TITLE PAGE

Long term efficacy, safety and immunogenicity of biosimilar infliximab after one year in a prospective nationwide cohort

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ABSTRACT

Background: It has been previously shown that biosimilar infliximab CT-P13 is effective and safe in inducing remission in inflammatory bowel diseases (IBD).

Aim: We report here the one-year outcomes from a prospective nationwide IBD cohort.

Methods: A prospective, nationwide, multicentre, observational cohort was designed to examine the efficacy and safety of CT-P13 in the induction and maintenance treatment of Crohn's disease (CD) and ulcerative colitis (UC). Demographic data were collected and a harmonized monitoring strategy was applied. Clinical remission, response and biochemical response was evaluated at week 14, 30 and 54. Safety data was registered.

Results: 353 consecutive IBD (209 CD and 144 UC) patients were included of which 229 patients reached the week 54 endpoint at final evaluation. Age at disease onset: 24/28 years (median, IQR: 19-34/22-39) in CD/UC patients. Forty-nine, 53, 48% and 86, 81 and 65% of CD patients reached clinical remission and response by week 14, 30 and 54, respectively. Clinical remission and response rates were 56, 41, 43% and 74, 66, 50% in UC patients. Clinical efficacy was influenced by previous anti-TNF exposure in patients with a drug holiday beyond 1-year. Mean CRP decreased significantly in both CD and UC by week 14 and was maintained throughout the 1-year follow-up (both UC/CD: $p<0.001$). 31 (8.8%) patients had infusion reactions and 32 (9%) patients had infections. ADA positivity rates were significantly higher throughout patients with previous anti-TNF exposure, concomitant AZA prevented ADA formation in anti-TNF naïve CD patients.

Conclusions: Results from this prospective nationwide cohort confirm that CT-P13 is

effective and safe in inducing and maintaining long-term remission in both CD and UC. Efficacy was influenced by previous anti-TNF exposure, no new safety signals were detected.

Key Words: Crohn's disease, ulcerative colitis, infliximab, biosimilar, antidrug antibody, trough level, therapeutic drug monitoring, efficacy, side effects

INTRODUCTION

Biosimilar infliximab (IFX) CT-P13 was approved by the European Medicines Agency (EMA) in September 2013 and by the U.S. Food and Drug Administration (U.S. FDA) in April 2016 for all indications of the originator product.[1,2] The extrapolation of the use of biosimilar IFX in inflammatory bowel diseases (IBD) was based on the results from two randomized-controlled trials (RCTs) conducted in ankylosing spondylitis (AS) and rheumatoid arthritis (RA), which demonstrated similarity in pharmacokinetics and clinical efficacy between the biosimilar IFX and the originator product.[3,4] Since May 2014, the use of biosimilar IFX is mandatory in Hungary in all anti-TNF naïve patients and in patients, who were previously treated with the originator product with a proven clinical benefit but have been on drug holiday for longer than 12 months.

The efficacy and safety of biosimilar IFX in IBD have been studied in the past 2 years and real-life cohorts show comparable outcomes as in patients treated with the originator IFX.[5,6,7,8,9,10,11,12,13,14] As previously reported in the prospective, nationwide, multicenter study by our study group published in 2016 including 210 IBD patients, high response and remission rates throughout 30 weeks were found in both Crohn's disease (CD) and ulcerative colitis (UC).[7] At week 30, 67.2% and 53.4% of CD patients showed clinical response or clinical remission, while clinical response or remission was demonstrated in 80 % and 68% of UC patients. Early efficacy was affected by previous anti-TNF exposure with no new signal in adverse events.

In the present study, our aim was to evaluate the medium- and long-term efficacy, safety and immunogenicity of biosimilar IFX CT-P13 (Inflectra®) in a Hungarian consecutive, nationwide cohort of IBD patients treated up-to 54 weeks.

MATERIALS AND METHODS

The present study is a multicenter, nationwide prospective observational study. Eligible patients older than 18 years started on biosimilar IFX therapy were consecutively enrolled. The inclusion started in May 2014 in 12 IBD centers in Hungary.

A harmonized monitoring strategy was applied in all participating centers, as requested by the National Health Fund. Patient demographics, previous and concomitant medications were collected and biochemical and clinical assessment was performed at start and every 3 months thereafter. Disease location and behavior in CD and disease extent in UC were assessed according to the Montreal classification.[15] Patients were either naïve to anti-TNF or had response to previous anti-TNF therapy, but were stopped due to non-medical reasons with a drug holiday beyond one-year. A more detailed description of the methodology and case ascertainment of the cohort was published previously.[7]

Patients received intravenous infusions of the biosimilar IFX CT-P13 at a dose of 5 mg/kg of body weight at Weeks 0, 2, and 6 and then every eight weeks. Only patients with a clinical response at week 14 were eligible for maintenance therapy. Clinical response, remission, biochemical response, immunogenicity and safety were evaluated at weeks 14, 30 and 54. Patients lost to follow-up or with missing data were regarded as non-responders.

Clinical remission was defined as a Crohn's Disease Activity Index (CDAI) < 150 points or no fistula drainage as assessed by the Fistula Drainage Assessment in CD, and as a partial Mayo Score (pMayo) of less than 3 points in UC.[16,17,18] Clinical response was defined as a decrease in CDAI with more than 70 points and/or at least 50% reduction in the number of draining fistulas in CD, and a decrease in the pMayo

score with more than 3 points in UC. Biochemical activity was evaluated by measuring total blood count [TBC], serum C-reactive protein [CRP, normal cut-off: 10 mg/l], and albumin.

For the measurement of biosimilar IFX trough level (TL) and antidrug antibody, a conventional and bridging enzyme-linked immunosorbent assay [ELISA] were used [LISA TRACKER, Theradiag, France]. The kit was formally validated for the use in patients treated with the biosimilar IFX before commencing on the study. All sample measurements were performed at the Department of Laboratory Medicine, Semmelweis University, Budapest. The ELISA kit was validated for accuracy and reproducibility of therapeutic drug level monitoring [TDM] of the biosimilar IFX [Theradiag, France/Hospira, UK]. The detection cut-off value of biosimilar IFX TL was 0.1 μg/ml, while 3-7 μg/ml was defined as therapeutic.[19,20] For ADA level, the standard cut-off value was 10 ng/ml.

Ethical considerations

Ethical approval was acquired from the National Ethical Committee 929772-2/2014/EKU [292/2014]). The study was registered at the EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [ENCEPP/SDPP/9053]. Written informed consent was obtained from all participants.

Statistical analysis

For the characterization of patients' demographic data, remission and response rates at weeks 14, 30 and 54 and adverse events, descriptive statistics were applied. Medians and interquartile ranges were calculated for continuous variables. For the comparison of clinical response, remission rates, and antidrug antibody positivity

rates between anti-TNF-exposed and naïve patients, Chi2 test or Fisher exact test were used. For the comparison of mean CRP levels at week 14, 30 and 54, paired-sample T test was used. Statistical analysis was performed using SPSS software v. 20.0 (Chicago, IL); $p < 0.05$ was considered statistically significant.

RESULTS

A total of 353 consecutive IBD (209 CD and 144 UC) patients were included of which 229 patients reached the week 54 endpoint at final assessment. Patient characteristics are shown in Table 1. Until week 54, CT-P13 treatment was stopped in 37 patients due to adverse events, in 11 patients due to primary non-response and in 27 patients due to loss of response. Two CD and two UC patients were lost to follow-up (Figure 1). Dose optimization was performed in 17 and 16 of CD/UC patients during the follow up period.

Clinical remission and response rates at week 14, 30 and 54

In CD, 49%, 53%, 48% and 86%, 81% and 65% of the patients reached clinical remission and response by week 14, 30 and 54, respectively (Figures 2A, 3A and 4A).

Stratifying CD patients according to previous anti-TNF exposure, 53.8%, 57% and 53.5% of the anti-TNF naïve patients reached clinical remission by weeks 14, 30 and 54, while 91.1%, 85.9% and 73.3% of the anti-TNF naïve patients reached clinical response by week 14, 30 and 54. In patients with a previous anti-TNF exposure, clinical remission and response rates were 36.7%, 43.5% and 32.4% and 67.3%, 67.4% and 44.1% by week 14, 30 and 54 (Figures 2B, 3B and 4B). Clinical response rates were significantly different at week 14, 30 and 54 ($p<0.01$, $p=0.005$ and $p=0.001$), while clinical remission rates were significantly different at week 14 and 54 ($p=0.04$, $p=0.02$) between anti-TNF naïve and anti-TNF exposed CD patients.

In UC patients, clinical remission and response rates were 56%, 41%, 43% and 74%, 66% and 50% of the patients by week 14, 30 and 54 (Figures 2A, 3A and 4A).

In anti-TNF naïve UC patients, 59.5%, 45.7% and 47.3% of the patients

reached clinical remission by week 14, 30 and 54 and 75%, 71.3% and 51.4% of the patients reached clinical response by week 14, 30 and 54. In UC patients with a previous anti-TNF exposure, 35.7%, 21.7% and 26.5% of the patients reached clinical remission and 67.9%, 43.5% and 42.1% reached clinical response by week 14, 30 and 54 (Figures 2B, 3B and 4B). Clinical response rates were significantly different at week 30 (p=0.01), while clinical remission rates were significantly different at weeks 14 and 30 (p=0.02, p=0.04) between anti-TNF naïve and previously anti-TNF exposed UC patients.

Biochemical response

In CD patients, the mean CRP level significantly decreased between week 0 and week 14 from 23.7 mg/L to 9.8 mg/L (p<0.001). Mean CRP levels were 9.4 mg/L and 9.6 mg/L at weeks 30 and 54 (p<0.001 and p=0.001 compared to baseline).

Trends were similar in UC. The mean CRP levels were 27.6, 8.7, 12.2 and 11.7 mg/L at weeks 0, 14, 30 and 54 with a significant decrease by week 14 (p<0.001), week 30 (p=0.002) and week 54 (p=0.009).

Therapeutic drug level monitoring

In CD patients, the mean biosimilar IFX TLs at weeks 2, 6, 14, 30 and 54 are presented in Table 2. Biosimilar IFX TLs were significantly lower in previously anti-TNF exposed patients at week 2 (p=0.03), week 14 (p=0.02) and week 30 (p=0.03) but not at week 6 (p=0.148) and week 54 (p=0.91) (Table 2).

In UC patients, the mean biosimilar IFX TLs at weeks 2, 6, 14, 30 and 54 are presented also in Table 2. No significant difference was found in biosimilar IFX TLs between anti-TNF naïve and previously exposed patients at any time points, with a

trend towards higher TLs in the anti-TNF naïve patient group (Table 2).

Cumulative ADA positivity rates were 9.8% (26/266), 18.6% (58/312), 24.1% (70/290) and 33.8% (71/210) at weeks 0, 14, 30 and 54 in all IBD patients. In anti-TNF naïve IBD patients, cumulative ADA positivity rates were 4.3% (9/213), 12% (30/249), 20.9% (48/230) and 28.6% (50/175) at week 0, 14, 30 and 54. The cumulative ADA positivity rates were significantly higher at all time points in anti-TNF exposed patients 32% (17/53), 34.9% (22/63), 36.6% (22/60) and 46.6% (21/45) at week 0, 14, 30 and 54 ($p<0.001$ for all).

Cumulative ADA positivity rates in CD and UC patients with and without previous anti-TNF exposure are presented in Table 3. In CD, a significant difference was found in ADA positivity rates between anti-TNF naïve and previously anti-TNF exposed patients at baseline ($p<0.001$), week 14 ($p<0.001$), week 30 ($p=0.03$) and week 54 ($p=0.03$).

In UC, the difference was significant in baseline ADA positivity rates between anti-TNF naïve and previously anti-TNF exposed patients ($p<0.001$), but this difference become non-significant by week 14 and thereafter (week 14: $p=0.14$; week 30: $p=0.16$; week 54: $p=0.27$).

Concomitant AZA prevented ADA formation at weeks 14 (6.5% vs. 21.2%, $p=0.01$) 30 (12.7% vs. 29.2%, $p=0.02$) and 54 (15% vs. 45.2%, $p=0.004$) in anti-TNF naive but not in previously exposed CD patients (week 14: 40% vs. 33.3% $p=0.75$, week 30: 37.5% vs. 38.5%, $p=0.95$, week 54: 50% vs. 50%, $p=1.0$).

In contrast, concomitant AZA did not prevent ADA formation either in anti-TNF naive (week 14: 19.2% vs. 18.4%, $p=0.91$, week 30: 24% vs. 22.4%, $p=0.85$, week 54: 29.3% vs. 35%, $p=0.58$) or in previously exposed UC patients (week 14: 30% vs. 36.4%, $p=0.76$, week 30: 40% vs. 36.4%, $p=0.86$, week 54: 40% vs. 50%,

p=0.71).

Clinical efficacy at week 14 or 30 was not affected by concomitant AZA use in either CD or UC patients (CD: week 14 response: 87.2% vs. 81.6%, p=0.28; week 14 remission: 52% vs. 47.4%, p=0.52; week 30 response: 84.1% vs. 76.8%, p=0.22; week 54 response: 69.1% vs. 56.9%, p=0.15; week 54 remission: 50.6% vs. 39.2%, p=0.2; UC: week 14 reponse: 73% vs. 74.3%, p=0.85; week 14 remission: 52.7% vs. 57.1%, p=0.59; week 30 response: 65.6% vs. 66.1%, p=0.95; week 30 remission: 41% vs. 41.1%, p=0.99; week 54 response: 48% vs. 51.2%, p=0.76; week 54 remission: 40% vs. 46.5%, p=0.53). Of note, the clinical remission rates were significantly different in CD at week 30 (63.7% vs. 40.6%, p=0.002) and clinical response at week 30 in previoulsy exposed CD patients (80.8% vs. 44.4%, p=0.01).

Adverse events

At week 54, the cumulative rate of adverse events was 24%. Infusion reactions occurred in 31 (8.8%) patients. Sixteen of 31 patients previously received anti-TNF therapy. Infections occurred in 32 (9%) patients with no cases of tuberculosis. One patient developed invasive fungal sepsis, resulting in death. No cases of malignancy occurred during follow-up of the cohort. Detailed adverse event data are presented in Table 4.

DISCUSSION

In the present prospective, multicenter, nationwide study of IBD patients treated with the biosimilar IFX, clinical remission and response rates were maintained throughout 54 weeks and were in line with the previously published data on the originator product or CT-P13 biosimilar. In addition, previous anti-TNF exposure affected clinical efficacy, while parallel AZA was effective in preventing ADA formation in anti-TNF naïve patients.

The efficacy of maintenance IFX therapy in active CD was demonstrated in the ACCENT I trial, where clinical remission rates at week 30 were significantly higher in week-2 responder patients receiving IFX 5 mg/kg and 10 mg/kg compared to the placebo group (39% and 45% vs. 21%) and the difference between the treatment groups remained significant also at week 54.[21] In a retrospective Hungarian study, the overall response rate was 86.2% (313 out of 363 patients) and the overall remission rate was 46% (167 out of 363 patients) at the end of induction therapy with the originator IFX in CD patients.[22] In addition, in the ACT 1 trial, clinical response and remission rates at week 54 were 45.5% and 34.7% in UC patients receiving 5 mg of IFX compared to 19.8% and 16.5% in the placebo group.[23]

Clinical response, remission rates and safety data[24] in the present cohort were in line with the above findings and with data presented in real life cohorts treated with IFX. In the retrospective study by Jung et al., clinical response and remission were achieved by 87.5% and 75% of the anti-TNF naïve CD and 100% and 50% of the anti-TNF naïve UC patients at week 54.[5] In a Norwegian single-center study, 34 (79%) CD patients achieved a Harvey-Bradshaw score of ≤4, and 18 (56%) UC patients achieved a pMayo score of ≤2 at week 14. In addition, mean serum CRP levels significantly decreased from baseline to week 14 both in CD (22.5 vs. 4.9 mg/l;

p=0.006) and UC (36.8 vs. 9.6 mg/l; p=0.012).[6] High early clinical remission and response rates were found in the previous publication from the present cohort in 210 IBD patients throughout 30 weeks. Clinical response and remission rates at week 14 were 81 and 54% in CD and 78 and 59% in UC. At week 30, steroid-free clinical remission was achieved in 50% of the CD and 56% of the UC patients.[7] In a Czech study including 52 patients, clinical response (≥70 point-decrease in CDAI score from baseline in CD and ≥2-point decrease in partial Mayo score from baseline) and remission rates (CDAI<150 in CD and total score on partial Mayo score index ≤2 points) at week 14 were 50% and 50% in CD and 54.4% and 40.9% in UC.[9]

We observed a cumulative adverse event rate of 24% in the present cohort. The rate of infusion reactions was 8.8%, of which about half of the patients was previously exposed to the originator anti-TNF therapy. The rate of infections (9%) is in line with published data on biosimilar or originator IFX. Of note, no cases of tuberculosis were identified during follow-up.[7] In the study by Keil et al. including 52 patients, four adverse events occurred during the 14-week follow-up period including allergic reaction, phlebothrombosis of the lower extremity, pneumonia and herpes labialis.[9] Balint et al. investigated the incidence and characteristics of infusion reactions in 384 patients from 13 Hungarian and one Czech IBD centers. The rate of infusion reactions was 7.2% (21 patients) among Hungarian patients and 13 patients of those received previous anti-TNF therapy.[25]

In the present study, ADA positivity rates were significantly higher in patients with previous exposure of anti-TNF therapy throughout week 54 in CD but this difference was non-significant after week 14 in UC. In addition, significantly lower early IFX TLs were observed in patients previously exposed to IFX, compared to naïve patients. Farkas et al. reported significantly higher IFX TLs in UC patients with

mucosal healing or steroid-free mucosal healing compared to patients without mucosal healing at week 14.[8] In a Norwegian single-center study, four CD and four UC patients had an IFX TL of 0 mg/l and three of them received anti-TNF therapy previously. Two of these patients had high (≥80 AU/l), five had medium/high (<80 AU/l), and one had low ADA levels (<10 AU/l).[6] ADA and TL data are awaited from the international cross-over study from CD patients treated with originator or biosimilar infliximab.[26,27]

Parallel AZA was effective in preventing ADA formation in anti-TNF naïve CD but not UC patients. Similarly, lower rates of antibodies against IFX were reported by Baert et al. in CD patients taking immunosuppressives compared to patients without immunosuppressive use during IFX therapy (43% vs. 75%, $p<0.01$).[28] Vermeire at al. studied the rate of ATI formation in a multicenter cohort of CD patients receiving methotrexate (MTX) and IFX, AZA and IFX or IFX alone. Lower ATI formation was observed in CD patients receiving MTX or AZA compared to patients receiving IFX alone (46% vs. 73%, $p<0.001$).[29]

Strengths of the present study are the prospective study design and the harmonized, standardized follow-up and monitoring strategy in all participating centers. A limitation of our study is, that mucosal healing was not systematically evaluated. Furthermore, our cohort includes patients with previous drug exposure and drug holiday, but not switch.

In conclusion, in the present multicenter, nationwide cohort including a large cohort of IBD patients treated with biosimilar IFX the efficacy, safety and immunogenicity of the biosimilar IFX was comparable that of the originator compound reported in previous studies. Data on immunogenicity and drug trough levels obtained in the present study support the routine use of TDM in patients treated

with biosimilar IFX. In addition, parallel AZA was effective in preventing ADA formation in anti-TNF naïve patients, while previous anti-TNF exposure affected clinical efficacy.

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***Authors' Contributions**:*

LG performed data collection, and drafted the manuscript. KBG, ZV, PAG, MR, RB, KF, JB, LB, BG, TK, LL, PM, MJ, KP, MP, AP, LL, AS, TS, ZS, GTT, AV, BDL, ZK, ZS, TM performed data collection. BS performed measurements for therapeutic drug level monitoring. PLL conceived the study and consulted the concept, performed data collection and validation, carried out statistical analysis, supervised the manuscript preparation and is acting as the submission's guarantor. All authors read and approved the final manuscript including the authorship list.

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Available at: https://www.ecco-ibd.eu/index.php/publications/congress-abstracts/abstracts-2017/item/dop062-biosimilar-infliximab-ct-p13-is-not-inferior-to-originator-infliximab-explorative-ibd-subgroup-analyses-in-crohn-s-disease-and-ulcerative-colitis-from-the-nor-switch-trial.html
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TABLES

Table 1. Baseline disease characteristics of patients with inflammatory bowel disease on biosimilar IFX therapy

	Crohn's disease (n=209)	**Ulcerative colitis (n=144)**
Gender (male/female)	99/110	74/70
Age at disease onset (median (IQR); years)	24 (19-34)	28 (22-39)
Disease duration (median (IQR); years)	5 (2-11)	5 (2-11)
Baseline disease activity (median (IQR); points)	CDAI: 319 (301-352; n=172) PDAI: 9 (5-11; n=77)	Mayo: 9 (7-11; n=136) pMayo: 7 (6-9; n=89)
Disease location (L1/L2/L3/L4/all L4; %)	16.3/31.1/41.1/1.5/8.3	-
Disease extent (E1/E2/E3; %)	-	9.7/34.1/56.2
Disease behavior (B1/B2/B3; %)	56.5/21.0/22.5	-
Perianal disease (%)	39.2	-
Previous surgery (%)	21.5	-
Previous anti-TNF therapy (%) **IFX** **Adalimumab** **IFX + adalimumab**	23.4 (n=49) 18.2 (n=38) 4.2 (n=9) 1 (n=2)	19.4 (n=28) 12.5 (n=18) 6.2 (n=9) 0.7 (n=1)
Concomitant steroid therapy (%)	42.6	64.6
Concomitant AZA therapy (%)	60.3	51.4

(IQR, interquartile range; CD, Crohn's disease; UC, ulcerative colitis; IFX, infliximab; 5ASA, 5-aminosalicylates; AZA, azathioprine; TNF, tumor necrosis factor; ADA, anti-drug antibody; PDAI, Perianal Disease Activity Index; CDAI, Crohn's Disease Activity Index)

Table 2. Mean trough levels in patients with inflammatory bowel disease on biosimilar IFX therapy

	week 2	week 6	week 14	week 30	week 54
CD Mean biosimilar IFX TLs	18.9 µg/mL (n=85)	17.3 µg/mL (n=74)	6.1 µg/mL (n=136)	4.3 µg/mL (n=119)	5.3 µg/mL (n=53)
Without previous anti-TNF	20.4 µg/mL*	16.5 µg/mL	6.5 µg/mL*	4.6 µg/mL*	5.4 µg/mL
With previous anti-TNF	11.7 µg/mL*	10.7 µg/mL	3.7 µg/mL*	2.1 µg/mL*	5.0 µg/mL
UC Mean biosimilar IFX TLs	19.0 µg/mL (n=67)	11.8 µg/mL (n=50)	4.9 µg/mL (n=97)	3.9 µg/mL (n=63)	4.5 µg/mL (n=39)
Without previous anti-TNF	20.6 µg/mL	12.9 µg/mL	4.9 µg/mL	4.0 µg/mL	4.9 µg/mL
With previous anti-TNF	9.9 µg/mL	5.7 µg/mL	4.8 µg/mL	3.3 µg/mL	1.9 µg/mL

* Mean biosimilar IFX TLs differed significantly between anti-TNF naïve and previously anti-TNF exposed patients at week 2 (p=0.03), at week 14 (p=0.02) and at week 30 (p=0.03) in CD

(CD, Crohn's disease; UC, ulcerative colitis; TNF, tumour necrosis factor; TL, trough level)

Table 3. Cumulative antidrug antibody positivity in patients with inflammatory bowel disease on biosimilar IFX therapy

	ADA positivity at baseline	ADA positivity at week 14	ADA positivity at week 30	ADA positivity at week 54
CD	15/169 (8.9%)	32/190 (16.8%)	39/170 (22.9%)	38/124 (30.6%)
Without previous anti-TNF	5/134 (3.7%)*	17/148 (11.5%)*	25/131 (19.1%)*	24/94 (25.5%)*
With previous anti-TNF	10/35 (28.6%)*	15/42 (35.7%)*	14/39 (35.9%)*	14/30 (46.7%)*
UC	11/97 (11.3%)	26/122 (21.3%)	31/120 (25.8%)	33/96 (34.4%)
*Without previous anti-TNF**	4/79 (5.1%)*	13/101 (18.8%)	23/99 (23.2%)	26/81 (32.1%)
With previous anti-TNF	7/18 (38.9%)*	7/21 (33.3%)	8/21 (38.1%)	7/15 (46.7%)

*ADA positivity rates differed significantly between anti-TNF naïve and previously anti-TNF exposed patients at baseline ($p<0.001$), at week 14 ($p<0.001$), at week 30 ($p=0.03$) and at week 54 ($p=0.03$) in CD and at baseline ($p<0.001$) in UC

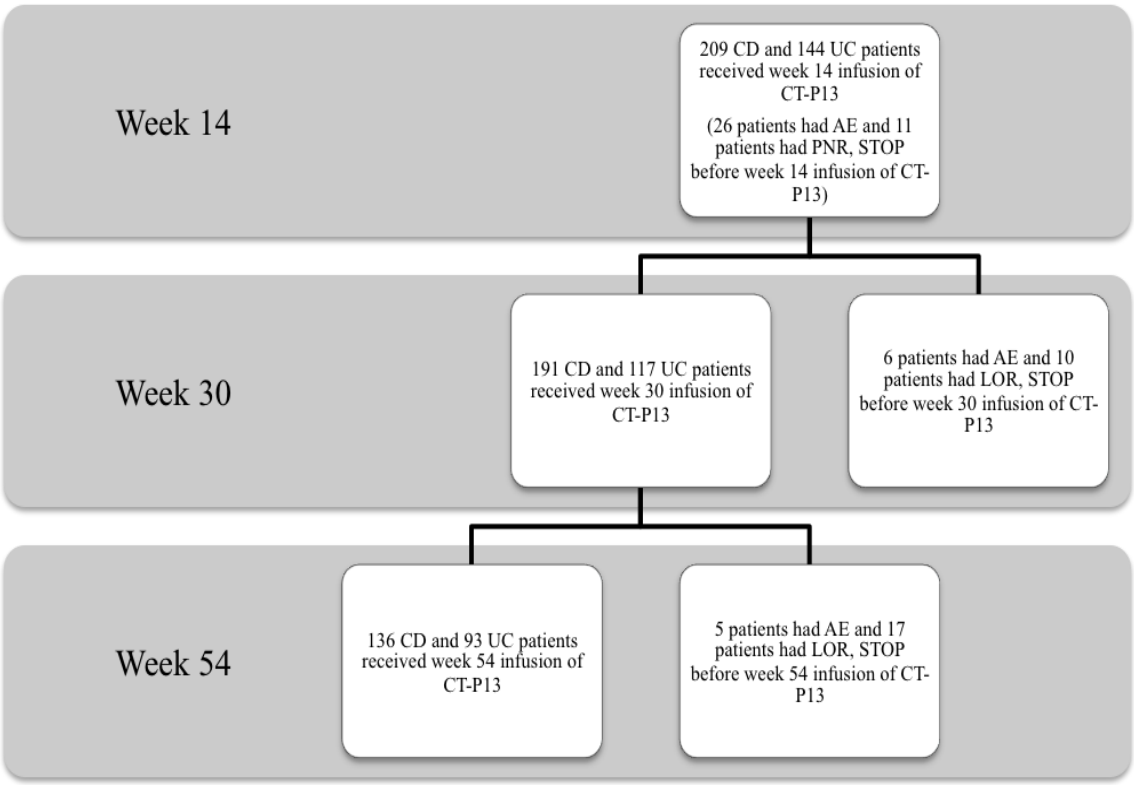
(CD, Crohn's disease; UC, ulcerative colitis; TNF, tumour necrosis factor; ADA, anti-drug antibody)

Table 4. Adverse events in patients with inflammatory bowel disease on biosimilar IFX therapy

Adverse event	Patients (%)
Mortality	1 (0.3%)
Infections	
• Upper respiratory tract infection	9 (2.5%)
• Gastroenteritis	10 (2.8%)
• Viral infections (influenza, herpes, varicella)	7 (2%)
• C. difficile colitis	3 (0.8%)
• Invasive fungal infection	1 (0.3%)
• Pneumonia	1 (0.3%)
• Urinary tract infection	1 (0.3%)
• Tuberculosis	0 (0%)
Allergy	
• Infusion reaction	31 (8.8%)
• Anaphylaxis	1 (0.3%)
Others	
• Arthralgia	11 (3.1%)
• Delayed hypersensitivity	10 (2.8%)
• Malignancy	0 (0%)

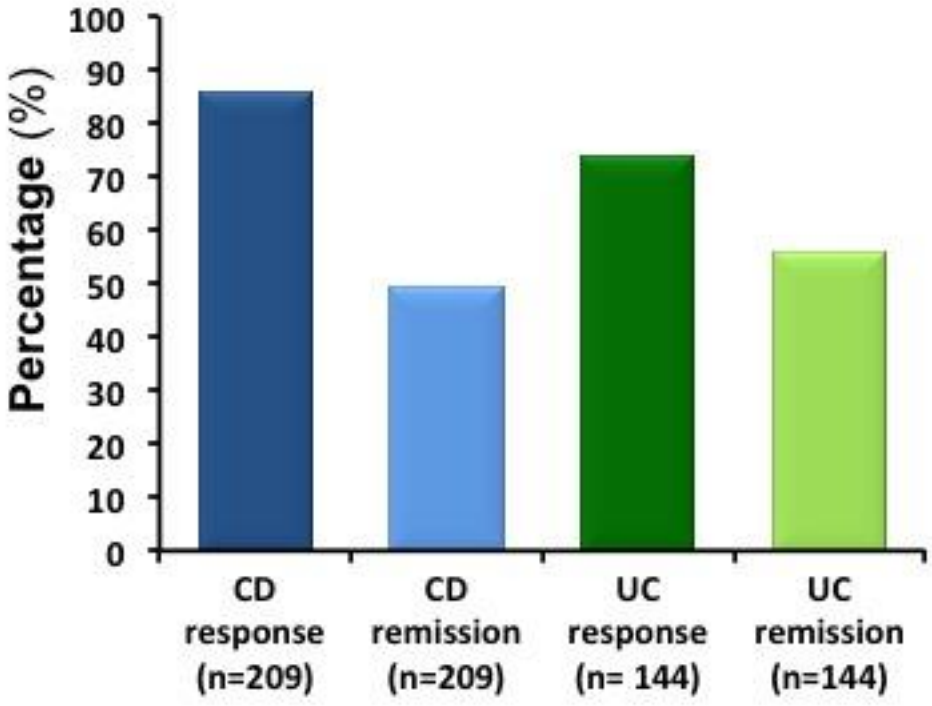
FIGURES

Figure 1. Patients and follow-up



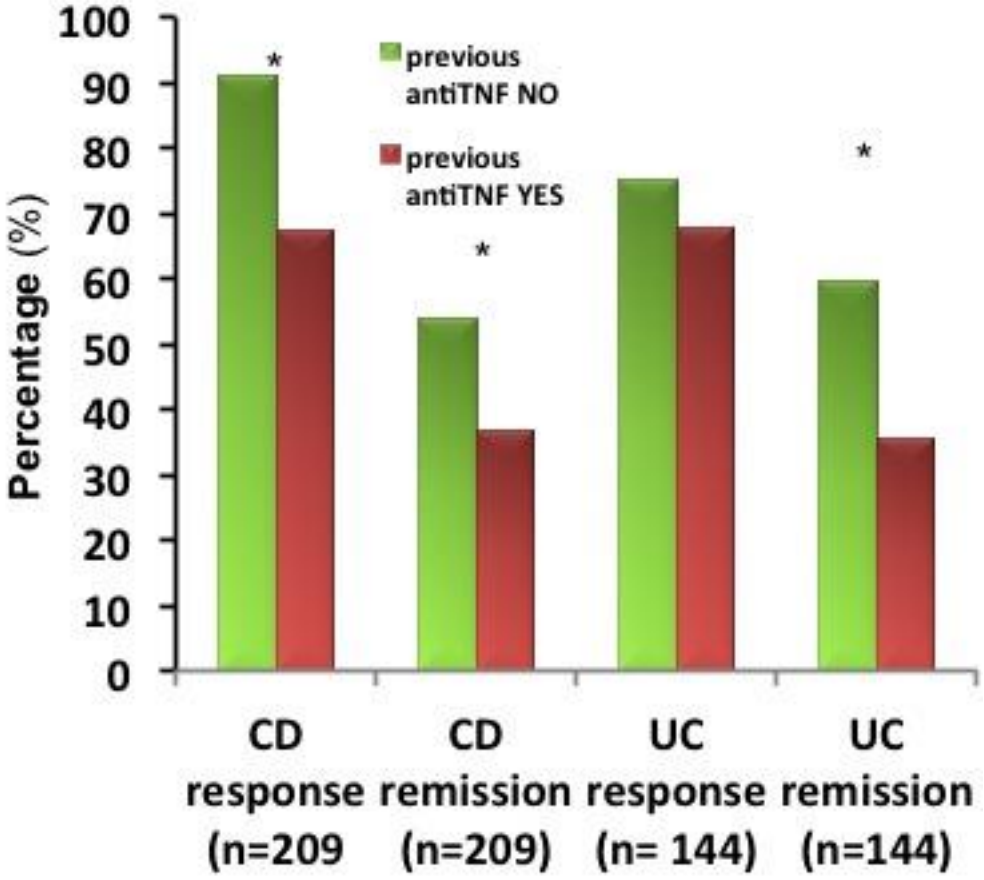
(PNR: primary non-response, LOR: loss of response, AE: adverse event; 2 CD patients and 2 UC patients were lost to follow-up.)

Figure 2A. Clinical response and remission rates at week 14 in patients with inflammatory bowel disease treated with the biosimilar IFX



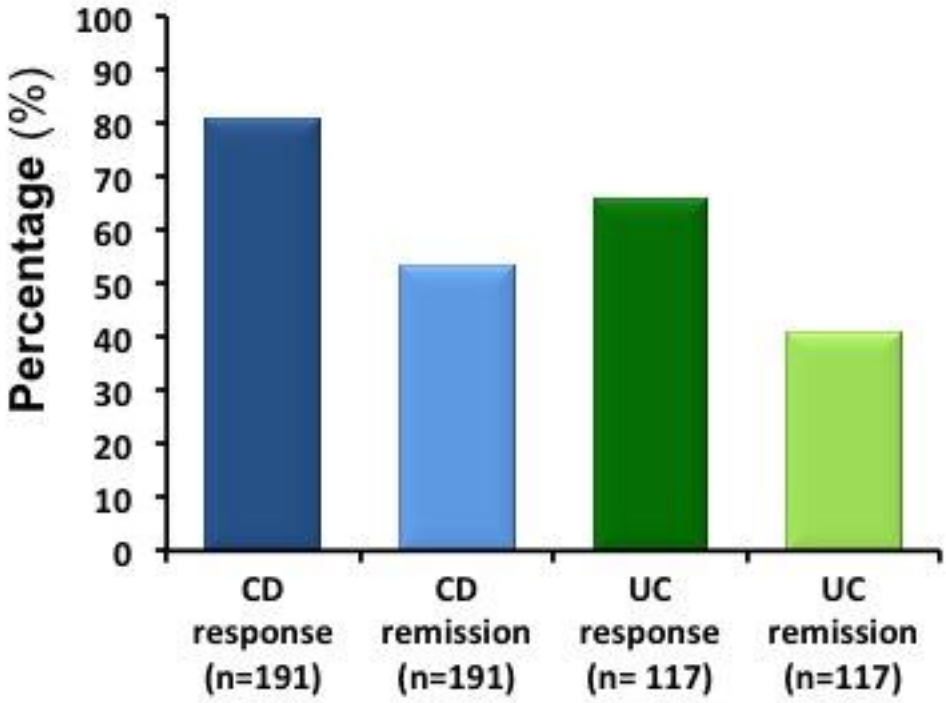
(CD, Crohn's disease; UC, ulcerative colitis)

Figure 2B. Clinical response and remission rates at week 14 in patients with inflammatory bowel disease treated with the biosimilar IFX stratified by previous anti-TNF exposure; *p<0.05



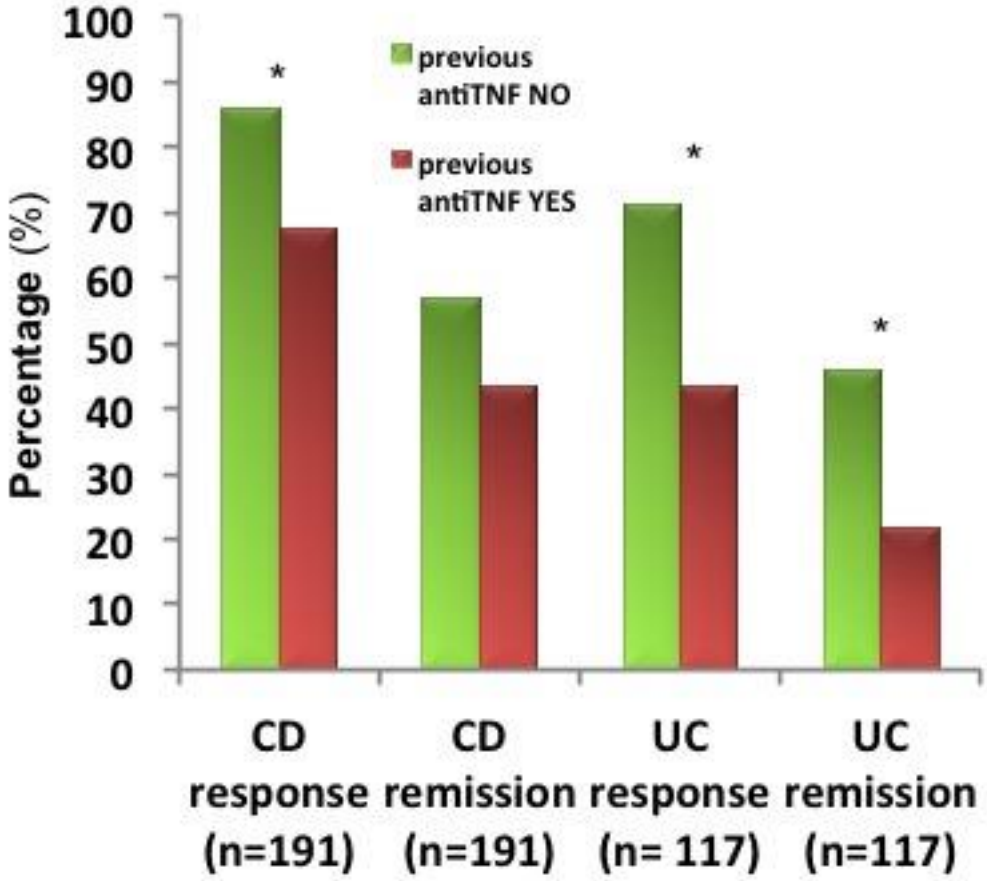
(CD, Crohn's disease; UC, ulcerative colitis)

Figure 3A. Clinical response and remission rates at week 30 in patients with inflammatory bowel disease treated with the biosimilar IFX



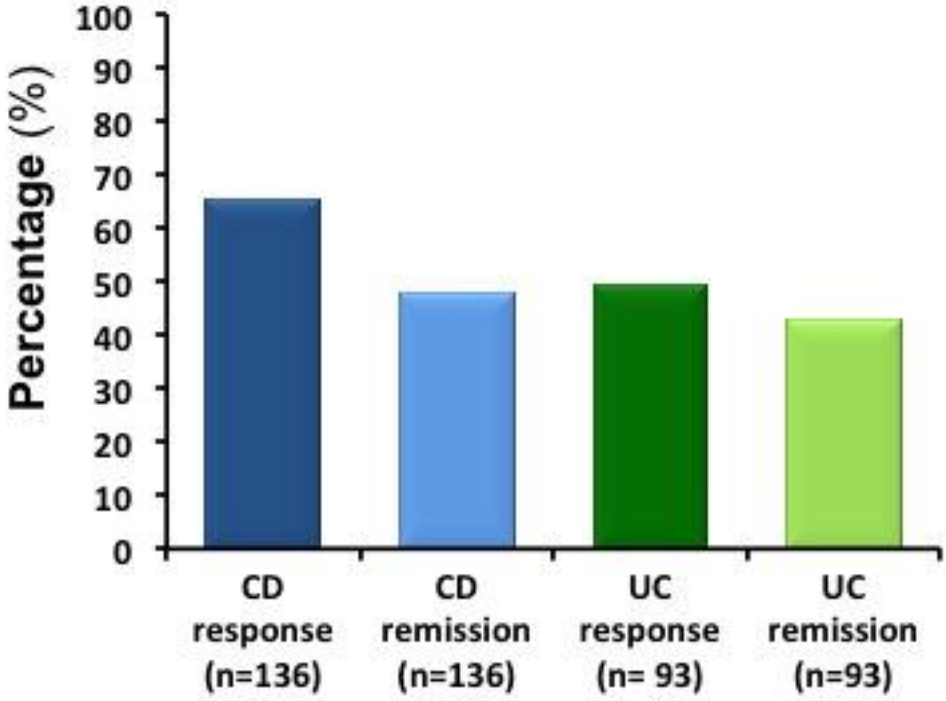
(CD, Crohn's disease; UC, ulcerative colitis)

Figure 3B. Clinical response and remission rates at week 30 in patients with inflammatory bowel disease treated with the biosimilar IFX stratified by previous anti-TNF exposure; *p<0.05



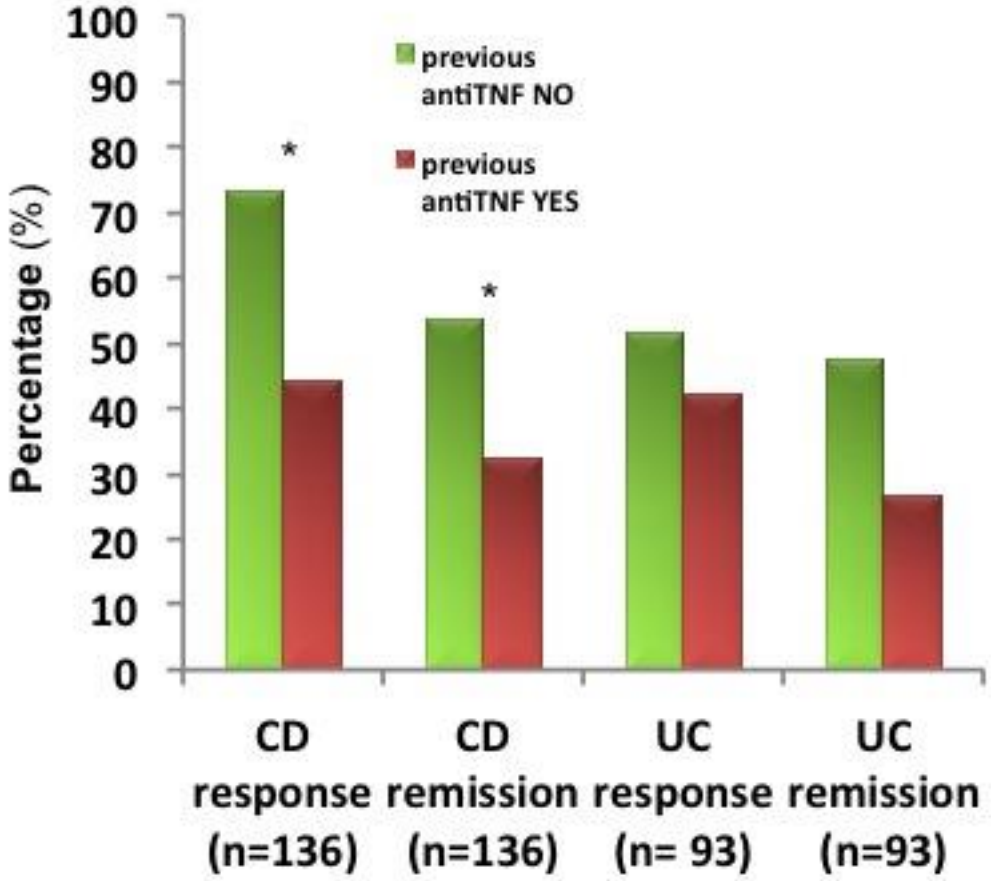
(CD, Crohn's disease; UC, ulcerative colitis)

Figure 4A. Clinical response and remission rates at week 54 in patients with inflammatory bowel disease treated with the biosimilar IFX



(CD, Crohn's disease; UC, ulcerative colitis)

Figure 4B. Clinical response and remission rates at week 54 in patients with inflammatory bowel disease treated with the biosimilar IFX stratified by previous anti-TNF exposure; *p<0.05



(CD, Crohn's disease; UC, ulcerative colitis)

Table and figure legends:

Table 1. Baseline disease characteristics of patients with inflammatory bowel disease on biosimilar IFX therapy

Table 2. Mean trough levels in patients with inflammatory bowel disease on biosimilar IFX therapy

Table 3. Cumulative antidrug antibody positivity in patients with inflammatory bowel disease on biosimilar IFX therapy

Table 4. Adverse events in patients with inflammatory bowel disease on biosimilar IFX therapy

Figure 1. Patients and follow-up

Figure 2A. Clinical response and remission rates at week 14 in patients with inflammatory bowel disease treated with the biosimilar IFX

Figure 2B. Clinical response and remission rates at week 14 in patients with inflammatory bowel disease treated with the biosimilar IFX stratified by previous anti-TNF exposure; *$p<0.05$

Figure 3A. Clinical response and remission rates at week 30 in patients with inflammatory bowel disease treated with the biosimilar IFX

Figure 3B. Clinical response and remission rates at week 30 in patients with inflammatory bowel disease treated with the biosimilar IFX stratified by previous anti-TNF exposure; *$p<0.05$

Figure 4A. Clinical response and remission rates at week 54 in patients with inflammatory bowel disease treated with the biosimilar IFX

Figure 4B. Clinical response and remission rates at week 54 in patients with inflammatory bowel disease treated with the biosimilar IFX stratified by previous anti-TNF exposure; *$p<0.05$

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[on the Title page 1 and page 3]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[pages 3-4]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[pages 5-6]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[page 6]**
Methods		
Study design	4	Present key elements of study design early in the paper **[pages 7-8]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[pages 7-8]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **[pages 7-8]**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **[NA]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[pages 7-8]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[pages 7-8]**
Bias	9	Describe any efforts to address potential sources of bias **[page 7]**
Study size	10	Explain how the study size was arrived at – **patients with no available week 14 outcomes were excluded from the analysis [page 7]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[pages 7-8] anti-TNF naïve patients and patients previously exposed to anti-TNF were analysed also separately**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[pages 8-9]**
		(*b*) Describe any methods used to examine subgroups and interactions **[pages 8-9]**
		(*c*) Explain how missing data were addressed – **an ITT analysis was applied, patients loss-to-follow up or with missing data were regarded as non-responder**s **[page 7]**

		(*d*) If applicable, explain how loss to follow-up was addressed - **an ITT analysis was applied, patients loss-to-follow up or with missing data were regarded as non-responder**s **[page 7]**
		(*e*) Describe any sensitivity analyses **[NA]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Figures 1-3]**
		(b) Give reasons for non-participation at each stage – **[page 7]**
		(c) Consider use of a flow diagram – **[page 22]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **shown as appropriate**
		(c) Summarise follow-up time (eg, average and total amount) **[pages 7 and 10]**
Outcome data	15*	Report numbers of outcome events or summary measures over time **[pages 10-14]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[pages 10-14] multivariate analysis was used as appropriate**
		(*b*) Report category boundaries when continuous variables were categorized **[pages 10-14]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[NA]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[pages 10-14]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[pages 15-17]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[pages 17-18]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **pages 15-18]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[page 18]**
Other information		

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[page 19]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

	Crohn's disease (n=209)	**Ulcerative colitis (n=144)**
Gender (male/female)	99/110	74/70
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Disease location (L1/L2/L3/L4/all L4; %)	16.3/31.1/41.1/1.5/8.3	-
Disease extent (E1/E2/E3; %)	-	9.7/34.1/56.2
Disease behavior (B1/B2/B3; %)	56.5/21.0/22.5	-
Perianal disease (%)	39.2	-
Previous surgery (%)	21.5	-
Previous anti-TNF therapy (%) **IFX** **Adalimumab** **IFX + adalimumab**	23.4 (n=49) 18.2 (n=38) 4.2 (n=9) 1 (n=2)	19.4 (n=28) 12.5 (n=18) 6.2 (n=9) 0.7 (n=1)
Concomitant steroid therapy (%)	42.6	64.6
Concomitant AZA therapy (%)	60.3	51.4

Table2

	week 2	**week 6**	**week 14**	**week 30**	**week 54**
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UC Mean biosimilar IFX TLs	19.0 µg/mL (n=67)	11.8 µg/mL (n=50)	4.9 µg/mL (n=97)	3.9 µg/mL (n=63)	4.5 µg/mL (n=39)
Without previous anti-TNF	20.6 µg/mL	12.9 µg/mL	4.9 µg/mL	4.0 µg/mL	4.9 µg/mL
With previous anti-TNF	9.9 µg/mL	5.7 µg/mL	4.8 µg/mL	3.3 µg/mL	1.9 µg/mL

Table3

	ADA positivity at baseline	**ADA positivity at week 14**	**ADA positivity at week 30**	**ADA positivity at week 54**
CD	15/169 (8.9%)	32/190 (16.8%)	39/170 (22.9%)	38/124 (30.6%)
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With previous anti-TNF	10/35 (28.6%)*	15/42 (35.7%)*	14/39 (35.9%)*	14/30 (46.7%)*
UC	11/97 (11.3%)	26/122 (21.3%)	31/120 (25.8%)	33/96 (34.4%)
*Without previous anti-TNF**	4/79 (5.1%)*	13/101 (18.8%)	23/99 (23.2%)	26/81 (32.1%)
With previous anti-TNF	7/18 (38.9%)*	7/21 (33.3%)	8/21 (38.1%)	7/15 (46.7%)

Table4

Adverse event	Patients (%)
Mortality	1 (0.3%)
Infections	
• Upper respiratory tract infection	9 (2.5%)
• Gastroenteritis	10 (2.8%)
• Viral infections (influenza, herpes, varicella)	7 (2%)
• C. difficile colitis	3 (0.8%)
• Invasive fungal infection	1 (0.3%)
• Pneumonia	1 (0.3%)
• Urinary tract infection	1 (0.3%)
• Tuberculosis	0 (0%)
Allergy	
• Infusion reaction	31 (8.8%)
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Others	
• Arthralgia	11 (3.1%)
• Delayed hypersensitivity	10 (2.8%)
• Malignancy	0 (0%)

Image1

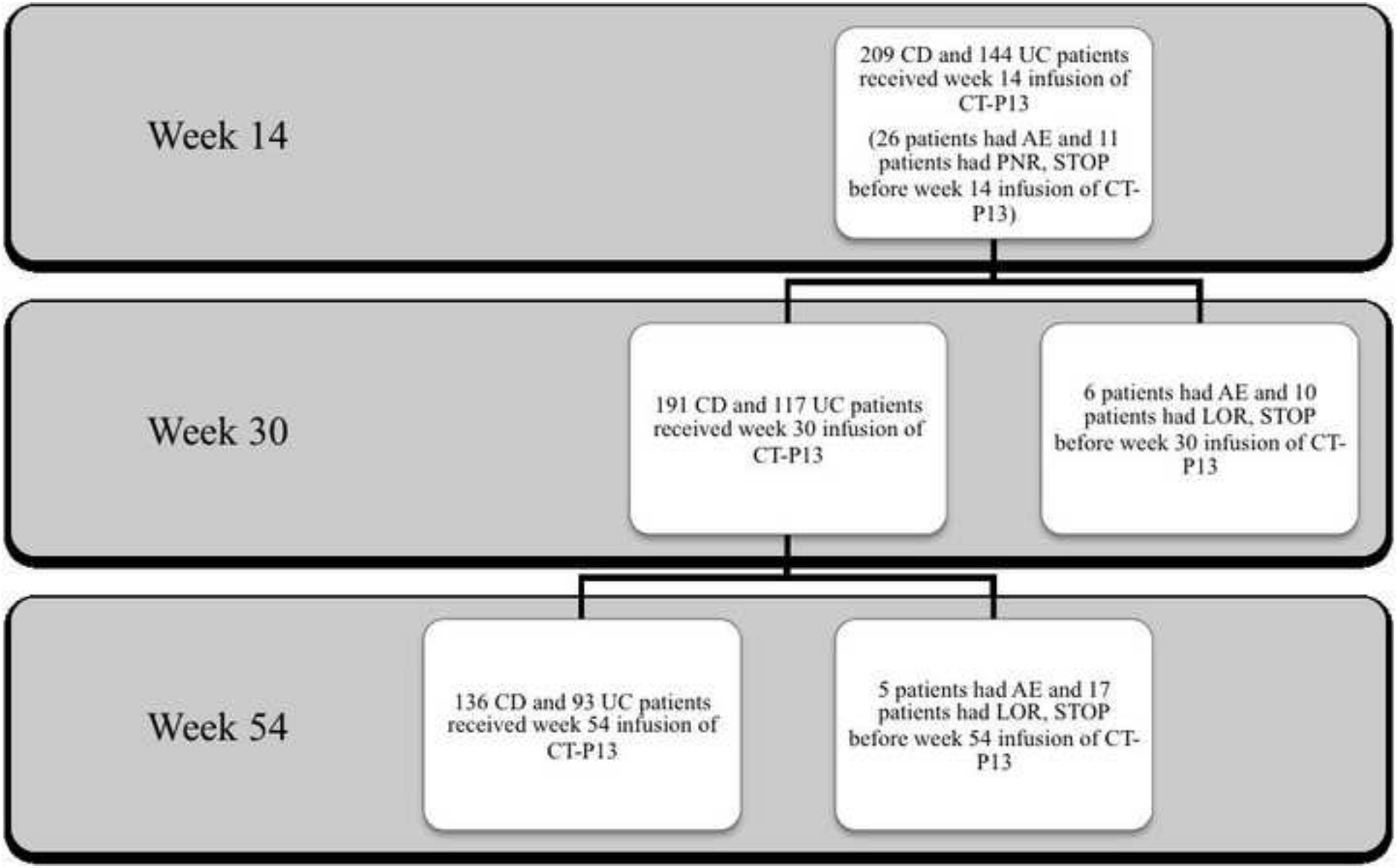

Image2a

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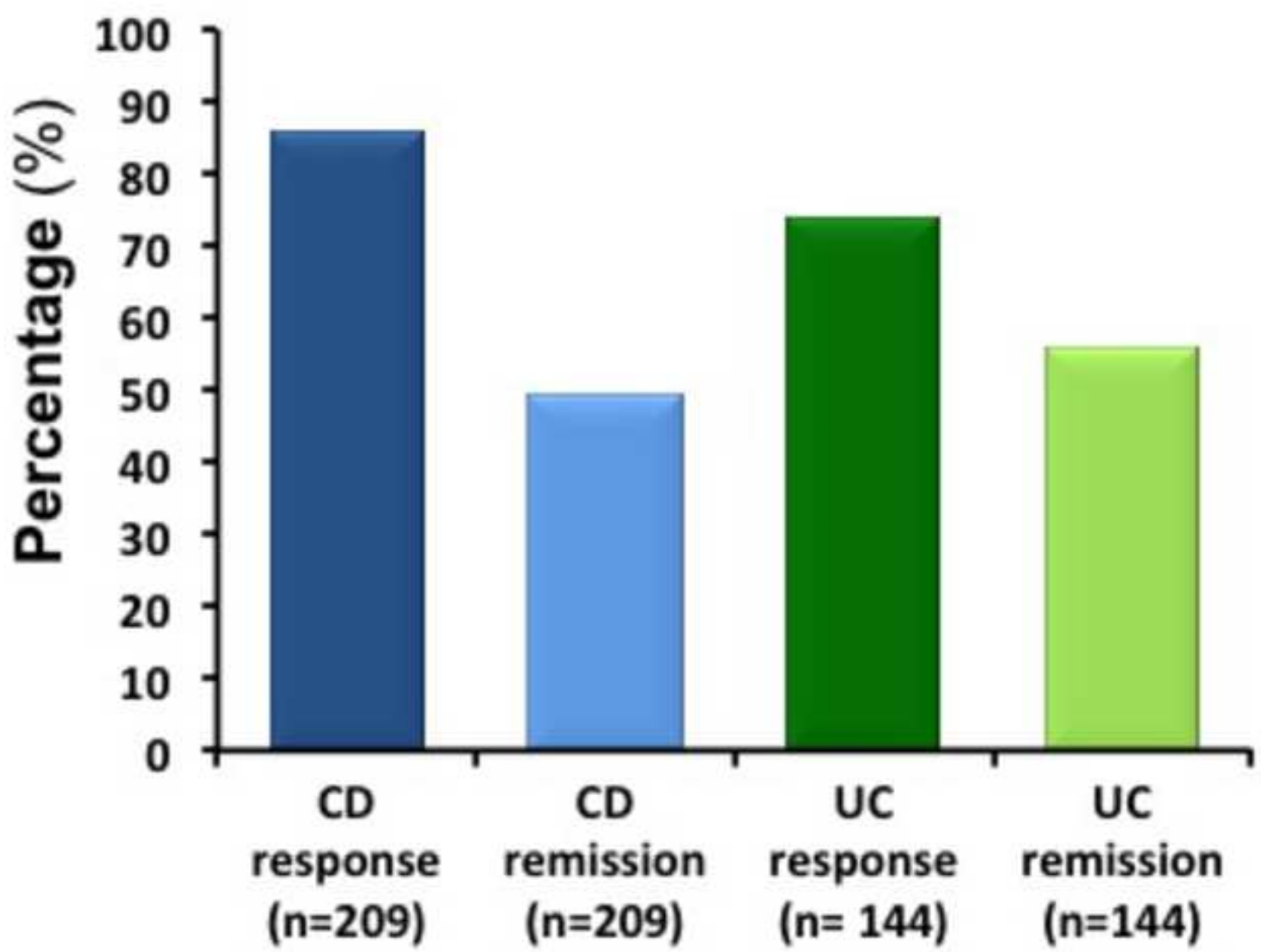

Image2b

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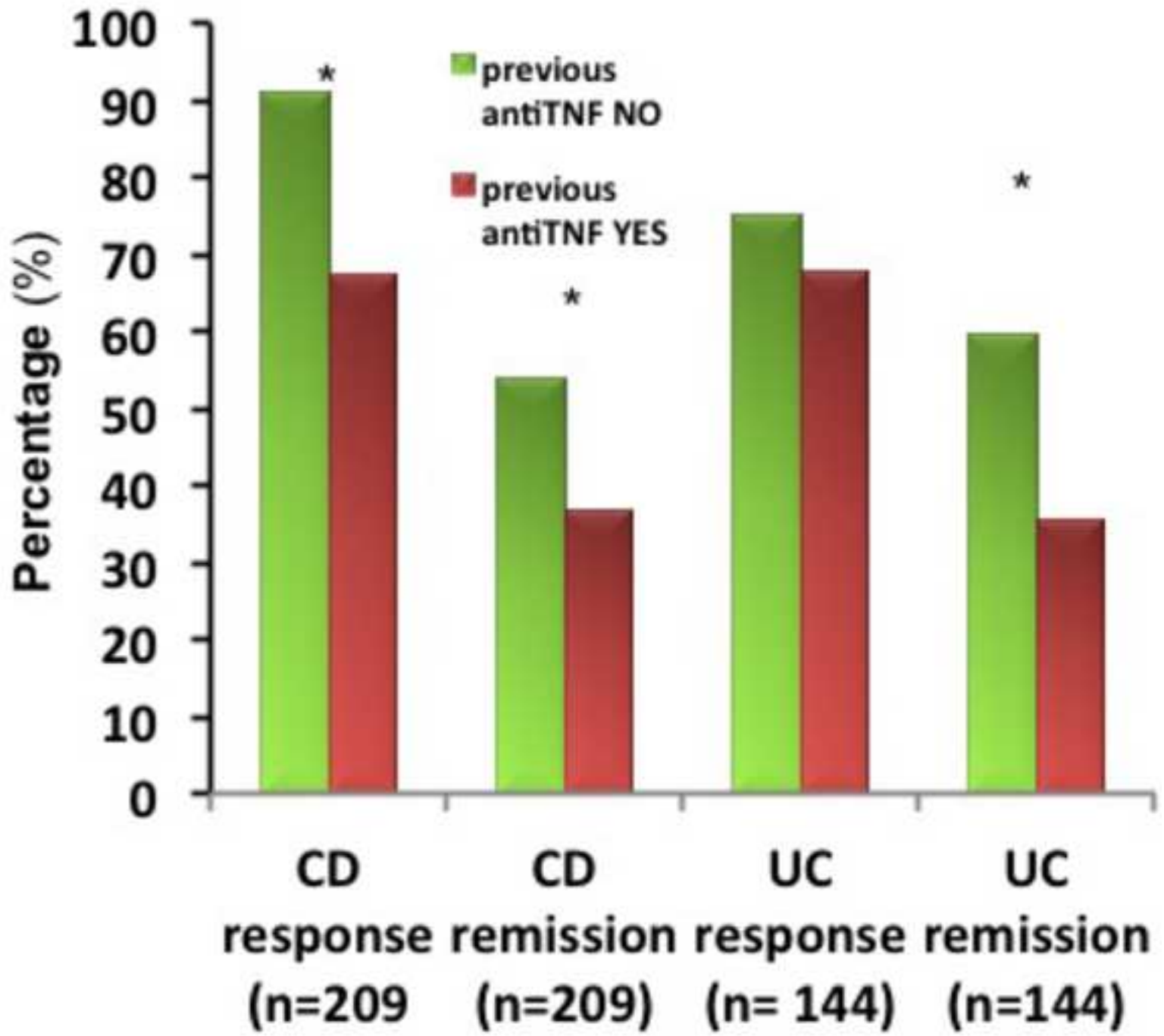

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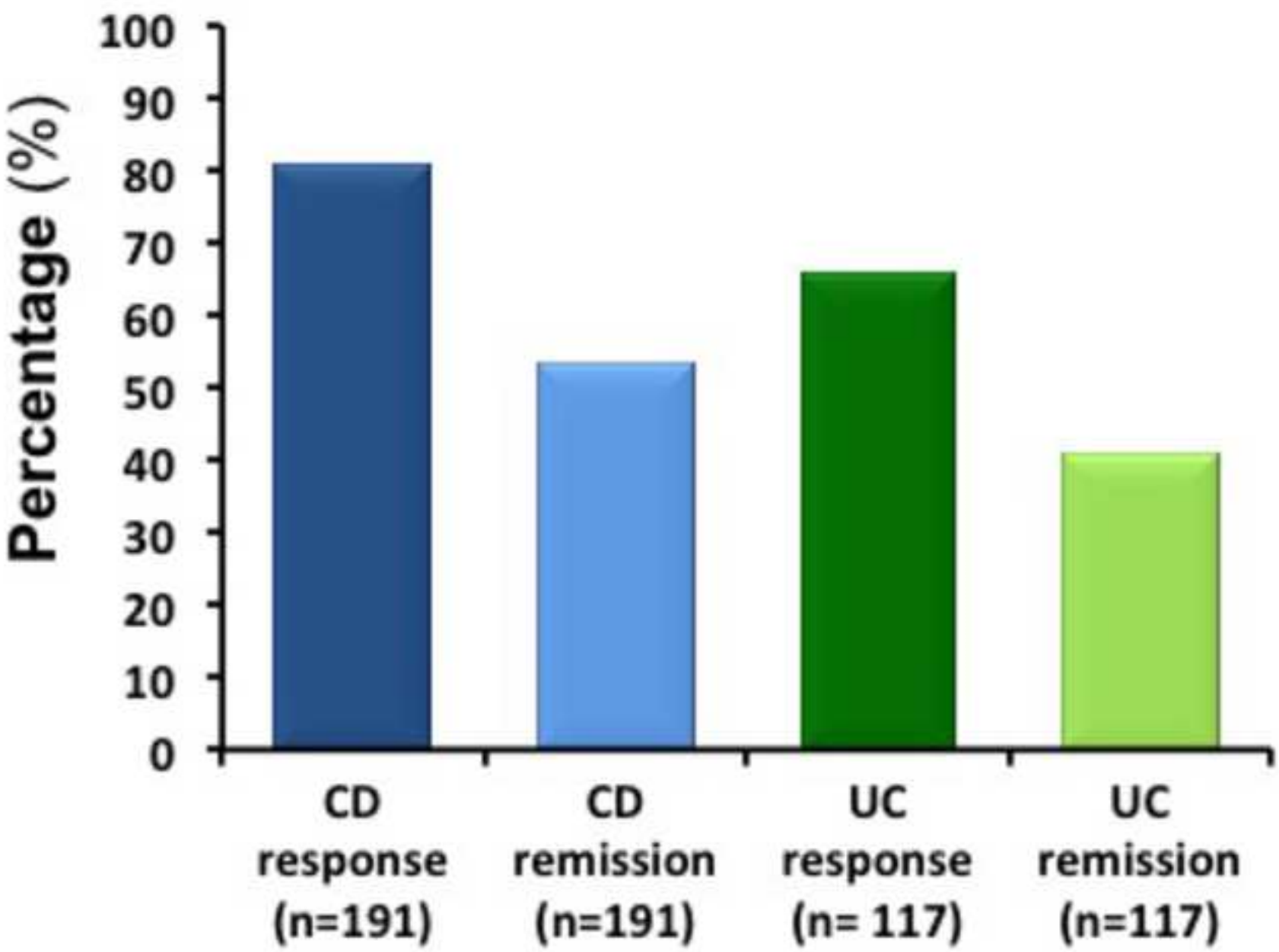

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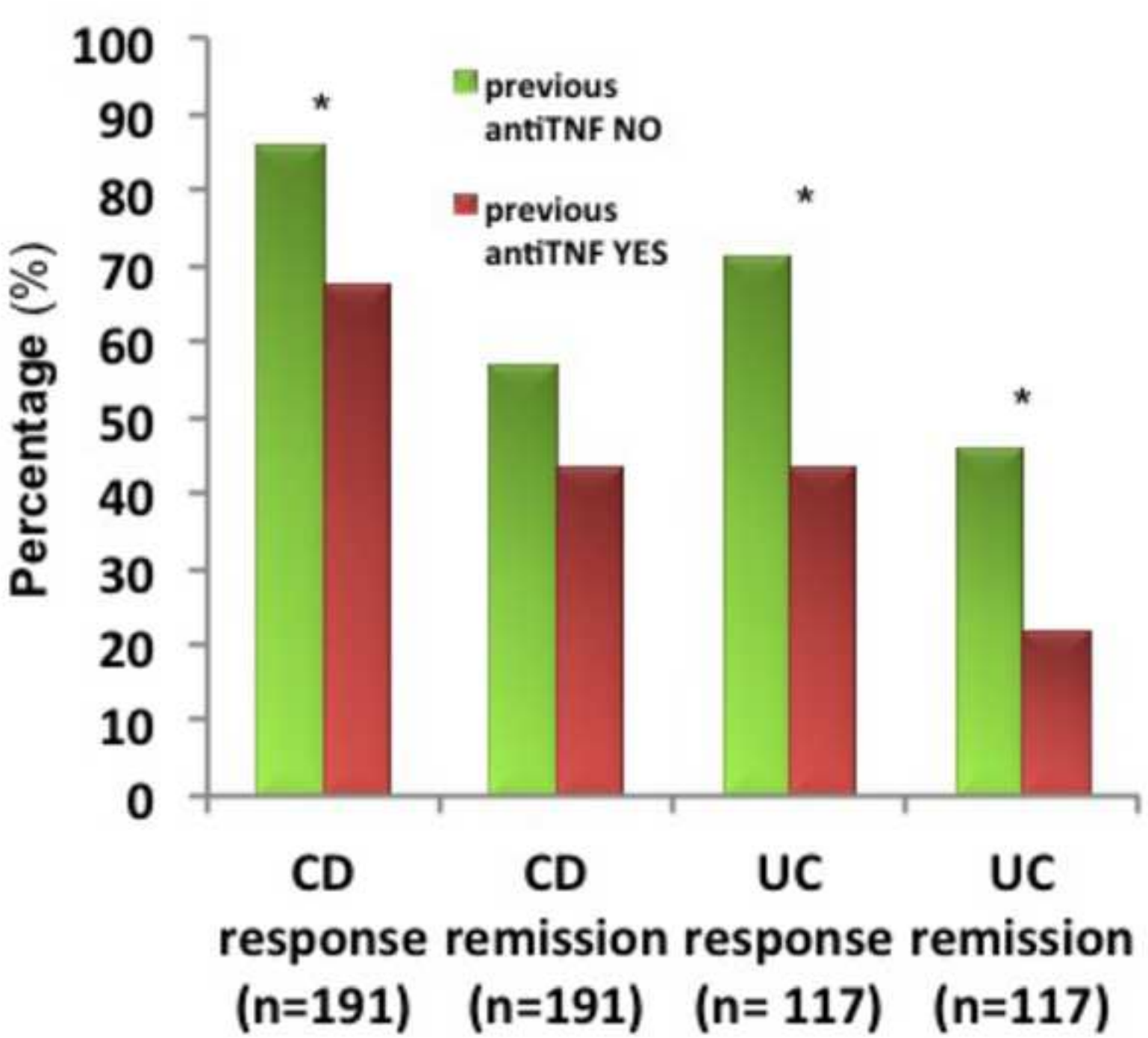

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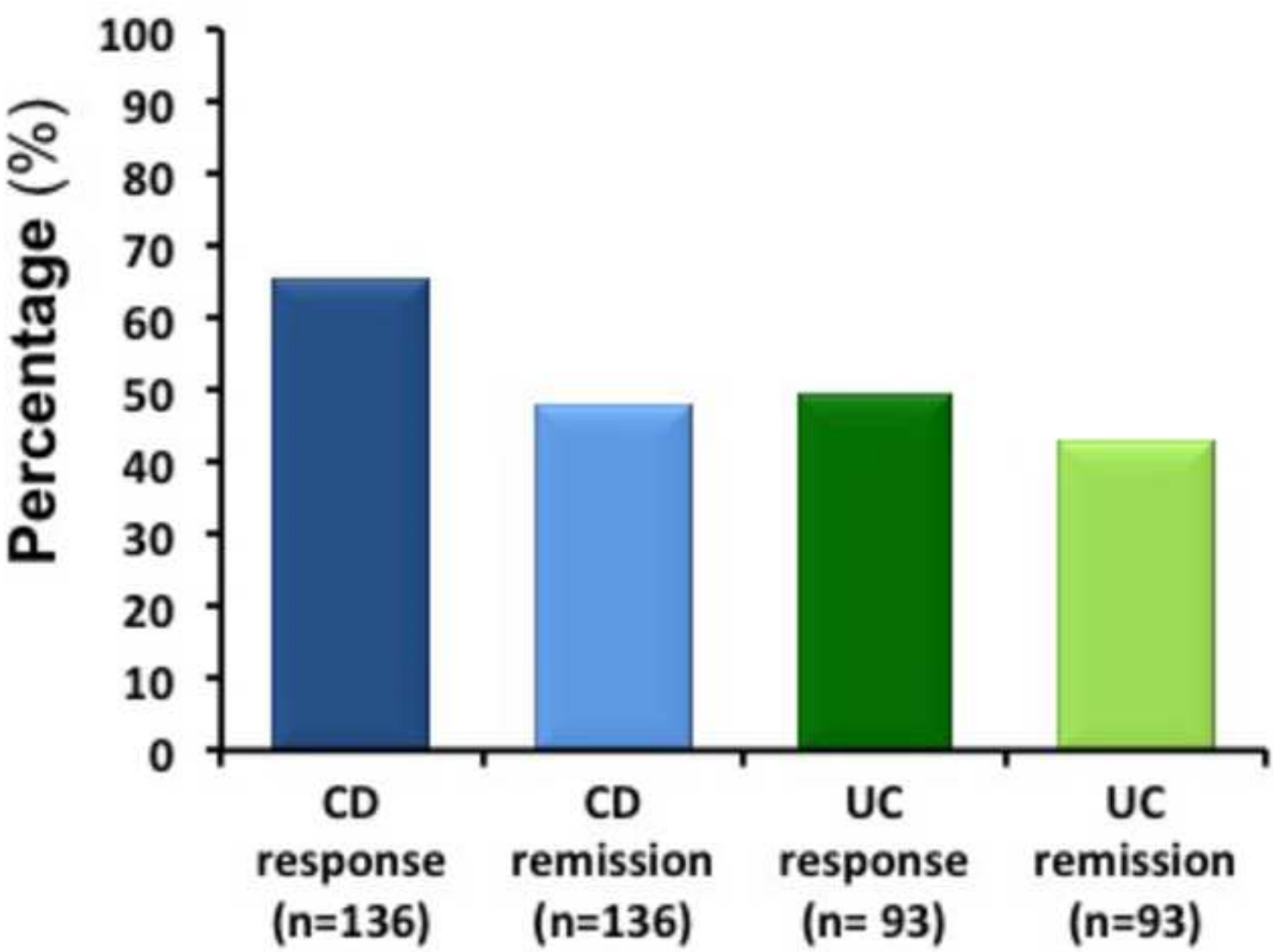

Image4b