patients), arthralgia (2 patients), and optic neuritis associated with the use of infliximab (1 patient). The frequency of side effects was similar between the two treatment groups (4 in the reference IFX group and 1 in the CPT-13 group, p = 0.220).

As previously mentioned, there were detectable ATIs in 12 (11.3 %) patients during the study period, and no significant differences were observed between the 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 and 45.0 (160.7) AU/mL (p = 0.210) in reference IFX-treated patients.

DISCUSSION

In this retrospective study pharmacokinetic characteristics, immunogenicity, safety profile, and drug survival were determined during the first two years of treatment with the reference IFX or CPT-13 in patients with IBD in a real clinical setting. 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 patients with IBD on a short-term basis. Smith et al. (20) performed a non-inferiority, multicenter, phase-4 trial to investigate whether serum concentrations of infliximab with CPT-13 were non-inferior to those obtained with the reference IFX 16 weeks after switching in patients with IBD. They showed that serum concentrations of infliximab 16 weeks after initiating CPT-13 were not inferior to those at baseline. Similar studies showed that there were no differences in the long term (13) after the switch to the biosimilar. In our study there were no differences between the two study cohorts. Our results are similar to those of other publications that

analyzed the trough levels between reference IFX and CPT-13 in other authorized indications, such as in the randomized controlled trial performed by Cohen et al. (21). This study analyzed the serum concentrations of both treatments in patients with rheumatoid arthritis, where trough serum concentrations at weeks 2, 4, 6, 14, 22, and 30, and immediate post-dose 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, or exposure to IFX (AUC). However, a difference was observed in median elimination half-life, which was approximately 28 hours, but we do not consider this 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, the percentage of patients who achieved infliximab trough concentrations in the therapeutic range in the medium and long term was evaluated (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 study, drug survival was evaluated 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 its 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, review studies (33) of patients with psoriasis demonstrate that CPT-13 is effective in infliximab-naïve patients, with an improvement in PASI score consistent with that of the reference infliximab. This review concluded that more rigorous and normative research studies are needed. However, there are increasingly more studies with a greater number of patients that show the similarity of both molecules in terms of safety and efficacy. A French study (34) in 5,050 patients with CD showed, by multivariate analysis, that there were no significant differences between both products in serious infections. This study also showed that the effectiveness of CT-P13 is equivalent to that of the reference IFX in infliximab-naïve patients with CD.

This study had some limitations. First, it had a retrospective design performed between 2015 and 2019, so the time frame of each patient could be different. For this reason, a drug survival study was performed 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 center. For this reason, the number of patients receiving CPT-13 was relatively small, and did not allow a sub-classification of the data according to the diagnosis of CD or of UC. Third, the lack of fecal calprotectin data and activity indices at different study periods did not allow an 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 pharmacokinetic profile, immunogenicity, and safety between the reference IFX and CPT-13 in a real clinical setting and in the long term.

In conclusion, the pharmacokinetic characteristics and incidence of immunogenicity of CPT-13 in a real clinical setting are comparable to those of the reference IFX. The two products also have a 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 a greater access to biological products.

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Table 1. Baseline characteristics of the study population

	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)	
L2 (colonic)	3 (7.1)	3 (8.8)	0.849
L3 (ileocolonic)	18 (42.9)	14 (41.2)	
CD behavior, n (%)			
B1 (non-stricturing, non-penetrating)	19 (48.1)	11 (32.3)	
B2 (stricturing)	14 (33.3)	16 (47.1)	0.153
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)	
E2 (left-sided colitis)	9 (47.4)	3 (27.3)	0.548
E3 (pancolitis)	9 (47.4)	7 (63.3)	
Previous biological therapy, n (%)	16 (26.2)	13 (28.9)	0.761

IFX: inflixmiab; CD: Crohn's disease; UC: ulcerative colitis.

Table 2. Estimated pharmacokinetics of reference infliximab versus CPT-13 at the maintenance period of the study population.

	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
Vc, L	3.71 (0.76)	3.82 (0.52)	0.743
Vp, L	1.41 (0.47)	1.42 (1.03)	0.372
Cl, $L \cdot h^{-1}$	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)	28,310 (7463)	28,643 (11766)	0.900

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

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

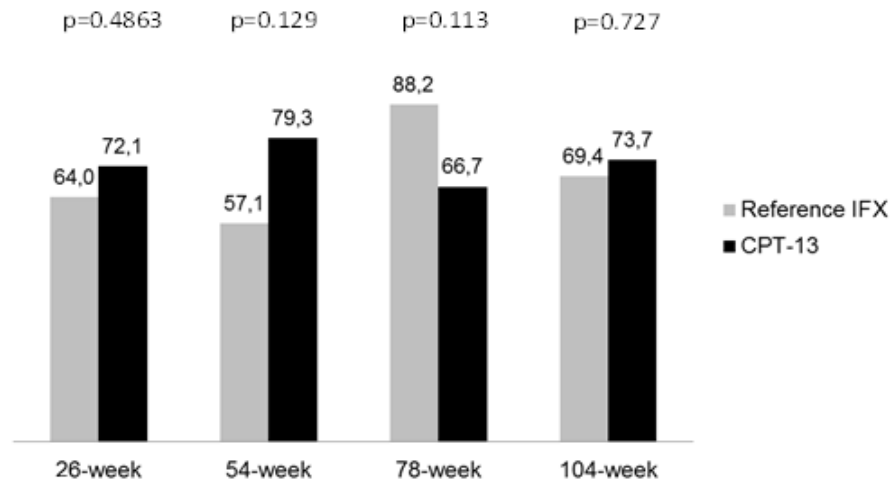|	Patients n (%)			Infliximab trough concentration		
	Reference IFX (n = 61)	CPT-13 (n = 45)	p	Reference IFX	CPT-13	p
Week 26	58 (95.1)	40 (88.9)	0.233	4.4 (4.8)	5.9 (5.5)	0.363
Week 54	54 (88.5)	36 (80.0)	0.226	4.9 (4.7)	5.9 (8.1)	0.158
Week 78	50 (82.0)	32 (71.1)	0.187	7.3 (5.8)	5.2 (7.2)	0.157
Week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

Fig. 1. Percentage of patients who achieved pharmacokinetic outcomes at weeks 26, 54, 78, and 104 (infliximab trough levels of 3-10 μg/mL and 5-10 μg/mL were considered the optimal therapeutic range values for CD and UC, respectively).
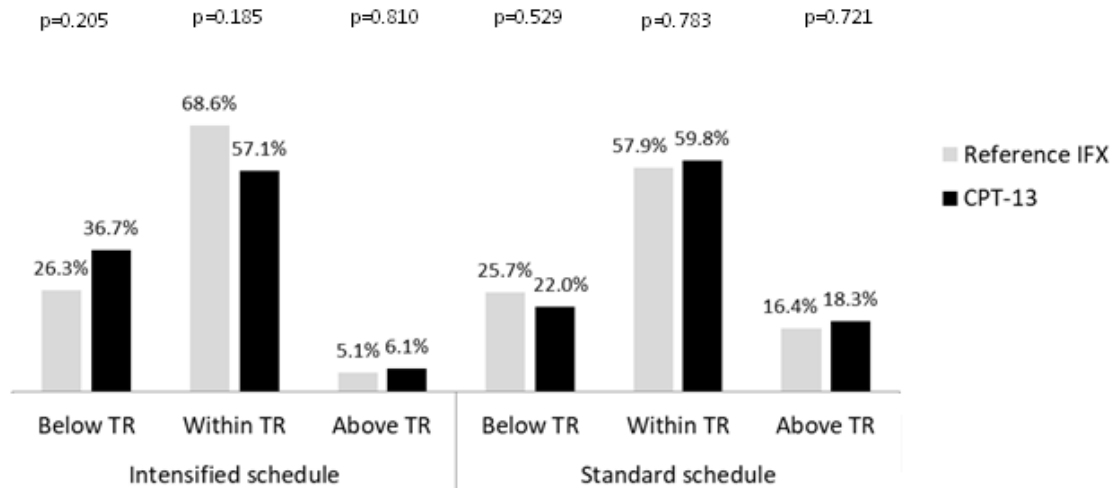
Fig. 2. Percentage of patients who achieved pharmacokinetic outcomes according to dosage regimen (TR: therapeutic range. Infliximab trough levels of 3-10 μg/mL and 5-10 μg/mL were considered as optimal therapeutic range values for CD and UC, respectively).
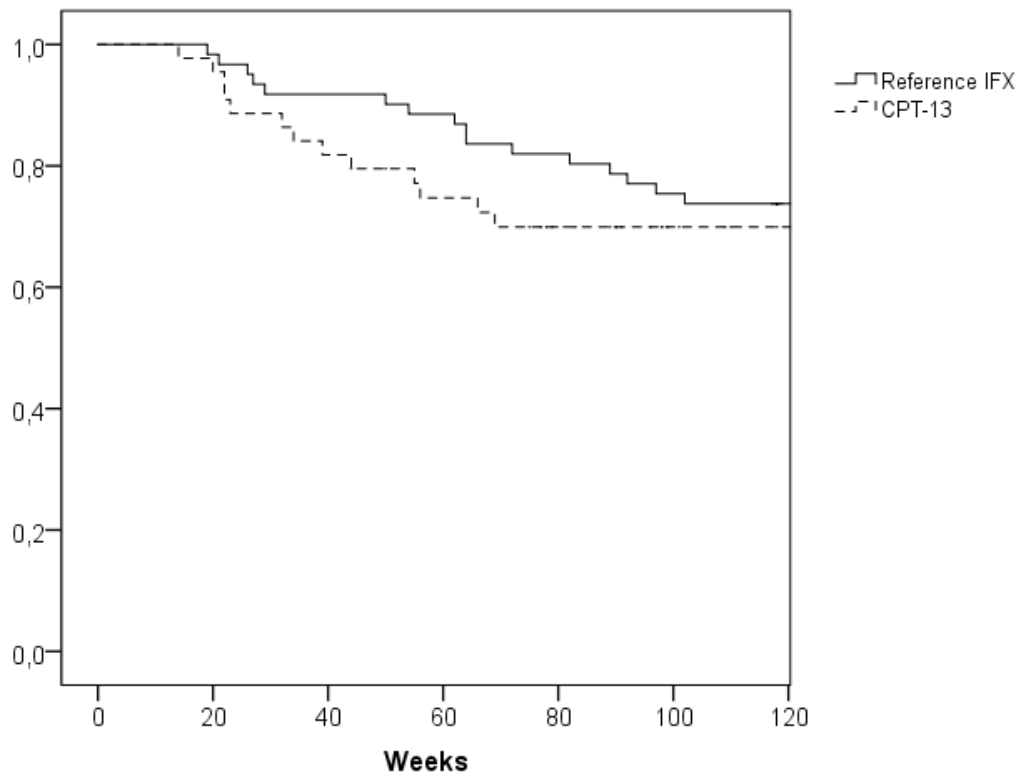
Fig. 3. Drug survival of reference IFX and CPT-13 at weeks 54 (log rank, p = 0.195) and 104 (log rank, p = 0.397) during the follow-up period.