Switching maintenance infliximab therapy to biosimilar infliximab in inflammatory bowel disease patients

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Short title: Switching maintenance infliximab to biosimilar one

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Abstract:

Background: Clinical use of biosimilar infliximab (CT-P13) in inflammatory bowel diseases (IBDs) is based on extrapolation of indication from clinical studies performed in rheumatological diseases. Only few data exist of behaviour of infliximab trough levels (TLs) and anti-drug antibodies (ADAs) during switching.

Aim: The objective of this study was to evaluate changes in TLs, ADA formation and disease activity after switching from originator infliximab to biosimilar one.

Methods: All our IBD patients receiving maintenance infliximab therapy were switched to biosimilar infliximab. TLs and ADAs were measured before the last originator infusion and before the third biosimilar infusion. Laboratory values, disease activity indices (Partial Mayo Score and Harvey-Bradshaw Index) and demographic data were collected from patient records.

Results: A total of 62 patients were included in the final analysis (32 Crohn's disease, 30 ulcerative colitis (UC) or IBD-unclassified). No significant changes in median TLs before (5.5mg/l) and after switching (5.5mg/l, p=0.05) occurred in the entire study group or in the Crohn's disease subgroup (5.75mg/l and 6.5 mg/l, p=0.68). However, in the subgroup of ulcerative colitis, the change in median TL was significantly different (from 5.2 to 4.25 mg/l, p=0.019). Two patients developed ADAs after switching. No changes in disease activity were detected during switching and no safety concerns occurred.

Conclusions: Switching from originator to biosimilar infliximab resulted in statistically significant differences in infliximab TLs in patients with UC but not in patients with

Crohn’s disease. The clinical significance for this difference is doubtful and in neither group changes in disease activity occurred.

Keywords : infliximab, biosimilar, CT-P13, Crohn´s disease, ulcerative colitis, trough levels, TNF-α antagonist.

1. Introduction

The use of chimeric monoclonal antibody (IgG1) infliximab (IFX) against TNF-α has emerged since the FDA approval in 1998 for the treatment of Crohn´s disease (CD) and in 2005 for ulcerative colitis (UC) [1]. IFX is effective in both children and adults with moderate to severe CD and UC in inducing and maintaining remission [2-6]. However, a considerable number of patients either fail to respond to TNF-α-antagonists (primary non-responders) or lose response over time (secondary loss of response). Formation of anti-drug antibodies (ADAs) is an important cause for secondary loss of response [7]. IFX trough levels (TLs) and ADAs can be measured from patients' serum samples by using commercial available immunoassays. These measurements are valuable tools in optimizing IFX therapy [8-10]. Recently, ADA cross-reactivity between originator IFX and CT-P13 has been described [11].

In June 2013, the European Medical Agency (EMA) accepted IFX biosimilar (CT-P13) for all indications of the originator product [12]. For CD and UC, the indication was extrapolated from studies showing efficacy of biosimilar IFX in ankylosing spondylitis and rheumatoid arthritis [13,14]. This extrapolation of indication raised concern among national and international IBD societies regarding the safety and interchangeability of biosimilars [15]. In IBD patients only limited data were available of the efficacy and safety of CT-P13 until recently. First real-life data of CT-P13 in induction therapy for IBD patients and switching from originator has recently been published [16-25].

The aim of our study was to evaluate changes in TLs, ADA formation and disease activity after switching from originator to biosimilar IFX during IBD maintenance therapy.

2. Patients and Methods

2.1. Switching programme design

All IBD patients receiving IFX (Remicade™, Janssen Biotech, Inc/ Schering-Plough, EU) maintenance therapy at Helsinki University Hospital were switched to biosimilar IFX (Remsima™, Celltrion Pharm, Inc**.,** South Korea) in the beginning of year 2016. IFX TLs and ADAs were measured before the last originator IFX infusion (baseline) and before the third biosimilar IFX infusion (follow-up). Blood samples for measurements of haemoglobin, leukocytes, platelets and serum C-reactive protein (CRP) were also taken at these time points. Faecal calprotectin (FC), Partial Mayo Score (PMS) and Harvey Bradshaw index (HBI) were used to assess clinical disease activity [26,27].

IFX TLs were measured with capture-ELISA (Promonitor EIA, Progenica) at United Medix Laboratories (Helsinki, Finland) and the levels of ADAs were analyzed with fluid-phase radioimmunoassay (Sanguin Laboratories, The Netherlands). IFX TLs below 0.03 mg/l and ADAs below 12 AU/ml were considered non-detectable. Patients having an originator IFX TL below or above the target level 3 – 7 mg/l [8] and needing dose adjustment were excluded from paired analyses.

FC was measured in the routine clinical laboratory by a quantitative enzyme immunoassay (PhiCal Test, Calpro AS, Oslo, Norway) and the values quoted as normal were <100 µg/g of stool [28].

2.2. Statistical analyses

Laboratory values are presented as median and interquartile Range (IQR). Disease activity is presented as mean and standard deviation (SD). Wilcoxon Signed-Rank test served as exploring changes between related variables. For further analysis of TLs, we used the nonparametric two

one-sided test of equivalence for paired samples [29]. Equivalence was established if the 95% confidence interval (CI) of the median difference in the TLs before and after switching fell within the equivalence boundaries. The boundaries were set to +/- the median absolute deviation about the median of the baseline IFX TL of all patients, indicating that the change of TL after switch for a patient tends to be smaller than the baseline TL difference between the patients. Matplotlib version 1.5.1. was used for figure-drawing. Significance was set at 0.05.

2.3. Ethical considerations

The change of maintenance originator IFX to biosimilar IFX and measurements of TLs and ADAs occurred as a part of the routine clinic work based on the hospital's medical decisions. The study was approved by the ethics committee of the Helsinki University Hospital (Dnro 32/13/03/01/2016) and research study permission was received from the Hospital District of Helsinki and Uusimaa (HUS-170-2016-2).

3. Results

3.1. Patients and infliximab trough levels

Switching from maintenance originator IFX to biosimilar IFX occurred in 78 patients (38 CD, 37 UC and 3 IBD-unclassified [IBD-u]). Because of the small number of IBD-u patients, the data of UC and IBD-u patients were pooled. During maintenance originator IFX therapy, 47 of 78 (60.5%) had a TL below (n=16) or above (n= 31) the target trough concentration 3 – 7 mg/l. Based on these baseline IFX TLs and clinical evaluation, 14 (17.9%) patients underwent dose adjustment (nine with a TL below 3 mg/l and five with a TL above 7 mg/l) and were excluded from the paired concentration analyses. Two patients were excluded because of changes in the infusion regime due to non-medical reasons.

Paired IFX TL and ADA measurements, clinical and laboratory data were available of 62 patients (32 CD, 30 CU/IBD-u) (Table 1). All UC patients had either left-sided colitis or

extensive colitis. The majority of CD patients had an ileocolic involvement (20 patients, 62.5%). Of 32 CD patients, 20 (62.5%) and of 30 UC patients 24 (80%) used concomitant immunomodulators. Median IFX infusion interval was 8 weeks (range 4 – 10 weeks).

During maintenance therapy with originator IFX, the median IFX TL of 62 patients was 5.5 mg/l (IQR 3.85 mg/l – 8.65 mg/l). The median follow-up IFX TL was 5.5 mg/l (IQR 3.15 mg/l – 7.8 mg/l). The median TL difference was 0.45 mg/l. There was no statistically significant change (p=0.05) in TLs before and after switching (Figure 1 and 2).

We also analysed the data separately for CD and UC. For CD patients, the median IFX TL was 5.75 mg/l (IQR 4.48 mg/l – 8.4 mg/l) before and 6.5 mg/l (IQR 3.98 mg/l – 8.35mg/l) after switch and no statistical significant difference was detected (p=0.68). The median TL difference in the CD subgroup was 0.4 mg/l (see Figure 3a). However, in UC/IBD-u patients the change in median IFX TLs before and after switching was statistically significant: from median baseline TL 5.2 mg/l (IQR 3.8 mg/l – 8.65 mg/l) to follow-up TL 4.25 mg/l (IQR 2.6 mg/l – 6.45 mg/l, p=0.019). The median TL difference was 0.9 mg/l (see Figure 3b).

When analysing these data further we noticed that the difference between baseline and follow-up TL in UC patients was mainly due to four patients that had TL difference greater than 3.2 mg/l. One of them had an undetectable TL with measurable ADAs after switching (baseline and follow-up TL 7.4 mg/l and < 0.03 mg/l, respectively, and ADA 35 AU/ml) and experienced a clinical disease relapse. Another patient with a great TL difference (11 mg/l before and 3.1 mg/l after switch) discontinued azathioprine medication a few weeks before the measurement of follow-up TL, which might at least partly explain the difference. For the other two patients, there was no obvious reason for the TL difference. These three patients remained in clinical remission.

3.2. Anti-drug antibodies

At baseline ADAs were detectable only in one of 78 (1.3%) patient with a titre of 18 AU/ml. Because of an IFX dose adjustment that patient was excluded from final paired analysis, but in follow-up after shortening of IFX interval the ADAs were undetectable. After switching, one patient on IFX monotherapy and one on a combination therapy with azathioprine developed ADAs (titres12 AU/ml and 35 AU/ml, respectively).

3.3. Disease activity

Disease activity at baseline and follow-up is shown in Table 2. Mean HBI was 1.22 (SD 2.29) before and 1.16 (2.22) after switching. Mean PMS was 1.2 (SD 1.76) before and 0.8 (SD 1.28) after switching. The disease activity during switching neither in UC nor in CD showed statistical difference (p=0.89 and p=0.07). In the whole study group, median FC concentration was 69 µg/g (IQR 10 – 251 µg/g) before and 26 µg/g (IQR 13 – 180 µg/g) after switching (p=0.78). Rate of infusion reactions was low after switching (4 out of 156 infusions, 2.5%): There was one reaction during biosimilar IFX infusion (throat sensation) and three potentially infusion related adverse effects after the first or second biosimilar infusion (rash, headache and nausea, fever and diarrhea). None of these effects resulted in discontinuation of the therapy.

4. Discussion

In this single-centre observational study all IBD patients receiving maintenance IFX therapy were switched to biosimilar IFX without any effects on IBD activity. Switching caused no statistically significant differences in IFX TLs in the whole IBD group or in CD subgroup. In the UC subgroup, however, TLs were statistically significantly lower after switching.

Since year 2013 EMA approval, evidence of biosimilar infliximab use in extrapolated indications, such as IBD has accumulated. In this study where all IBD patients on maintenance originator infliximab were switched to biosimilar one, we observed no differences in disease activity, laboratory values, infusion reactions and adverse effects. Our findings are in line with results from recently published studies [19-25]. Razanskaite and co-workers found no significant differences between originator and CT-P13 in terms of drug persistence, side effects, adverse effects, disease activity, or blood tests. TLs and ADAs did not show significant difference before and after switch [19]. Smits and co-workers showed that switching to biosimilar IFX led to a nonsignificant slight increase in median TL at week 16 (from 3.6 ug/ml at week 0 to 4.2 ug/ml), but not at week 52 (3.6 ug/ml and 3.7 ug/ml). There was no effect on disease activity [20,21]. Also in the study of Buer and co-workers disease activity, laboratory values and IFX TL remained stable in a six months follow-up period after switching [23]. In the large randomized NOR-SWITCH study no significant differences were observed one year after switch in clinical activity indices, serum CRP, FC or TLs in UC patients. In CD patients, changes in patient's and physician's global assessment of disease activity showed some improvement in those receiving originator IFX compared to those on biosimilar IFX [24]. Different from the NOR-SWITCH results, we detected significantly lower TLs after switching in UC patients. Although this difference is statistically significant, the clinical relevance of this finding remains unclear and should be interpreted with caution because of the rather low patient number in the UC subgroup. We point out that no changes in disease clinical activity occurred and a constantly low FC concentration in these patients suggested a stable remission after switching. As the follow up time in our study was only 16 weeks we cannot make any further statement about the behaviour of patients' TLs and ADA development after that period. It is known that the clearance of biologicals is influenced by various patient dependent factors like weight, disease severity, concomitant medication, albumin, and other pharmacokinetic and

pharmacodynamic factors [30,31]. Furthermore, the use of a concomitant immunosuppressive medication is a well-known factor that reduces the clearance of IFX, increases trough concentrations and reduces the risk of ADA formation [32]. In current study, however, the use of concomitant immunomodulators does not explain the observed differences in TLs in UC patients, because the use of these medications was even higher in the UC than in the CD subgroup. Another limitation of our study was a lack of a control group continuing on originator IFX. Therefore, it remains unresolved whether the change in median TL in UC patients is due to switching to the biosimilar IFX or due to other patient dependent or pharmacological factors. It is unlikely that the difference in IFX TLs could be explained by the ELISA test used. It has been shown in a recent real-life study, that the ELISA tests used for measuring originator IFX TLs and ADAs are feasible also for biosimilar IFX measurements [33].

During maintenance IFX therapy over a half of the patients in our study had TLs either below or above the suggested target level of 3 to 7 mg/l. This parallels the results of the TAXIT trial, where 43.7 % of patients on maintenance IFX therapy had a TL between 3 and 7 mg/l [8]. In that trial either reducing IFX dose in patients in clinical remission with TL over the target level or dose escalation in those with a low TL was safe and feasible. In our study de-escalation in clinically stable patients occurred less often that dose escalation. Recently published data suggest that even higher target TL for infliximab than that used in the TAXIT trial should be obtained especially in perianal CD: patients with fistula healing had significantly higher median serum IFX levels (15.8 mg/l) than those with active fistulas (4.4 mg/l) [34].

The amount of infusion related reactions and potential adverse effects was low in our study (2.5% of infusions). No severe adverse effects were reported. All patients continued therapy with the biosimilar IFX. Thus, in IBD patients being in stable remission, switching from maintenance originator IFX therapy to biosimilar one seems to be safe.

To conclude, in this study, TLs before and after switch did not differ significantly in CD patients, but a statistically significant decrease in TLs in UC patients occurred. The clinical relevance of this decrease remains unclear as we could not observe any changes in clinical disease activity or faecal calprotectin. No safety concerns occurred during switching.

Acknowledgments

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There is no conflict of financial interests.

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TABLES:

Table 1: Patients Demographic and Baseline Characteristics

	CD (n= 32)	*UC /IBD-u(n=30)*
Gender: Male, n (%)	21*(65.6)*	14*(46.7)*
Age, years, median (IQR)	35 (28-45)	37 (31-43)
Age at diagnosis, years, median (IQR)	19 (16-25)	27 (18-35)
Duration of disease, years, median (IQR)	13 (9-24)	9 (5-13)
Smoking, n (%)		
no	19 *(59.4)*	25 *(83.3)*
yes	8 *(25)*	1 *(3.3)*
former	5 *(15.6)*	4 *(13.3)*
Montreal classification (%)		
A1, A2, A3	9, 22, 1 *(28.1, 68.8, 3.1)*	-
L1, L2, L3, L4	5, 7, 20, 5 *(15.6, 21.9, 62.5, 15.6)*	-
B1, B2, B3	14, 10, 8 *(43.8, 31.3, 25)*	-
Perianal disease	8, (*25*)	-
E2, E3	-	15 (*50*), 15 *(50)*
Time using IFX, days, median (IQR)	1544 (531-2072)	361 (216-957)
Concomitant medication n (%)		
Azathioprine	16 *(50)*	18 *(60)*
6-Mercaptopurin	1 *(3.1)*	2 *(6.7)*
Methotrexate	3 *(9.4)*	4 *(13.3)*
Mesalamine	3 *(9.4)*	12 *(40)*
Corticosteroids	1 *(3.1)*	2 *(6.7)*

CD, Crohn's Disease; UC, Ulcerative Colitis; IBD-U, IBD-unclassified

Table 2: Disease activity

	CD (n=32)			*UC /IBD-u (n=30)*		
	Baseline	*after switch*	*p-value*	*Baseline*	*after switch*	*p-value*
HBI, mean (SD)	1.22 (2.29)	1.16 (2.22)	0.89	-	-	-
PMS, mean (SD)	-	-	-	1.2 (1.76)	0.8(1.28)	0.07
Calprotectin µg/g						
median (IQR)	22 (10-189)	17 (5-312)	0.35	82 (9-270)	32 (20-169)	0.54
Haemoglobin g/l						
median (IQR)	140 (131-150)	146 (133-152)	0.14	138 (124-150)	141 (123-148)	0.31
Leucocytes E9/l						
median (IQR)	6.7 (6.1-7.8)	6.7 (6.2-7.8)	0.21	7.0 (5.0-7.9)	6.1 (5.0-7.5)	0.16
Platelets E9/l						
median (IQR)	252 (227-298)	160 (224-309)	0.91	281 (242-315)	249 (220-312)	0.26
CRP mg/l						
median (IQR)	3 (3-3)	3 (3-5)	0.875	3 (3-3)	3 (3-3)	0.577

CD, Crohn's Disease; UC, Ulcerative Colitis; IBD-U, IBD-unclassified

HBI, Harvey-Bradshaw Index; PMS, Partial Mayo Score

Figure legends:

Figure 1: Trough levels before (BASE IFX) and after (FU IFX) switching from originator to biosimilar infliximab in Crohn's disease (CD) patients. The dotted line presents the median trough level.

Figure 2: Trough levels before (BASE IFX) and after (FU IFX) switching from originator to biosimilar infliximab in ulcerative colitis (UC) patients. The dotted line presents the median trough level.

Figure 3a & b: Distribution of trough level differences before (BASE IFX) and after (FU IFX) switching from originator infliximab (IFX) to biosimilar IFX in CD patients (a) and in UC patients (b).

The median differences and its 95% confidence intervals (CI) are marked with a solid dot and arrows. The difference is statistically significant ($p < 0.05$) if zero is not covered by the interval between the arrows. Trough levels are considered equivalent if the interval between the arrows does not cross the equivalence margins shown with dashed vertical lines.

Figure 1:

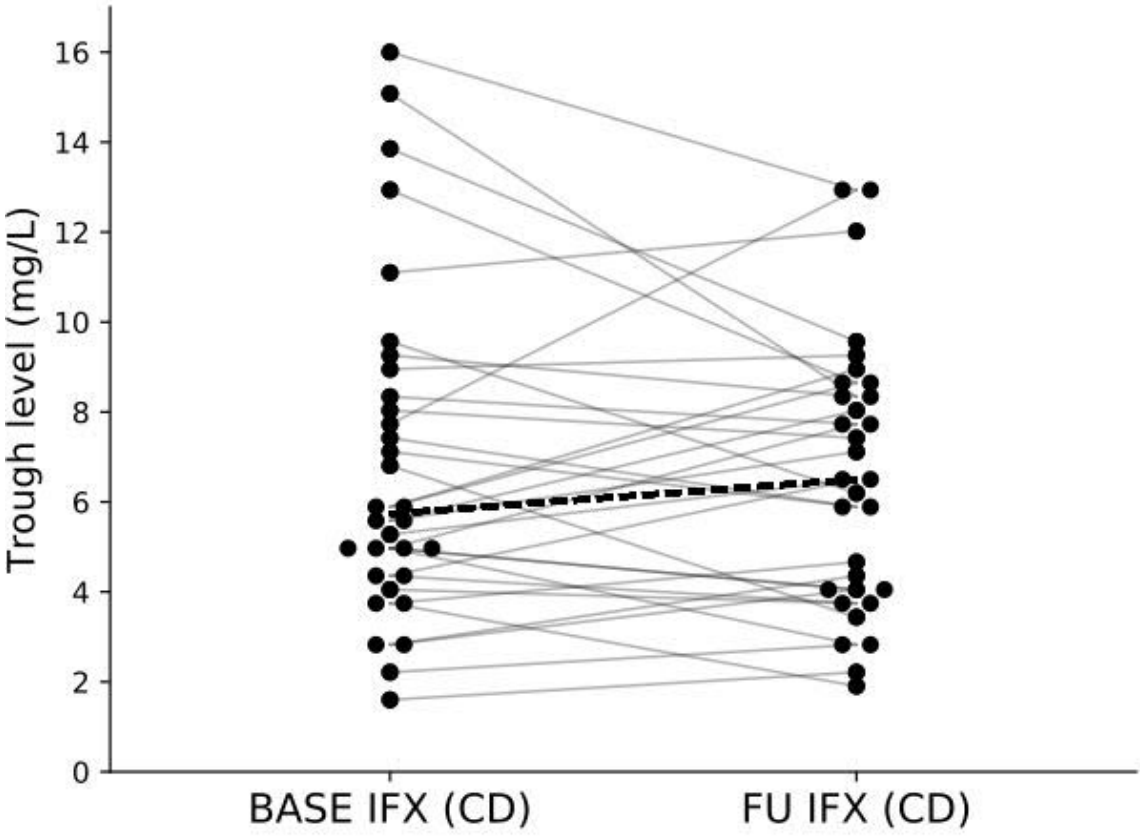


Figure 2:

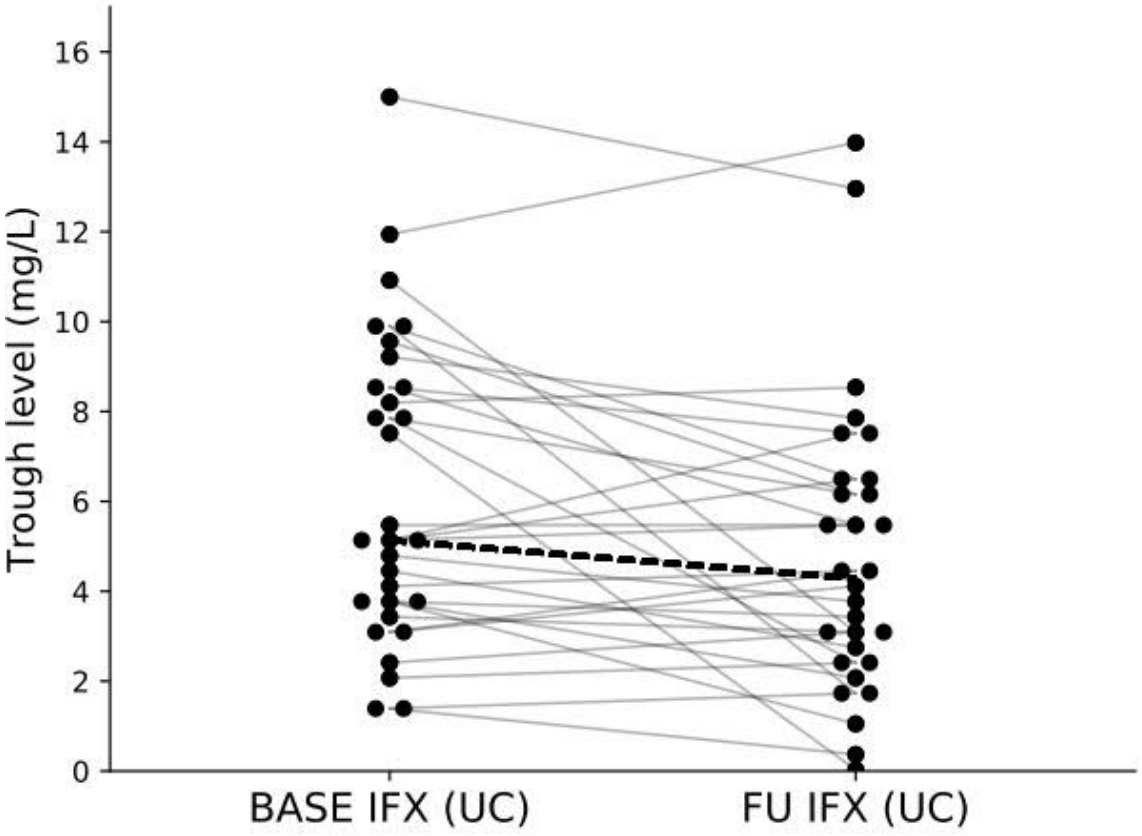


Figure 3a.

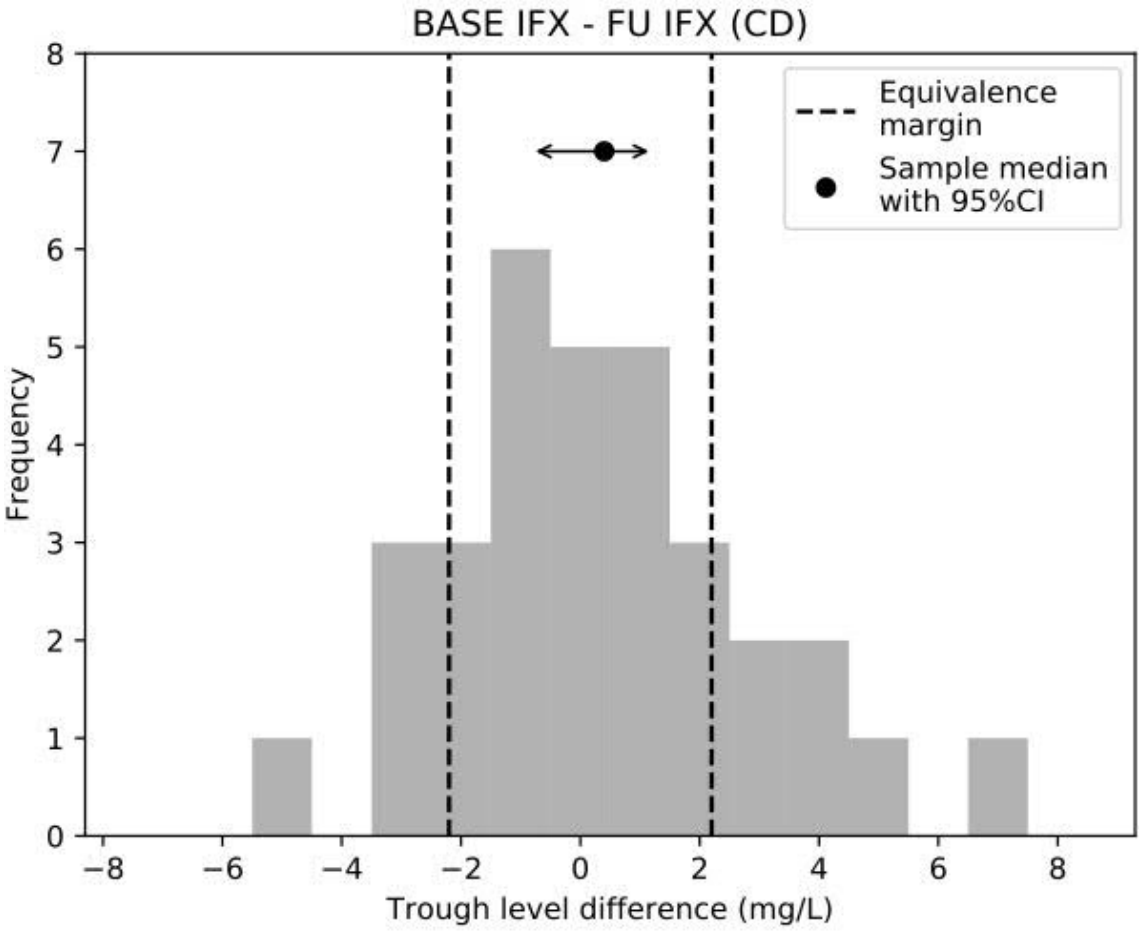
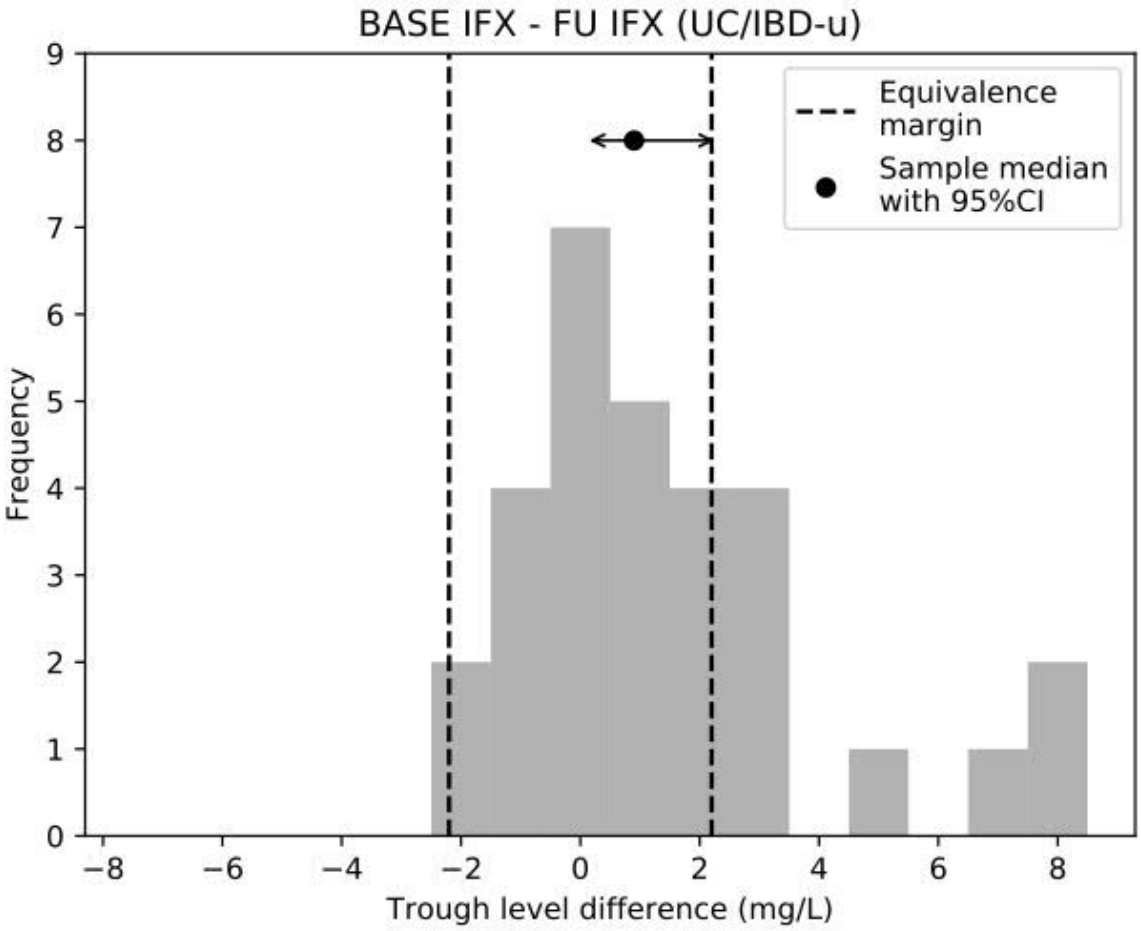

BASE IFX - FU IFX (CD)
Equivalence margin
Sample median with 95%CI
Frequency
Trough level difference (mg/L)
0
1
2
3
4
5
6
7
8
−8
−6
−4
−2
0
2
4
6
8

Figure 3b.


BASE IFX - FU IFX (UC/IBD-u)
Equivalence margin
Sample median with 95%CI
Frequency
Trough level difference (mg/L)
0
1
2
3
4
5
6
7
8
9
−8
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−2
0
2
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6
8