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Trough Concentrations of Infliximab Guide Dosing for Patients With Inflammatory Bowel Disease

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This article has an accompanying continuing medical education activity on page e13. Learning Objective: Upon completion of this exam, successful learners will be able to discuss the impact of dose escalation of infliximab in Crohn's disease patients with low troughs; identify patients where dose reduction is appropriate based on symptoms, trough concentrations, and inflammatory markers; and review timing and frequency of testing for anti-infliximab antibody testing.

See Covering the Cover synopsis on page 1261; see editorial on page 1268.

BACKGROUND & AIMS: Infliximab, a tumor necrosis factor antagonist, is effective for treating patients with Crohn's disease (CD) and ulcerative colitis (UC). We aimed to determine whether dosing based on therapeutic drug monitoring increases rate of remission and whether continued concentration-based dosing is superior to clinically based dosing of infliximab for maintaining remission in patients with CD and UC. **METHODS:** We performed a 1-year randomized controlled trial at a tertiary referral center, including 263 adults (178 with CD and 85 with UC) with stable responses to maintenance infliximab therapy. Doses were escalated or reduced using an algorithm to reach a target trough concentration (TC) of 3–7 μg/mL in all patients (optimization phase). Patients were randomly assigned (1:1) to groups that received infliximab dosing based on their clinical features (n = 123) or continued dosing based on TCs (n = 128) (maintenance phase). The primary end point was clinical and biochemical remission at 1 year after the optimization phase. **RESULTS:** At screening, 115 of 263 patients had a TC of infliximab of 3–7 μg/mL (43.7%). Of 76 patients with TCs <3 μg/mL, 69 patients (91%) achieved TCs of 3–7 μg/mL after dose escalation. This resulted in a higher proportion of CD patients in remission than before dose escalation (88% vs 65%; $P = .020$) and a decrease in the median concentration of C-reactive protein, compared with before the dose increase (3.2 vs 4.3 mg/L; $P < .001$); these changes were not observed in patients with UC. Of 72 patients with TCs >7 μg/mL, 67 patients (93%) achieved TCs of 3–7 μg/mL after dose reduction. This resulted in a 28% reduction in drug cost from before dose reduction ($P < .001$). Sixty-six percent of patients whose dosing was based on clinical features and 69% whose dosing was based on TC achieved remission, the primary end point ($P = .686$). Disease relapsed in 21 patients who received clinically based dosing (17%) and 9 patients who received concentration-based dosing (7%) ($P = .018$). **CONCLUSIONS:** Targeting patients' infliximab TCs to 3–7 μg/mL results in a more efficient use of the drug. After dose optimization, continued concentration-based dosing was not superior to clinically based dosing for achieving remission after 1 year, but was associated with fewer flares during the course of treatment. ClinicalTrialsRegister.eu number: 2011-002061-38.

Keywords: Monoclonal Antibody; Personalized Medicine; Pharmacokinetics; Therapeutic Drug Monitoring.

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Biological therapies have revolutionized the management of chronic inflammatory diseases, such as rheumatoid arthritis, spondylarthropathies, psoriatic arthritis, and inflammatory bowel diseases (IBD). Results from pivotal clinical trials showed that infliximab (Remicade) is effective for inducing and maintaining clinical remission in patients with Crohn's disease (CD) and ulcerative colitis (UC).[1,2] Infliximab is a chimeric IgG1 monoclonal anti-tumor necrosis factor (TNF) antibody and is

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Abbreviations used in this paper: **ATI, antibodies to infliximab; CD, Crohn's disease; CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; IQR, interquartile range; PMS, partial Mayo score; QALY, quality adjusted life years; TC, trough concentration; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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administered as an intravenous infusion with weight-based dosing (5 mg/kg) and a regimen that includes an induction phase (intravenously at weeks 0, 2, and 6) followed by maintenance treatment (intravenously every 8 weeks) in responder patients.[3] Despite its proven efficacy, up to 60% of patients with an initial response later experience secondary loss of response requiring dose escalation or a switch to another TNF antagonist to recapture response.[4,5] Loss of clinical benefit can be due to increased clearance of the drug in the presence or absence of antibodies to infliximab (ATI).[6–8] Cohort studies and post-hoc analyses showed that serum infliximab trough concentrations (TCs) are correlated with clinical response, clinical remission, and mucosal healing in patients with IBD.[9–12] In general, low infliximab TCs and the presence of ATI are associated with worse clinical outcomes and an infliximab TC within the interval of 3–7 μg/mL during maintenance therapy correlated with sustained clinical outcomes.[11–15] TNF antagonists account for a large part of the health care costs of IBD.[16] Decreasing the drug in patients with supra-optimal TCs would lead to important cost savings and potentially also to fewer adverse events.[17] Stratified dosing based on therapeutic drug monitoring has not yet been evaluated prospectively.

Our aim was to compare the efficacy, cost-effectiveness, and safety of concentration-based dosing to clinically based dosing of infliximab in a cohort of CD and UC responder patients treated with infliximab maintenance therapy, that is, the Trough Concentration Adapted Infliximab Treatment (TAXIT) randomized controlled trial.

Methods

Design Overview

This randomized controlled trial was conducted at the University Hospitals Leuven, an academic and tertiary referral center from August 2011 to April 2013. The protocol was approved by the Institutional Review Board (ClinicalTrialsRegister.eu number, 2011-002061-38). All patients provided written informed consent.

Setting and Participants

Eligibility criteria included age of at least 18 years and a diagnosis of moderate-to-severe CD or UC confirmed by endoscopy and histology. Patients needed to be treated with maintenance infliximab therapy for at least 14 weeks and needed to be in stable clinical response. Stable clinical response was assessed by the treating physician and defined as being symptom-free (full responder) or having clear clinical improvement with an obvious decrease of disease activity, but with clinical symptoms still present (partial responder). Stable doses of concomitant immunomodulators were permitted (azathioprine or methotrexate) when initiated before the study, oral corticosteroids were allowed at a low dose if kept stable throughout the study. At screening, the infliximab dosing regimen was allowed to differ from the standard dosing regimen of 5 mg/kg every 8 weeks (eg, because of previous secondary loss of response in patients in whom response was restored). Patients who were on a nonstandard higher dosing regimen because of secondary loss of response to infliximab therapy at the time of screening were ineligible and patients with ATI >8 μg/mL equivalents, which was previously shown to be a clinically relevant cut-off.[7]

Randomization and Intervention

Upon inclusion, we randomly assigned patients (1:1) to receive clinically based or concentration-based dosing of infliximab during the maintenance phase. All patients were first dose optimized to have an infliximab TC within the interval of 3–7 μg/mL (optimization phase) according to the TAXIT algorithm (Figure 1). Individual infliximab TCs were evaluated at each infusion and the dosing regimen was changed for the next infusion according to the algorithm, until

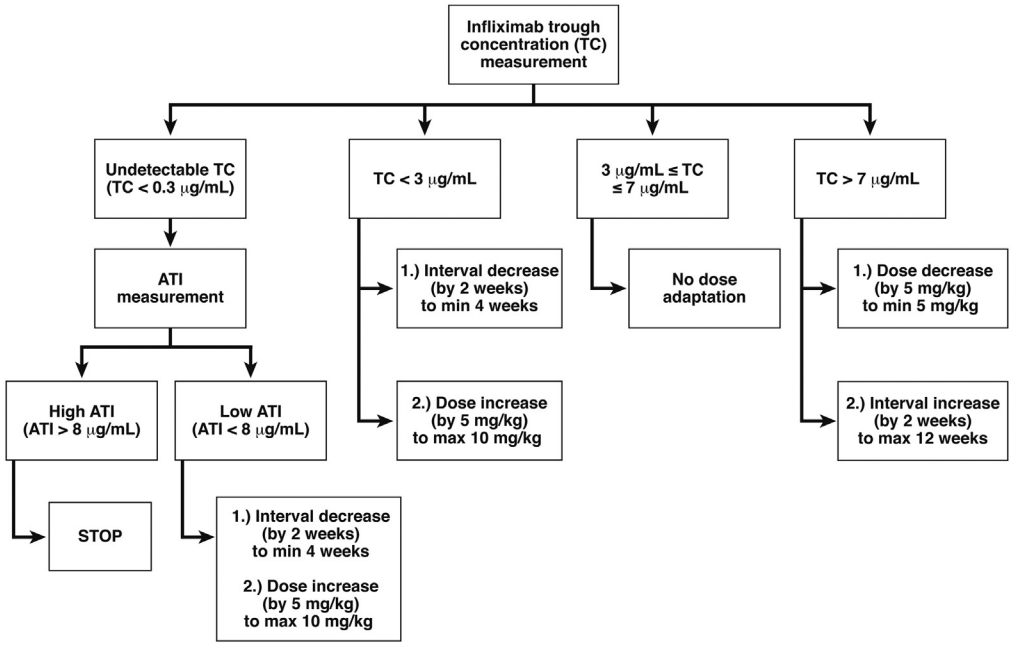


Figure 1. TAXIT algorithm based on infliximab TC and ATI to achieve infliximab TC of 3–7 μg/mL. max, maximum; min, minimum. ATI are μg/mL expressed in equivalents.

patients had a TC within the interval of 3–7 μg/mL. Briefly, in patients with supra-optimal concentrations, first the dose was reduced to 5 mg/kg (if on 10 mg/kg), after which the interval between infusions was prolonged each time by 2 weeks (to a maximum interval of 12 weeks). In patients with suboptimal concentrations, the interval between infusions was reduced each time by 2 weeks (to a minimum interval of 4 weeks), after which the dose was increased to a maximum of 10 mg/kg. Patients who successfully achieved an infliximab TC within the optimal interval were then assigned to infliximab dosing based on clinical symptoms and C-reactive protein (CRP), or to continue dosing based on infliximab TC (maintenance phase). In the clinically based dosing group, dosing of infliximab was guided based on symptoms and CRP (recorded at each infusion) according to standard clinical practice criteria. In the concentration-based dosing group, individual infliximab TCs were evaluated at each infusion and the dosing regimen was changed for the next infusion according to the TAXIT algorithm to keep patients within the optimal infliximab TC interval.

Randomization was performed by one person (VB) not in charge of the clinical care of patients using a computer-generated randomization schedule, with random block sizes. Both patients and treating physicians were blinded to individual infliximab trough and ATI concentrations.

Outcomes and Follow up

Primary end point was defined as the proportion of patients in each group in clinical (Harvey-Bradshaw index [HBI] $\leq$4 for CD and partial Mayo score [PMS] $\leq$2 with no individual subscore $>$1 for UC) and biological (CRP concentration of $\leq$5 mg/L) remission at year 1 after optimization.

Secondary end points were durable remission (defined as a HBI $\leq$4 or PMS $\leq$2 with no individual subscore $>$1 and CRP $\leq$5 mg/L throughout the entire randomized maintenance phase), relapse (defined as the need for infliximab dose escalation, ie, interval decrease and/or dose increase, the addition of steroids, or switch to another anti-inflammatory agent as decided by the treating physician), infliximab TC within the optimal interval, ATI positivity, total cost of infliximab treatment, and quality adjusted life years (QALY).

Each study visit, the treating physician evaluated data for HBI or PMS, adverse events, and concomitant medications. Patients completed the EuroQol-5D instrument (standardized measure for health outcomes comprising 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[18] Criteria for early termination included safety and failure of infliximab therapy, defined as persisting clinical symptoms (HBI $>$4 or PMS $>$2) on 2 consecutive visits (including unscheduled visits) and active inflammation based on increased CRP concentration or endoscopic activity. These patients were considered failures for the primary end point. In patients who terminated the study early because of other reasons (pregnancy, lost to follow-up, noncompliant with treatment recommendations), the last observation carried forward method was used.

Infliximab TC and ATI concentrations were determined using an in-house developed enzyme-linked immunosorbent assay method as described previously.[19] The lower limit of quantification for infliximab and ATI was 0.3 μg/mL and 1.0 μg/mL equivalents, respectively. ATI were not detectable in serum if infliximab concentration was $\geq$0.3 μg/mL and were regarded as inconclusive for ATI.

For the pharmaco-economic evaluation of the optimization phase, infliximab costs of the optimized treatment regimen were compared with those of the treatment regimen at baseline in year 2012 values. For the maintenance phase, the drug costs, QALY, and cost to utility ratio of the concentration-based dosing strategy were calculated as compared with the clinically based dosing strategy from the perspective of a third-party payer. The incremental cost-effectiveness ratio was calculated by dividing the difference in cost associated with the concentration-based and clinically based dosing strategies by the difference in QALY. QALY were adjusted for differences in baseline utility scores (EuroQol-5D score) using a multiple regression approach.[20] Uncertainty in incremental QALY and costs was investigated by means of a nonparametric bootstrapping consisting of 1000 iterations, the results of which are shown as a cloud of points on the cost-effectiveness plane.

Statistical Analysis

We estimated a 60% remission rate in the clinically based group and therefore randomization of 132 patients in each group (screening of 300 patients, assuming a 90% eligibility rate) would allow detection of a 16% difference in proportion of patients achieving the primary end point with a power of 80% at a .05 significance level based on a 2-sided χ^2 test. In the absence of available data, an effect size of 16% was chosen as the minimal clinically relevant difference to be detected.

Statistical programs GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, CA) and IBM SPSS Statistics 22 (IBM SPSS, Costa Mesa, CA) were used for statistical analysis. Data were expressed as median (interquartile range [IQR]) unless stated otherwise. D'Agostino-Pearson test was used to assess the normality of continuous variables. For the univariate analysis of unpaired continuous variables, either an unpaired t test or independent 2-group Mann-Whitney U test was used. A paired t test or dependent 2-group Wilcoxon signed rank test was used for paired continuous variables as appropriate. To quantify correlation, the Spearman's rank correlation coefficient (r) was calculated. For the univariate analysis of discrete variables, the Fisher's exact test or χ^2 test was used where appropriate. For time to event or survival analysis, a Kaplan-Meier graph was constructed. The intention-to-treat population consisting of all subjects that were randomized and included in the maintenance phase was used for the primary efficacy analysis and proportional based end points. Subjects who terminated the study early because of safety or failure of infliximab therapy were considered failures in the intention-to-treat analysis, and for subjects with early termination because of other reasons, the last observation carried forward method was used. P values were calculated 2-tailed and the threshold for significance was set at $P < .05$.

All authors had access to the study data and had reviewed and approved the final manuscript.

Results

Screening

A consecutive cohort of 275 IBD patients (186 CD and 89 UC) receiving maintenance infliximab were screened from

Table 1. Demographic and Baseline Characteristics of Patients in the Optimization and Maintenance Phase

Optimization phase			
Characteristics	CD (n = 178)	UC (n = 85)	Total (n = 263)
Male sex, n (%)	89 (50.0)	54 (63.5)	143 (54.4)
Age, *y*, median (IQR)	40.0 (28.0–48.0)	43.0 (34.0–49.0)	41.0 (30.0–48.5)
Weight, *kg*, median (IQR)	74.0 (63.3–84.0)	81.0 (70.0–88.0)	76.0 (65.0–86.0)
Duration of disease, *y*, median (IQR)	13.7 (6.7–21.2)	10.6 (5.3–14.7)	12.3 (6.1–9.6)
Prior surgery, n (%)	70 (39.3)	6 (7.1)	76 (28.9)
History of fistulizing disease, n (%)	81 (45.5)	NA	82 (31.2)
Active smoker, n (%)	44 (24.7)	22 (25.9)	66 (25.1)
Duration of disease at first IFX, *y*, median (IQR)	5.6 (1.5–14.2)	5.8 (2.3–10.4)	5.7 (1.7–13.3)
Time since first IFX, *y*, median (IQR)	5.3 (2.8–8.6)	3.2 (1.5–5.3)	4.5 (2.0–7.4)
Remission, n (%)[a]	131 (73.6)	72 (84.7)	203 (77.2)
CRP concentration, *mg/L*, median (IQR)	2.0 (0.7–5.6)	1.2 (0.6–2.6)	1.7 (0.6–4.7)
IFX trough concentration, *μg/mL*, median (IQR)	4.8 (3.0–7.8)	4.0 (1.8–6.7)	4.6 (2.5–7.7)
Immunomodulatory drug at baseline, n (%)	9 (5.1)	5 (5.9)	14 (5.3)
Maintenance phase			
	Clinically based dosing (n = 123)	Concentration-based dosing (n = 128)	Total (n = 251)
Male sex, n (%)	72 (58.5)	66 (51.6)	138 (55.0)
CD, n (%)	82 (66.7)	91 (71.1)	173 (68.9)
Age, *y*, median (IQR)	42.0 (32.0–48.0)	41.0 (30.0–50.3)	41.0 (30.5–49.0)
Weight, *kg*, median (IQR)	77.0 (67.0–87.0)	75.0 (63.0–84.0)	75.0 (65.5–86.0)
Duration of disease, *y*, median (IQR)	12.5 (7.1–19.3)	12.0 (5.6–20.8)	12.5 (6.3–19.9)
Prior surgery, n (%)	36 (29.3)	39 (30.5)	75 (29.9)
History of fistulizing disease, n (%)	41 (33.3)	40 (31.3)	81 (32.3)
Active smoker, n (%)	38 (30.9)	26 (20.3)	64 (25.5)[b]
Duration of disease at first IFX, *y*, median (IQR)	5.9 (1.7–14.0)	5.6 (1.7–13.1)	5.8 (1.7–13.5)
Time since first IFX, *y*, median (IQR)	4.5 (2.2–7.2)	4.7 (2.1–7.7)	4.6 (2.1–7.5)
Remission, n (%)[a]	101 (82.1)	106 (82.8)	207 (82.5)
CD, n (%)	63 (76.8)	75 (82.4)	138 (79.8)
UC, n (%)	38 (92.7)	31 (83.8)	69 (88.5)
CRP concentration, *mg/L*, median (IQR)	1.3 (0.6–4.5)	1.5 (0.7–4.0)	1.4 (0.6–4.2)
IFX trough concentration, *μg/mL*, median (IQR)	4.9 (3.8–5.9)	5.0 (4.0–5.7)	4.9 (3.9–8.5)
Immunomodulatory drug at baseline, n (%)	7 (5.7)	6 (4.7)	13 (5.2)

IFX, infliximab; NA, not applicable.
[a]For CD patients, this is based on the HBI, where a score of $\leq$4 corresponds to remission and for UC patients, this is based on the PMS, where a score of $\leq$2 with no individual subscore $>$1 corresponds to remission.
[b]$P < .01$.

August through October 2011. Overall median CRP was 1.8 mg/L (IQR, 0.7–4.8 mg/L) and median infliximab TC was 4.6 μg/mL (IQR, 2.4–7.3 μg/mL). Of 275 patients, the infliximab TC was >7 μg/mL in 72 patients (26.2%); between 3 and 7 μg/mL in 121 patients (44.0%); detectable but <3 μg/mL in 58 patients (21.1%); and undetectable in 24 patients (8.7%). Of the 24 patients with an undetectable infliximab TC, 18 (75%) were positive for ATI (median concentration 5.2 μg/mL; IQR, 2.8–9.1 μg/mL equivalents). Patients with an infliximab TC <3 μg/mL had significantly higher CRP levels (median 2.8 mg/L; IQR, 1.0–8.0 mg/L) vs patients with infliximab TC between 3 and 7 μg/mL (median CRP, 1.5 mg/L; IQR, 0.6–3.9 mg/L; $P = .001$) and infliximab TC >7 μg/mL (median CRP, 1.2 mg/L; IQR, 0.6–4.8 mg/L; $P = .009$). Twelve patients were ineligible; 6 patients had an ATI concentration of >8 μg/mL equivalents, 3 patients had active disease as confirmed by endoscopy (part of routing clinical follow-up), and 3 patients withdrew consent.

Patients

Baseline characteristics and demographics of the 263 patients included in TAXIT are depicted in Table 1. Median duration since first infliximab before inclusion was 4.5 years (IQR, 2.0–7.4 years) and 5% of patients received concomitant immunomodulator therapy at baseline. For CD, an inverse correlation was observed between infliximab trough and CRP concentration ($r = -0.27$; $P < .001$).

Optimization Phase

Of 263 eligible patients, 115 (43.7%) had an infliximab TC of 3–7 μg/mL at screening and were immediately

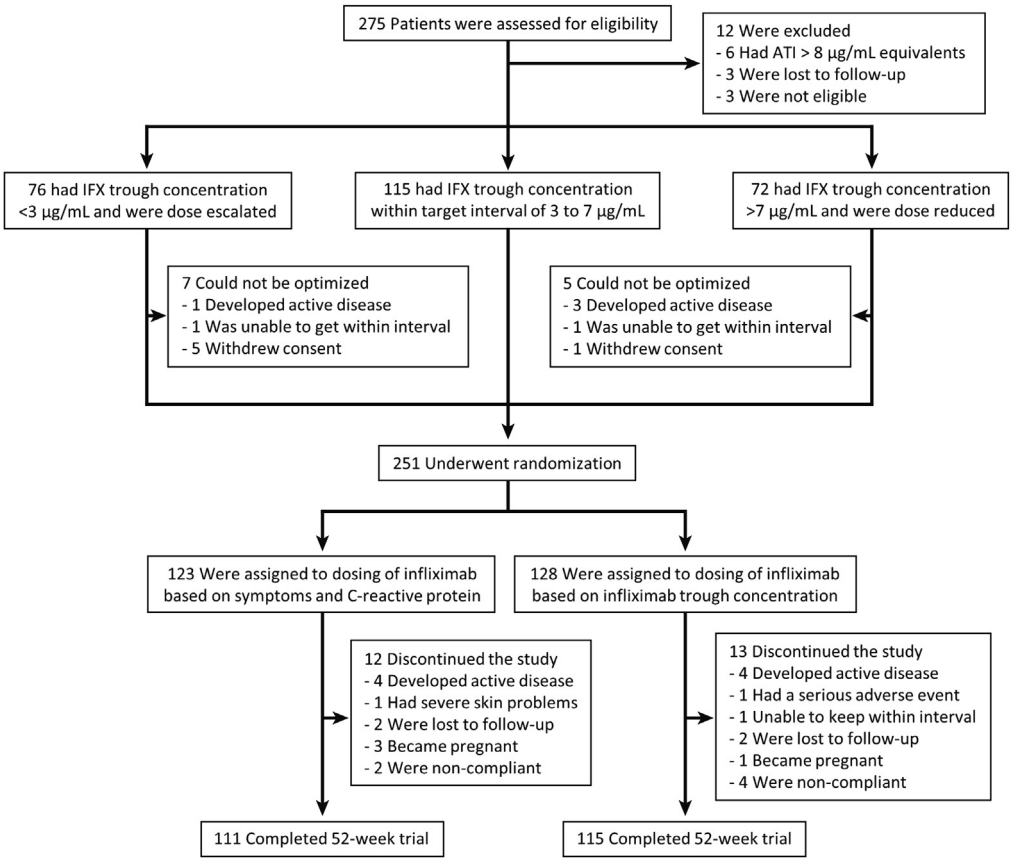


Figure 2. Patient disposition of the screening, optimization, and randomized maintenance phase.

randomized. Of the remaining 148 patients, 76 (51.4%) underwent dose escalation and 72 (48.6%) underwent dose reduction. Baseline characteristics and preoptimization dosing regimen are depicted in Supplementary Table 1 per the optimization group.

In the dose-escalation group, 43 of 44 CD (98%) and 26 of 32 UC (81%) patients achieved infliximab TCs of 3–7 μg/mL (Figure 2). On average, 2.1 optimizations were needed to get patients within the optimal interval. After optimization, the median interval between infusions was 6 weeks (range, 4–8 weeks) and 3 patients (2 CD and 1 UC) were on a 10 mg/kg dosing regimen. Before dose escalation, 28 of 43 CD patients (65%) were in remission (HBI $\leq$4), increasing to 38 of 43 patients (88%) after optimization (odds ratio = 4.1; 95% confidence interval: 1.3–12.5; $P = .020$) (Figure 3*A*). A significant decrease in median CRP concentration was also observed in CD patients from 4.3 mg/L (IQR, 2.0–11 mg/L) to 3.2 mg/L (IQR, 1.0–7.3 mg/L) ($P < .001$) (Figure 3*C*). For UC patients, dose escalation did not significantly affect the proportion of patients in remission or CRP concentration (Figure 3*A* and *C*). Of 76 patients undergoing dose escalation, 12 patients had detectable ATI (<8 μg/mL equivalents) at screening. Eight of the 12 patients (67%) were successfully dose optimized (on average, 5.4 dose optimizations were needed) and ATI became inconclusive (from median ATI concentration of 2.9 μg/mL; IQR, 2.3–5.6 μg/mL before to <1.0 μg/mL; IQR, 1.0–1.0 μg/mL equivalents after dose escalation; $P = .008$).

In the dose-reduction group, 48 of 52 CD (92%) and 19 of 20 UC (95%) patients achieved infliximab TCs of 3–7 μg/mL (Figure 2). On average, 1.4 optimizations were needed. After optimization, the median interval between infusions was 8 weeks (range, 6–12 weeks) and all patients were on a 5 mg/kg dosing regimen. No significant change was observed in the proportion of CD and UC patients in remission or in CRP concentration (Figure 3*B* and *D*).

Maintenance Phase

Of the 251 patients subsequently entering the maintenance phase, 123 (49.0%) were randomized to clinically based and 128 (51.0%) to concentration-based infliximab dosing (Figure 2). Demographic and clinical characteristics of the randomized patients are depicted in Table 1.

Primary End Point

The randomized maintenance phase did not show an additional benefit to continue concentration-based dose adjustments over clinically based dose adjustments. As shown in Figure 4*A*, a similar proportion of patients in both groups achieved the primary end point; 81 of 123 patients (66%) in the clinically based and 88 of 128 patients (69%) in the concentration-based dosing group ($P = .686$). In subgroup analysis, no significant difference was observed between both treatment arms for patients with CD or UC (Figure 4*B* and *C*).

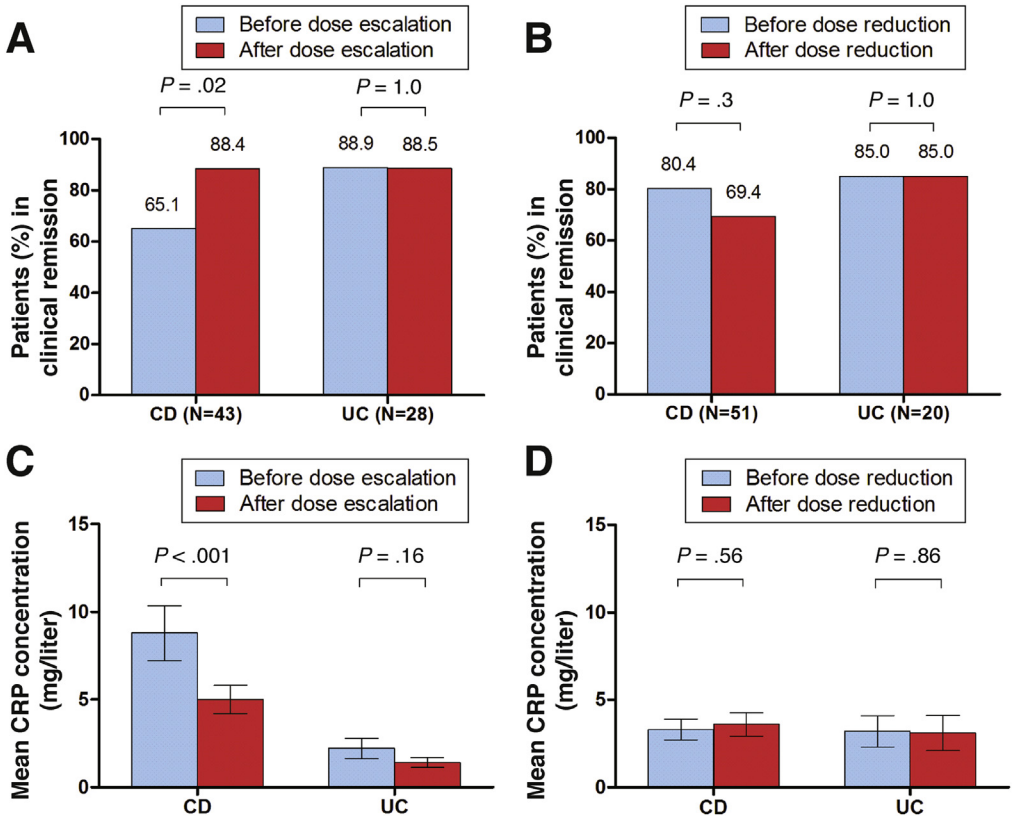


Figure 3. Illustrates the effect of concentration-based dose escalation (*A*, *C*) and dose reduction (*B*, *D*) during the optimization phase on the proportion of patients in remission (*A*, *B*) and on the CRP concentration (mg/L) (*C*, *D*) for patients with CD and UC. Patients who discontinued the optimization phase due to personal reasons (ie, noncompliant with treatment algorithm or consent withdrawal) were excluded from the analysis (1 CD and 4 UC patients from the dose-escalation group and 1 UC patient from the dose-reduction group). Remission was defined as an HBI $\leq$4 or PMS $\leq$2 with no individual subscore of $>$1.

Secondary End Points and Exploratory Analyses

Durable Remission and Relapse. The proportion of patients in durable clinical remission was not different for the concentration-based and clinically based dosing group (26% and 27%, respectively; $P = .880$) (Supplementary Figure 1) and did not differ for both disease indications. During the randomized maintenance phase, 21 patients (17%) from the clinically based dosing group compared with 9 patients (7%) from the concentration-based dosing group relapsed and needed rescue therapy (relative risk = 2.4; 95% confidence interval: 1.2–5.1; $P = .018$). In the clinically based dosing group, 9 of 21 patients (43%) had infliximab TCs of <3 μg/mL at time of relapse compared with 2 of 9 patients (22%) in the concentration-based dosing group. Time to relapse was evaluated using Kaplan-Meier analysis for patients randomized to clinically based compared with concentration-based dosing (Figure 5).

In an additional exploratory analysis restricted only to patients who entered the randomized maintenance phase in remission (82.5% of the patients), there was no difference in the rate of primary outcomes between the clinically based and concentration-based dosing group (data not shown). Similarly, in additional analysis, there was no difference in the median time of being in remission for the 2 arms (data not shown).

Infliximab and Antibody to Infliximab Concentrations. Throughout the maintenance phase, 74% of patients randomized to concentration-based dosing compared with 57% of patients randomized to clinically based dosing had infliximab TCs of 3–7 μg/mL ($P < .001$) (Supplementary Figure 2). Undetectable infliximab TCs were more frequently observed in the clinically based compared with the concentration-based dosing group (relative risk = 3.7; 95% confidence interval: 1.7–8.0; $P < .001$). At the end of the randomized maintenance phase, 3 patients were positive for ATI in the clinically based dosing group vs none in the concentration-based dosing group ($P = .116$). All 3 patients were inconclusive for ATI at screening and developed detectable ATI during the maintenance phase. Of the 8 patients who were positive for ATI at screening and were randomized, 6 patients completed the maintenance phase, 1 patient developed leukocytoclastic vasculitis and 1 patient was unable to keep within the predefined TC interval. At the end of follow-up, 2 of 8 patients had undetectable ATI and 6 of 8 were inconclusive for ATI.

Pharmaco-Economic Evaluation

For successfully optimized patients, dose escalation resulted in a mean increase in drug cost per patient per 4 weeks of €963 and €635, respectively, for ATI-positive and ATI-negative patients at baseline ($P = .006$). This was partly compensated by a decrease in drug cost of €421 (27.9%) per patient per 4 weeks in whom the dose was reduced ($P < .001$) (Supplementary Table 2).

For the randomized maintenance phase, concentration-based dosing yielded less QALY but was also less costly than clinically based dosing (0.8227 vs 0.8421, respectively, and €20,723 vs €21,023, respectively, per patient per

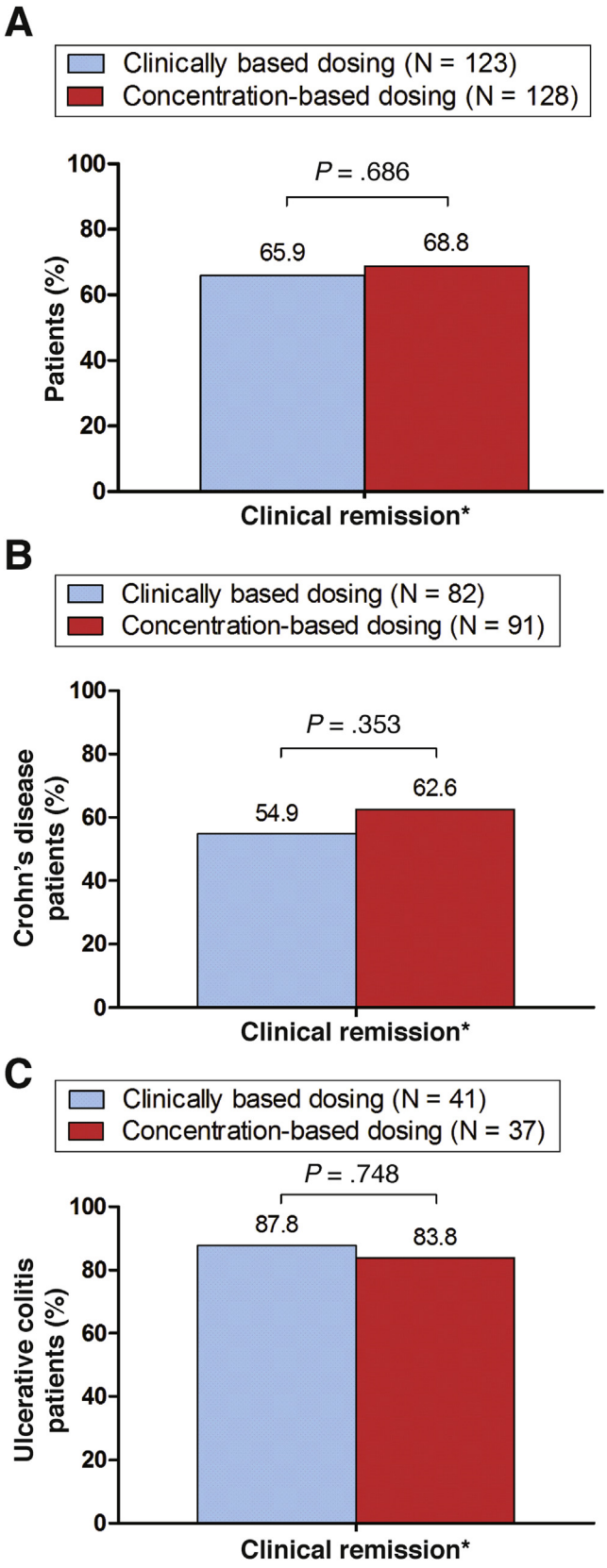
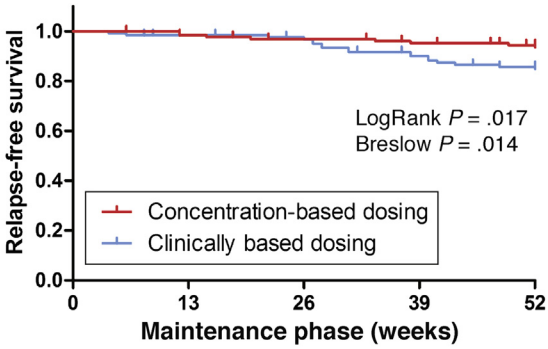


Figure 4. Primary end point defined as the proportion of patients in clinical (HBI $\leq$4 or PMS $\leq$2 with no individual subscore of $>$1) and biological (CRP concentration of $\leq$5 mg/L) remission in the total population of patients that was randomized (*A*), the subpopulation of CD patients (*B*) and UC patients (*C*).



Week	0	13	26	39	52
N at risk	128	127	121	117	111
	123	120	116	107	97

Figure 5. Kaplan-Meier curve and number of patients at risk representing the time to relapse during the maintenance phase for patients randomized to clinically based or concentration-based dosing. Relapse was defined as the need for infliximab dose escalation (interval decrease and/or dose increase), the addition of steroids or switch to another anti-TNF and was based on the physician's global assessment.

year), but overall differences were small (Supplementary Table 3 and Supplementary Figure 3).

Safety and Adverse Events

One patient randomized to concentration-based dosing experienced a severe adverse event (leukocytoclastic vasculitis) leading to discontinuation of infliximab treatment. One patient from the clinically based dosing group experienced severe skin problems (psoriasiform eczema), for which infliximab treatment was discontinued. Six patients from the clinically based vs 1 patient from the concentration-based dosing group experienced an acute infusion reaction (P = .062). The proportion of patients reporting adverse events that were considered to be linked to anti-TNF by the treating clinician, were similar in both treatment groups (Table 2). No deaths occurred and, during the trial, 2 of 263 patients needed to be hospitalized. One patient for an appendectomy due to acute appendicitis and 1 patient because of ileostomy complications; both patients were in the clinically based dosing group.

Discussion

Fewer than half of the patients treated with maintenance infliximab had optimal infliximab TCs. Dose escalation in CD patients with a suboptimal infliximab TC led to a significant increase in patients in clinical remission and a concomitant significant drop in CRP concentrations. A similar effect was not seen for UC patients, most likely because the majority had a PMS of 0 and a normal CRP at baseline. Dose reduction in CD and UC patients with a supra-optimal infliximab TC did not lead to flares or an increase of inflammatory markers, but did result in significant cost savings. The maintenance phase did not show superiority for continued

Table 2. Adverse Events Reported as Linked to Anti–Tumor Necrosis Factor Treatment by Treating Clinician

Event	Clinically based dosing (n = 123), n (%)	Concentration-based dosing (n = 128), n (%)
Adverse event		
Pharyngitis	20 (16.3)	25 (19.5)
Upper respiratory tract infection	55 (44.7)	59 (46.1)
Pneumonia	3 (2.4)	6 (4.7)
Aphthous stomatitis	1 (0.8)	3 (2.3)
Headache	4 (3.3)	3 (2.3)
Arthralgia	37 (30.1)	33 (25.8)
Infusion reaction	6 (9.4)	3 (2.3)
Acute reaction	6 (9.4)	1 (0.8)
Delayed hypersensitivity	0 (0)	2 (1.6)
Serious adverse event	0 (0)	1 (0.8)

infliximab TC-based dosing compared with clinically based dosing for the composite primary end point of clinical and biochemical remission after 1 year. However, in the clinically based dosing group, significantly more patients needed an intervention to treat a relapse as compared with the concentration-based dosing group. Endoscopy data as part of routine follow-up were available for 55% CD and 44% UC patients within a time frame of 6 months before or after the end of the randomized maintenance phase. Of these, 78% of CD patients and 85% of UC patients had complete mucosal healing, defined as the absence of mucosal ulcerations and an endoscopic Mayo score of $\leq$1, respectively. The approach of concentration-based dosing was not associated with an increased drug cost as shown by the cost-effectiveness analysis of the maintenance phase. In order to increase infliximab TCs, we intentionally chose to decrease the interval between infusions with one half-life of drug (2 weeks) as a first approach rather than to double the dose. Both interventions will have a similar effect on the drug TC; although in case of the latter, the patient is exposed to a higher maximum concentration and the treatment will be more costly.

The use of therapeutic drug monitoring to guide treatment decisions in patients with loss of response to infliximab was shown to be cost-effective compared with empiric dose escalation.[21] Here we evaluated an approach of preemptive dose optimization in responder patients based on therapeutic drug monitoring to maximize drug efficacy in the individual patient and to achieve better long-term clinical outcomes. Our results indicate that adaptive dosing of infliximab based on exposure results in better short-term clinical outcomes and that by maintaining this adequate exposure, the risk for loss of response can be reduced. This confirms previous retrospective results based on post-hoc analyses of the ACCENT I (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen) and ACT (Active Ulcerative Colitis Trials 1 and 2) studies showing an association between serum infliximab TCs and sustained long-term response for patients with CD and UC, respectively.[11,12] Given the high similarity in previously defined infliximab concentration cut-offs between both types of IBD, we did not make a distinction based on disease type, although we cannot exclude that individual patients might benefit from infliximab TCs higher than 3–7 μg/mL and that this cut-off might depend on outcome measure. Indeed, we observed that median infliximab TCs at endoscopy were higher in patients with mucosal healing: 5.2 μg/mL (IQR, 3.9–7.7 μg/mL) vs 2.8 μg/mL (IQR, 1.5–6.0 μg/mL) in patients without mucosal healing ($P = .009$). The predefined optimal interval of 3–7 μg/mL for infliximab TCs is applicable for responder patients treated with maintenance infliximab therapy. Future research should focus on the optimal level of exposure to induce remission in patients with active disease (during the induction and maintenance phase), as here other pharmacokinetics factors might also play an important role, such as the maximum concentration and the area under the concentration curve. We used an in-house developed enzyme-linked immunosorbent assay to measure infliximab trough and ATI concentrations that was clinically validated in various retrospective studies and also prospectively evaluated in comparative tests with other commonly used assays in the European Union and United States.[19,22] Finally, our results will be of interest to other disease indications where infliximab is used to induce and maintain remission, such as in rheumatoid arthritis, ankylosing spondylitis, and psoriasis as similar exposure–response relationships were observed.[23–25] Although we hypothesize that this is a class effect that is applicable to other TNF antagonists, adequate exposure needs to be defined for each disease indication and will be drug specific, as there are known differences in the adsorption, distribution, and elimination.

After a search of the medical literature (eg, PubMed) and clinical trial registries (eg, ClinicalTrials.gov), we believe that the TAXIT study was the first randomized controlled trial in any immune-mediated disease in which TNF plays a central role to evaluate the efficacy and cost-effectiveness of dosing based on TNF antagonist drug exposure. On the basis of baseline disease measures, such as the HBI, PMS, and CRP concentrations, our study sample was representative of patients with CD and UC who were stable responders to maintenance infliximab therapy. Inclusion criteria were sufficiently broad to allow patients on different dosing regimens to enter the study, although the majority of patients were treated according to the standard 5 mg/kg every 8 weeks dosing regimen, representing a real-life clinical cohort of patients treated with TNF antagonists and managed according to standard guidelines.[26,27] We were required to set a baseline that was regarded as an infliximab TC within the interval of 3–7 μg/mL in each patient. Otherwise, there was a risk of having an imbalance in serum infliximab TC between both treatment arms at start.

Based on a previously reported clinically relevant cut-off for ATI, we chose to exclude 6 patients with high ATI and to discontinue their infliximab, as ATI are associated with impaired response to treatment and serious adverse events, such as acute infusion reactions.[7] Therapeutic drug

monitoring at screening allowed us to identify these patients at risk for worse clinical outcomes. Dose escalation in patients positive for low-concentration ATI was associated with a high increase in drug costs, but confirmed previous findings that development of ATI might be transient and can be overcome and adequate drug TCs can be restored.[22,28] However, our study was not designed to evaluate whether this was a superior strategy compared with switching to another anti-TNF. Future research should also focus on refining the cut-off for high vs low ATI and explore inter-individual differences for its clinical relevance. The proportion of patients treated with concomitant immunomodulators was low (5%), and reflects standard clinical practice in Leuven for patients on maintenance infliximab therapy.[29] Our study covered a clinically relevant sample and, from the efficacy and safety results presented here, we conclude that treat-to-target dosing of infliximab based on exposure in responder patients on maintenance infliximab therapy can lead to better short-term outcomes and a lower risk for loss of response.

Some important study limitations should be noted. The duration of the randomized maintenance phase was 1 year and although continued infliximab TC-based dosing was not superior, we cannot estimate the long-term clinical and pharmaco-economical outcomes of both strategies beyond that period. Especially because clinically based dosing was associated with a higher need for rescue therapy, undetectable infliximab TCs were more frequently observed and 3 patients developed ATI in the clinically based dosing group. Another primary end point could have been chosen that allows for testing the pre-emptive goal of therapeutic drug monitoring in maintaining adequate drug exposure and decreasing the risk for relapse. Our study focused specifically on maintenance therapy with infliximab, but studies are now needed that focus on early dose optimization utilizing therapeutic drug monitoring in patients during the induction phase or shortly after to increase primary remission rates and sustained response rates. Because of the longer turnaround time of current assays for therapeutic drug monitoring, a change in treatment was only possible for the next administration of drug, thereby delaying the implementation of the algorithm. Finally, other objective parameters documenting disease activity could have been used, including centrally read endoscopy and measurement of fecal calprotectin.

In conclusion, this is the first study prospectively evaluating the use of individualized dosing based on drug exposure in responder IBD patients treated with maintenance infliximab, and shows that by using therapeutic drug monitoring, individual TCs within a certain window can be targeted. The causal relationship between drug exposure and drug efficacy is now prospectively confirmed, as targeting infliximab TCs of ≥ 3 μg/mL resulted in a higher proportion of CD patients in remission. Targeting concentrations of ≤ 7 μg/mL allowed safe reduction of the dose, resulting in substantial drug cost savings. After the initial dose optimization no additional benefit was observed for systematic concentration-based dosing over clinically based dosing of infliximab, although a higher proportion of patients in the clinically based dosing group needed rescue therapy over time. Randomized clinical trials with dose optimization during the induction phase and with longer follow-up are warranted. A similar approach to dosing of TNF antagonists based on exposure could prove to be superior in other chronic inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis, and psoriasis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2015.02.031.

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Conflicts of interest
These authors disclose the following: Niels Vande Casteele reports consultancy fees from MSD, Janssen Biologics, UCB, and speaker's fees from Abbvie, outside the submitted work. Marc Ferrante reports consultancy fees from Abbvie, Merck, Janssen Biologics, grants from Janssen Biologics, and speaker's fees from Merck, Tillots, Ferring, Abbvie, outside the submitted work. Gert Van Assche reports consultancy fees from Zealand Pharma, Shire, Abbott/Abbvie, Novartis, MSD, Janssen, BMS, Ferring, Chiesi, Takeda, grants from MSD, Abbott/Abbvie, Zealand Pharma, and speaker's fees from Janssen, Abbott/Abbvie, Ferring, Aptalis, Ferring, MSD, outside the submitted work; Vera Ballet has nothing to disclose; Griet Compernolle has nothing to disclose. Paul Rutgeerts reports consultancy fees from Amgen, Merck, UCB Pharma, Genentech, BMS, Abbvie, Janssen Biologics, Millennium, Neovacs, Actogenics, Prometheus Laboratories, Inc., grants from UCB Pharma, Abbvie, Janssen Biologics, Merck, Prometheus Laboratories, Inc., and speaker's fees from Abbvie, Merck, outside the submitted work. Ann Gils reports grants from Pfizer, and speaker's fees from MSD, Janssen Biologicals, Pfizer, outside the submitted work. Séverine Vermeire reports consultancy fees from Takeda, Roche/Genentech, Merck, Centocor, Abbvie, UCB, Pfizer, Ferring, grants from Centocor, Abbvie, Merck, and speaker's fees from Merck, Abbvie, Takeda, Pfizer, Ferring, Falk, Centocor, outside the submitted work. The remaining authors disclose no conflicts.

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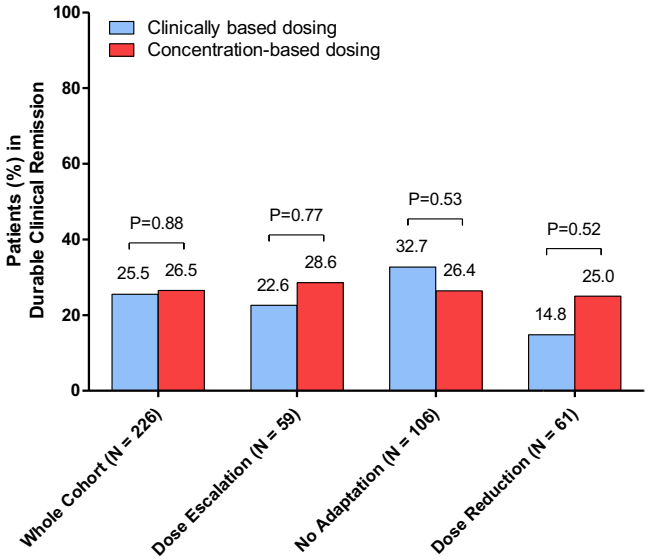
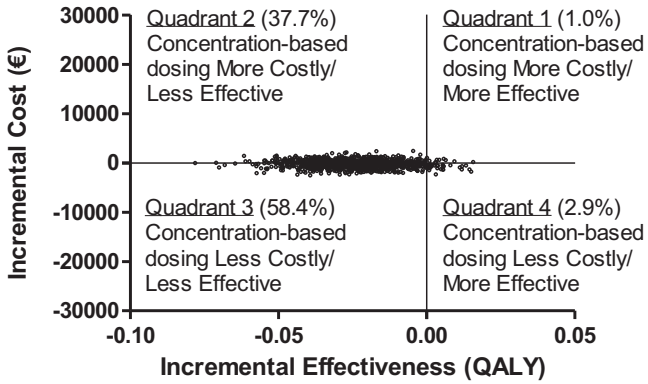
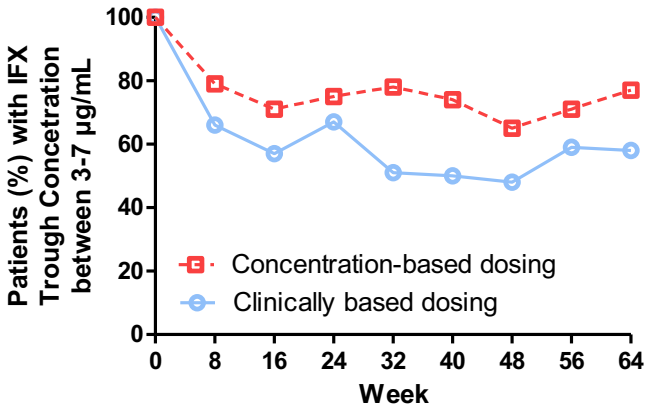


Supplementary Figure 1. Shows the proportion of patients who were in durable clinical remission throughout the maintenance phase both in the clinically based and the concentration-based dosing group. This is a per-protocol analysis including only those patients who completed the randomized maintenance phase (n = 226). Durable clinical remission was defined as clinical (HBI ≤4 or PMS ≤2 with no individual subscore of >1) and biological (CRP concentration of ≤5 mg/L) remission throughout the entire randomized maintenance phase.



Supplementary Figure 3. Cost-effectiveness plane showing the probabilistic sensitivity analysis of the incremental cost in Euros (€) vs incremental effectiveness in QALY for the clinically based vs concentration-based dosing strategy.



Supplementary Figure 2. Shows the proportion of patients with an infliximab (IFX) trough concentration within the interval of 3–7 μg/mL, both in the clinically based and concentration-based dosing group, throughout the duration of the randomized maintenance phase.

Supplementary Table 1. Baseline Characteristics Per Optimization Group

Characteristic	Dose escalation (n = 76)	No adaptation (n = 115)	Dose reduction (n = 72)
CD, n (%)	44 (57.9)	82 (71.3)	52 (72.2)
HBI, median (IQR)	2 (1–5)	2 (0–4)	2 (0–3)
UC, n (%)	32 (42.1)	33 (28.7)	20 (27.8)
PMS, median (IQR)	0 (0-0)	0 (0–1)	0 (0–0.75)
IFX trough concentration, *μg/mL*, median (IQR)	1.5 (0.57–2.1)	4.7 (3.8–5.8)	9.1 (8.2–11)
CRP concentration, *mg/L*, median (IQR)	2.7 (0.9–7.3)	1.4 (0.6–2.9)	1.2 (0.6–4.8)
Dosing regimen			
5 mg/kg dose, n (%)	76 (100)	114 (99.1)	70 (97.2)
Interval, *wk*, median (range)	8 (4–12)	8 (4–10)	6 (4–11)
Intensified dosing regimen, n (%)	16 (21.1)	29 (25.2)	47 (65.3)

IFX, infliximab.

Supplementary Table 2. Pharmaco-Economic Evaluation for Patients Who Completed the Optimization Phase[a]

Characteristic	CD	UC	Total
Dose escalation (ATI negative), n (%)	38 (62.3)	23 (37.7)	61
IFX cost suboptimal treatment, €	1.282	1.196	1.250
IFX cost optimized treatment, €	1.945	1.784	1.885
ΔCost[b] IFX, €	664	588	635
Dose escalation (ATI positive), n (%)	5 (62.5)	3 (37.5)	8
IFX cost suboptimal treatment, €	1.194	1.118	1.166
IFX cost optimized treatment, €	2.167	2.064	2.129
ΔCost[b] IFX, €	973	946	963
Dose reduction, n (%)	48 (71.6)	19 (28.4)	67
IFX cost suboptimal treatment, €	1.410	1.752	1.507
IFX cost optimized treatment, €	1.071	1.124	1.086
ΔCost[b] IFX, €	−339	−627	−421

IFX, infliximab.
[a]Values represent the mean infliximab cost per patient per 4 weeks. ATI denotes antibodies to infliximab at baseline.
[b]ΔCost represents the difference in cost between suboptimal and optimized treatment.

Supplementary Table 3. Pharmaco-Economic Evaluation of the Randomized Maintenance Phase[a]

		Concentration-based dosing		Clinically based dosing				ICER
	n	QALY	Cost, €	QALY	Cost, €	ΔQALY[b]	Δ Cost,[c] €	ΔCost/ΔQALY
Total population	251	0.8227	20,723	0.8421	21,023	−0.0193	−300	15,525
Dose escalation during optimization	69	0.8457	25,345	0.8350	25,778	0.0108	−433	Dominant
ATI negative at baseline	61	0.8450	24,441	0.8362	25,547	0.0088	−1106	Dominant
ATI positive at baseline	8	0.8685	30,971	0.7909	28,279	0.0776	2692	34,695
No adaptation during optimization	115	0.8186	18,944	0.8549	20,178	−0.0363	−1234	34,009
Dose reduction during optimization	67	0.8098	19,645	0.8249	17,230	−0.0151	2415	Dominated

ICER, incremental cost-effectiveness ratio.
[a]Cost represents mean drug cost per patient per year. QALYs were adjusted for differences in baseline EuroQoL-5D score.
[b]ΔQALY represents the difference in QALY between concentration-based and clinically based dosing.
[c]ΔCost represents the difference in costs between concentration-based and clinically based dosing.