Increased versus conventional adalimumab dose interval for patients with Crohn's disease in stable remission (LADI): a pragmatic, open-label, non-inferiority, randomised controlled trial

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Summary

Background Despite its effectiveness in treating Crohn's disease, adalimumab is associated with an increased risk of infections and high health-care costs. We aimed to assess clinical outcomes of increased adalimumab dose intervals versus conventional dosing in patients with Crohn's disease in stable remission.

Methods The LADI study was a pragmatic, open-label, multicentre, non-inferiority, parallel, randomised controlled trial, done in six academic hospitals and 14 general hospitals in the Netherlands. Adults (aged ≥18 years) diagnosed with luminal Crohn's disease (with or without concomitant perianal disease) were eligible when in steroid-free clinical and biochemical remission (defined as Harvey-Bradshaw Index [HBI] score <5, faecal calprotectin <150 µg/g, and C-reactive protein <10 mg/L) for at least 9 months on a stable dose of 40 mg subcutaneous adalimumab every 2 weeks. Patients were randomly assigned (2:1) to the intervention group or control group by the coordinating investigator using a secure web-based system with variable block randomisation (block sizes of 6, 9, and 12). Randomisation was stratified on concomitant use of thiopurines and methotrexate. Patients and health-care providers were not masked to group assignment. Patients allocated to the intervention group increased adalimumab dose intervals to 40 mg every 3 weeks at baseline and further to every 4 weeks if they remained in clinical and biochemical remission at week 24. Patients in the control group continued their 2-weekly dose interval. The primary outcome was the cumulative incidence of persistent flares at week 48 defined as the presence of at least two of the following criteria: HBI score of 5 or more, C-reactive protein 10 mg/L or more, and faecal calprotectin more than 250 µg/g for more than 8 weeks and a concurrent decrease in the adalimumab dose interval or start of escape medication. The non-inferiority margin was 15% on a risk difference scale. All analyses were done in the intention-to-treat and per-protocol populations. This trial was registered at ClinicalTrials.gov, NCT03172377, and is not recruiting.

Findings Between May 3, 2017, and July 6, 2020, 174 patients were randomly assigned to the intervention group (n=113) or the control group (n=61). Four patients from the intervention group and one patient from the control group were excluded from the analysis for not meeting inclusion criteria. 85 (50%) of 169 participants were female and 84 (50%) were male. At week 48, the cumulative incidence of persistent flares in the intervention group (three [3%] of 109) was non-inferior compared with the control group (zero; pooled adjusted risk difference 1·86% [90% CI −0·35 to 4·07). Seven serious adverse events occurred, all in the intervention group, of which two (both patients with intestinal obstruction) were possibly related to the intervention. Per 100 person-years, 168·35 total adverse events, 59·99 infection-related adverse events, and 42·57 gastrointestinal adverse events occurred in the intervention group versus 134·67, 75·03, and 5·77 in the control group, respectively.

Interpretation The individual benefit of increasing adalimumab dose intervals versus the risk of disease recurrence is a trade-off that should take patient preferences regarding medication and the risk of a flare into account.

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Introduction

Adalimumab is a subcutaneous anti-tumour necrosis factor (TNF) agent that is effective for induction and maintenance of steroid-free remission in patients with Crohn's disease. The recommended induction dose is 160 mg at week 0 and 80 mg at week 2, followed by maintenance dosing of 40 mg every 2 weeks.[1] Despite its therapeutic effectiveness, adalimumab also comes with

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Research in context

Evidence before this study

We searched PubMed without language restrictions from inception until Oct 27, 2022, with the following search query: ("dose" AND (("increas*" AND "interval") OR "de-escalation" OR "spac*")) AND "adalimumab" AND ("inflammatory bowel diseas*" OR "crohn") to find literature that compared increasing adalimumab dose intervals with the conventional dose interval. We found 32 studies, of which none were randomised controlled trials. We found one recent systematic review on the broader topic of dose de-escalation of biologics in patients with inflammatory bowel disease, one systematic review on the effect of de-escalation of anti-TNF agents on adverse events in a wide range of immune-mediated diseases, and three observational studies on increased adalimumab and infliximab dose intervals in patients with Crohn's disease. These retrospective observational studies showed that increasing adalimumab dose intervals failed in around 30–40% of patients and that increased intervals might lead to a reduction in adverse events. Considering the retrospective and observational nature of these studies and the absence of controlled data, we aimed to answer this research question with a randomised controlled trial.

Added value of this study

To our knowledge, this is the first randomised controlled trial that compared increased adalimumab dose intervals with the conventional dose interval in patients with Crohn's disease who were in clinical and biochemical remission. Increased dose intervals were non-inferior to conventional intervals for persistent flares and led to a reduction in infectious adverse events. However, patients in the intervention group were less likely to be in clinical and biochemical remission at the end of the study and needed more escape medication during the study. Two patients in the intervention group had a serious adverse event after increasing adalimumab dose intervals, which subsided after returning to the conventional dose interval. Overall, more than half the patients could extend their dose interval without disease recurrence or need for escape medication.

Implications of all the available evidence

Increasing adalimumab dose intervals is feasible and provides a benefit for the majority of carefully selected patients by maintaining remission, reducing side-effects, or both, while lowering adalimumab dosing. This strategy allows for dose reduction while stopping short of discontinuation. The individual benefit of increasing adalimumab dose interval versus the risk of disease recurrence remains a trade-off that should take patient preferences regarding medication and the risk of a flare into account. Future research should focus on cost-effectiveness of the intervention and identifying subgroups of patients who would benefit most from this strategy.

limitations. Well known adverse events include injection site reactions and increased risk of infections.[2] In addition, biologicals are leading to high and increasing costs for health-care systems worldwide.[3]

Stopping adalimumab therapy might aid in reducing risk of side-effects, lowering medication costs, and avoiding prolonged immunosuppression during a quiescent disease course.[2] The downside of this approach in Crohn's disease is the relatively high recurrence rate after discontinuation. Approximately 38% of patients with Crohn's disease had a flare within 1 year, and 52% within 2 years, after discontinuing anti-TNF therapy, as described in a meta-analysis including 1317 patients from 14 studies.[4]

An alternative strategy to discontinuation of adalimumab is to increase dose intervals. A previous randomised controlled trial on adalimumab dose reduction in patients with rheumatoid arthritis compared the cumulative incidence rate of persistent clinical flares between conventional adalimumab dosing (every 2 weeks) and a stepwise increase of the adalimumab dose interval. The strategy of increasing adalimumab dose intervals was non-inferior to the conventional adalimumab dose interval and reduced health-care costs.[5–7]

In inflammatory bowel disease, the feasibility of adalimumab dose reduction was investigated in retrospective cohort studies, which showed that 26 (65%) of 40 patients could increase adalimumab dose intervals to every 3 weeks, while maintaining clinical remission.[8–10] No prospective study has evaluated the feasibility of increasing adalimumab intervals in patients with Crohn's disease or whether this intervention might reduce side-effects. We aimed to assess the clinical outcomes of increasing adalimumab dose intervals compared with a conventional adalimumab dose interval in patients with Crohn's disease who were in stable clinical and biochemical remission.

Methods

Study design

The LADI study was a pragmatic, investigator-initiated, open-label, multicentre, non-inferiority, parallel, randomised controlled trial. The study was conducted in six academic hospitals and 14 general hospitals in the Netherlands. This study was initiated by the Radboud University Medical Centre in Nijmegen and Erasmus University Medical Centre in Rotterdam, the Netherlands. The study protocol was approved by the medical ethical review committee of the Radboud University Medical Centre (registration number NL58948.091.16). The protocol has been published previously.[11]

Patients

Adults (aged ≥18 years) diagnosed with luminal Crohn's disease according to the European Crohn's and Colitis

Organisation guideline[12] (with or without concomitant perianal disease) were eligible when in steroid-free clinical and biochemical remission for at least 9 months on a stable dose of 40 mg adalimumab every 2 weeks. Patients on long-term low-dose budesonide could be granted a waiver at the discretion of the primary investigators. Clinical and biochemical remission was defined as a Harvey-Bradshaw Index (HBI) score of less than 5 points, faecal calprotectin less than 150 µg/g, and C-reactive protein less than 10 mg/L. Endoscopic assessment before enrolment was not mandatory, but if a baseline colonoscopy was performed and mucosal healing was demonstrated (defined as a Simple Endoscopic Score for Crohn's disease <3 or no ulcerations as reported by the endoscopist), faecal calprotectin less than 250 µg/g was accepted.

The following concomitant Crohn's disease therapies were permitted at inclusion: aminosalicylates, azathioprine, mercaptopurine, methotrexate, and thioguanine at a stable dose for at least 12 weeks. Physicians were advised not to change dosing of concomitant therapy except for urgent medical reasons (ie, clinically relevant adverse events). Exclusion criteria were actively draining perianal fistulas, inflammatory comorbidities that did not allow for increasing the adalimumab dose interval, pregnancy, and comorbidities interfering with the study. Detailed inclusion and exclusion criteria have been described in the published study protocol.[11] Patients were recruited from the gastroenterology outpatient clinics of the participating hospitals. Written informed consent was obtained from each patient who participated in the study.

Randomisation and masking

Patients were enrolled by local investigators. After enrolment, patients were randomly assigned (2:1) by the coordinating investigator using a secure web-based system (Castor Electronic Data Capture) to the intervention (increasing dose intervals) or control group (continue 2-weekly dose interval). The 2:1 ratio for randomisation was selected to stimulate patient inclusion, as patients would generally prefer to participate to de-escalate their therapy rather than continuing usual care. Thus, the 2:1 ratio made it more likely for patients to be randomly assigned to the intervention group. Moreover, the 2:1 ratio would lead to a larger sample size in the intervention group for development of a prediction model. Allocation took place with variable block randomisation, with block sizes of 6, 9, and 12. Randomisation was stratified on concomitant use of thiopurines and methotrexate (yes or no). Local and coordinating investigators were masked to the allocation sequence. Patients and health-care providers were not masked to treatment allocation. As outcomes were assessed locally, outcome assessors were not masked to study treatment.

Procedures

At baseline, patients allocated to the intervention group increased adalimumab dose intervals to 40 mg delivered subcutaneously every 3 weeks. Patients who remained in clinical and biochemical steroid-free remission at week 24 further increased their dose interval to 40 mg every 4 weeks. In case of a flare (as defined below), the treating physician was advised to return to the former effective dose interval. Final treatment decisions, including the use of escape medication, were made by the treating physician. Patients allocated to the control group continued subcutaneous adalimumab at 40 mg every 2 weeks throughout the study period.

Patients in both groups were followed up for 48 weeks. Follow-up and assessment of clinical and biochemical disease activity, laboratory results, and adverse events were done at the outpatient clinic at baseline and at weeks 12, 24, 36, and 48, with additional evaluation in case of a suspected flare. Between clinic visits, patients were followed-up by telephone consultations at weeks 6, 18, 30, and 42 to assess clinical disease activity and adverse events.

Serum samples for adalimumab drug concentrations and antibodies were frozen and stored at baseline and at weeks 24 and 48 for central analysis. Two hospitals performed adalimumab analysis locally. Serum adalimumab concentrations were measured using a validated ELISA. Anti-adalimumab antibodies were measured with drug-sensitive assays, centrally with ELISA (at 18 hospitals for 151 patients), and locally using a radio-immunoassay (at two hospitals for 16 patients).[13,14]

Outcomes

The primary outcome was the cumulative incidence of persistent flares (a flare for a consecutive period of ≥8 weeks) during the study period. A flare was defined as the presence of at least two of the following criteria: HBI score of 5 or more, C-reactive protein 10 mg/L or more, faecal calprotectin more than 250 µg/g, and a subsequent decrease in the adalimumab dose interval or start of escape medication. The primary outcome was selected on the basis of focus groups of the Dutch Crohn's and colitis patient organisation. The primary endpoint of flares persisting for 8 weeks or longer was selected to reflect flares that would have a substantial negative effect on patients due to the persistent nature. Transient flares were considered an acceptable risk of the intervention if quickly reversed and were viewed as non-inferior care because the transient nature of these flares would indicate that these patients responded well to dose intensification and disease control was quickly regained. Therefore, persistent flares were selected as the primary endpoint rather than transient flares or disease activity in general.

Secondary outcomes were the cumulative incidence of transient flares (lasting for ≥2 weeks and <8 weeks) at week 48, the proportion of patients in clinical and

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biochemical remission at week 48, adalimumab use over the study period (including the cumulative dose), the proportion of patients in the intervention group with an adalimumab dose interval of 3 or 4 weeks at week 48, the proportion of patients treated with budesonide, prednisone, or other immunomodulators (escape medication), quality of life, patient-reported disease activity, drug concentrations and anti-adalimumab antibodies, and adverse events.

Clinical and biochemical remission at week 48 was defined as an HBI score of less than 5, C-reactive protein less than 10 mg/L, and faecal calprotectin less than 150 µg/g, overruled by results from endoscopy. Because this approach might introduce bias, as not all patients were evaluated similarly, we also did a post-hoc sensitivity analysis in which we assessed the difference in clinical and biochemical remission without endoscopic results. We also did a post-hoc assessment of the proportion of patients in corticosteroid-free clinical and biochemical remission, whether patients lost clinical and biochemical remission during the study, and whether this led to therapy changes and if remission was regained.

Quality of life and patient-reported disease activity were measured at baseline and at weeks 12, 24, 36, and 48. Quality of life was assessed with the Short IBD Questionnaire (SIBDQ), which ranges from 0 to 70, with higher scores indicating better quality of life.[15] The HBI and Patient Reported Outcome-2 (PRO-2) were used to assess patient-reported disease activity, with higher scores indicating more disease activity.[16] Safety of the intervention was assessed using documented adverse events, classified per organ system and grade (mild, moderate, severe, life-threatening, and death) using National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

To facilitate interpretation and use of outcomes in clinical decision making, we also did a post-hoc analysis of the composite outcome of intervention failure. This was defined for the intervention group as major failure (persistent flare or possibly intervention-related serious adverse event) or minor failure (transient flare, use of escape medication, loss of remission at week 48, re-escalation of adalimumab to a conventional dose interval at week 48, or discontinuation of adalimumab). Successful dose interval increase was defined as the absence of intervention failure. In the protocol, we planned to develop a prediction model for the outcome of persistent flares. However, because the number of persistent flares was low, the effective sample size was too small. As such, we decided to take intervention success as the outcome for the prediction model. For the prediction model, patients who used budesonide or had a transient flare during the study period were not considered to have failed the intervention, as long as they were on an increased adalimumab dose interval and in clinical and biochemical remission at week 48. We also assessed health-care costs (medication and other health-care costs). Health-care use in the past 12 weeks was assessed with the Institute of Medical Technology Assessment Medical Consumption Questionnaire every 12 weeks, supplemented with information on medication use related to Crohn's disease, outpatient clinic visits, and diagnostics extracted from the medical chart. Health-care costs were valued according to the Dutch guideline.[17,18] If no unit prices were available in the guideline, insurer tariffs were used.[19] All costs were adjusted to 2022 Euros using the consumer price index.[20]

We compared adalimumab drug concentrations and antibodies between groups. Antibody titres were considered clinically relevant if the drug concentration was less than 1 µg/mL and antibody concentration was more than 10 ng/mL. Subtherapeutic levels are reported as the proportion of patients with adalimumab drug concentrations less than 5 µg/mL at each timepoint, while drug concentrations of 5 µg/mL or more were considered therapeutic.[21–23]

Statistical analysis

A sample size of 174 patients was estimated as adequate to determine non-inferiority with a margin of 15% on the risk difference scale. The non-inferiority margin of 15% was based on the NOR-SWITCH[24] and DRESS[7] trials and discussions with our study group. We believed a 15% margin would balance the potential harms of a flare and the benefits of dose reduction, such as fewer injections, reduced risk of side-effects, and cost savings. This is lower than the 20% margin used in the DRESS study because there are fewer alternative biologics for inflammatory bowel disease than for rheumatoid arthritis, and we put more weight on loss of effect of one biologic than in the DRESS study. The power calculation was further based on an expected cumulative incidence of persistent flares of 15% in both groups[7,25] with 80% power, a 5% one-sided α, and assuming a 10% drop-out rate.[26] More details are in the published protocol.[11]

Before the start of the trial, we specified both a per-protocol analysis as well as an intention-to-treat analysis (the intention-to-treat population was defined as all randomly assigned patients). As all patients met the per-protocol criteria for their respective group,[11] the per-protocol and intention-to-treat populations were the same. Cochran-Mantel-Haenszel adjusted risk differences (aRD) were used to compare the cumulative incidence of persistent and transient flares, use of escape medication, and clinical and biochemical remission at week 48.[27] The analysis was stratified on concomitant immunosuppressant use, as this was also used for stratified randomisation.[28]

The difference in quality of life and disease activity between the intervention and control group was assessed using a linear mixed model for the SIBDQ, negative binomial generalised linear mixed models for the HBI and PRO-2, and a gamma generalised linear mixed model for faecal calprotectin. All generalised linear mixed

models used a log link function. A gamma distribution was used to model faecal calprotectin due to the continuous and right-skewed nature of this variable. We modelled the outcomes at weeks 12, 24, 36, and 48 with a model containing the variables visit, randomisation group, interaction between visit and randomisation group, concomitant immunosuppressant use, age, and a quadratic term for the baseline value of the outcome.[28] We added a random intercept for each patient and assumed these to be normally distributed. The effect of randomisation group (main effect and interactions with visit) on evolution of disease activity and quality of life was tested with a multivariate Wald test. Health-care costs were compared between groups using bias-corrected accelerated confidence intervals (95% BCa) from bootstrapping. For the primary outcome, the upper limit of the 90% CI, equating to a one-sided α of 0·05, was compared with the non-inferiority margin. For secondary outcomes, a two-sided α of 0·05 was used for significance testing. Adverse events were reported as incidence rates per 100 person-years. Drug concentrations at weeks 0, 24, and 48 were analysed for all patients who used adalimumab at that timepoint. Anti-adalimumab antibodies are reported as the number and proportion of patients who developed antibodies during the study.

In a post-hoc analysis, we also evaluated whether baseline characteristics were predictive of intervention success (ie, no intervention failure) using logistic regression analysis. Candidate baseline predictors were selected on the basis of a consensus meeting within our LADI study group. These included baseline disease activity parameters (HBI, faecal calprotectin, and C-reactive protein), smoking, concomitant immunosuppressant use, disease duration, remission duration, time on adalimumab, previous therapy with infliximab or adalimumab, surgical history, Montreal classification, and adalimumab drug concentrations with a possible non-linear relationship. We used a univariable selection approach ($p<0·2$) followed by a multivariable approach with backward selection as specified in the study protocol.[11] The final model was created by averaging the parameter estimates for the selected variables from each imputed dataset where dropped variables counted as zero. The model was evaluated on discrimination and calibration and internally validated using bootstrap optimism correction.

Drug exposure, drug concentrations, and adverse events were analysed as observed. For all other outcomes, missing data were imputed in long format using the MICE algorithm in R assuming that data were missing at random.[29] Normally distributed variables were imputed using linear mixed models, and other variables with type 2 predictive mean matching. To ensure that the imputation models at least contained the same variables and interactions as the analysis models, all outcomes were added in the imputation models, as well as the design variables (randomisation group and concomitant immunosuppressant use). For auxiliary variables, we added variables that had a low proportion of missing data and were likely to be related to the outcomes. Risk differences, parameter estimates, and Wald tests from the (generalised) linear mixed models were pooled using Rubin's rules.

To assess the robustness of the primary outcome against drop-out, worst–best and best–worst case sensitivity analyses were done post-hoc in which all dropouts in one group were assumed to have a persistent flare, and vice versa. That is, worse–best case sensitivity analysis assumed all intervention dropouts had persistent flare and best–worst case sensitivity analysis assumed all control dropouts had persistent flare. Analyses were done with R version 4.2.0. An independent data and safety monitoring committee reviewed the data and decided that no interim analysis was needed. This trial was registered at ClinicalTrials.gov, NCT03172377.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 3, 2017, and July 6, 2020, 174 patients were enrolled in the study (appendix p 4). Of these, 113 patients were randomly assigned to the intervention group and 61 to the control group (figure 1). At the end of follow-up, 60 (98%) of 61 patients were eligible for analysis in the control group and 109 (96%) of 113 were eligible for analysis in the intervention group. Five (3%) of

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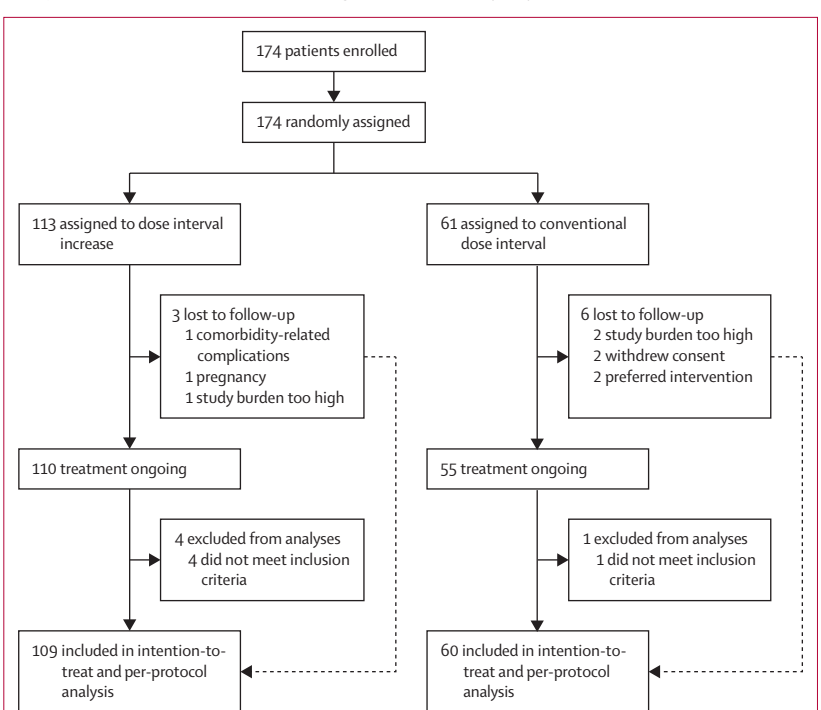

Figure 1: **Trial profile**

174 patients were excluded from the analyses for not meeting the inclusion criteria (four in the intervention group and one in the control group).

Patient baseline characteristics are shown in table 1. Two (2%) of 109 patients in the intervention group were on long-term (>3 years) low-dose budesonide at baseline, one 3 mg per day and one alternating 3 mg per day and 6 mg per day, for which they received a waiver to participate in the study. Disease location was most often ileocolonic, non-stricturing, and non-penetrating, while 51 (30%) of 169 patients had perianal involvement sometime in their disease course. Disease history, including previous therapies and surgery, are shown in table 1. More than half of patients in both groups had at least one comorbidity (appendix p 4). Previous episodes of adalimumab use were reported for 17 (16%) patients in the intervention group and five (8%) in the control group; only one (6%) of the 17 patients in the intervention group stopped adalimumab during the previous treatment episode for loss of clinical response. Other reasons for stopping were stable remission (intervention group: four [23%] of 17; control group: three [60%] of five), patient initiative (intervention group: three [18%]: control group: one [20%], pregnancy (intervention group: four [24%]; control group: none), vaccination (intervention group: one [6%]; control group: one [20%]), infections (intervention group: three [18%]; control group: none), and arthralgia (intervention group: one [6%]; control group: none). Drug concentration data were missing for 19 (11%) of 169 observations at baseline and for a maximum of 32 (19%) at one of the visits, drug exposure and adverse events were missing for the visits of the nine patients after they dropped out (zero missing data at baseline and maximum nine [5%] of 169 with missing data from week 30 onwards).

	Intervention group (n=109)	Control group (n=60)
Demographics		
Age, years	40 (32–48)	44 (30–54)
Sex		
Female	55 (50%)	30 (50%)
Male	54 (50%)	30 (50%)
BMI, kg/m²	24·2 (21·8–26·4)	24·6 (22·5–27·5)
Smoking status		
Active	17 (16%)	11 (18%)
Never	49 (45%)	35 (58%)
Ex-smoker	43 (39%)	14 (23%)
Disease history		
Concomitant immunosuppressants	18 (17%)	13 (22%)
Disease duration, years	13·6 (7·1–19·9)	12·1 (6·3–21·7)
Remission duration, years	2·9 (1·6–6·0)	2·8 (1·5–5·2)
Time on adalimumab, years	4·9 (2·4–7·0)	4·3 (2·2–7·5)
Previous therapy with infliximab	48 (44%)	24 (40%)
Previous therapy with adalimumab	17 (16%)	5 (8%)
Previous therapy with vedolizumab	1 (1%)	0
Previous therapy with ustekinumab	0	0
Previous inflammatory bowel disease-related surgery	60 (55%)	27 (45%)
Montreal classification		
Age at diagnosis		
A1	15 (14%)	8 (13%)
A2	83 (76%)	41 (68%)
A3	11 (10%)	11 (18%)
Disease extent		
L1, ileal	27 (25%)	11 (18%)
L2, colonic	22 (20%)	20 (33%)
L3, ileocolonic	60 (55%)	29 (48%)
L4, upper disease	15 (14%)	5 (8%)
Disease phenotype		
B1, non-stricturing, non-penetrating	64 (59%)	36 (60%)
B2, stricturing	27 (25%)	15 (25%)
B3, penetrating	18 (17%)	9 (15%)
P, perianal disease	32 (29%)	19 (32%)
Disease activity		
HBI score	1·0 (0·0–3·0)	1·0 (0·0–2·0)
Faecal calprotectin, µg/g	30·0 (16·0–65·0)	27·5 (15·8–50·0)
C-reactive protein, mg/L	1·3 (1·0–3·0)	2·0 (1·0–3·0)
Therapeutic drug monitoring		
Adalimumab drug concentration, µg/mL*	9·9 (6·9–11·6)	10·3 (7·3–12·0)
Anti-adalimumab antibodies*	1 (1%)	0

Data are median (IQR) or n (%). HBI=Harvey-Bradshaw Index. *Missing samples in the control group (n=8) and intervention group (n=11).

Table 1: **Baseline characteristics**

At 48 weeks, the cumulative incidence of persistent flares in the intervention group (three observed [3%]) was non-inferior compared with the control group (zero observed; pooled aRD 1·86% [90% CI –0·35 to 4·07]) as the 15% non-inferiority margin was outside the 90% CI (figure 2). Two of the three patients with a persistent flare met the flare criteria on the basis of increased C-reactive protein and faecal calprotectin, one of whom also met the HBI criteria after 4 weeks. The third patient met flare criteria for all three parameters from the start of their flare.

Two patients had transient flares: one patient met flare criteria on the basis of faecal calprotectin and HBI score,

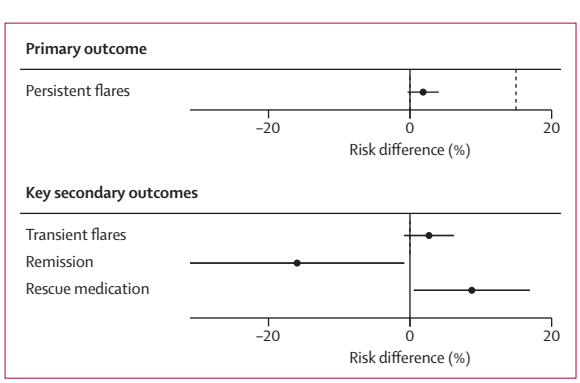

Figure 2: **Risk differences for the primary and key secondary outcomes comparing increased dose intervals with the conventional dose interval**
The dotted line indicates the 15% non-inferiority margin for the primary outcome.

and one met the criteria on basis of increased C-reactive protein and faecal calprotectin, while also meeting the HBI criteria 3 weeks later. The pooled aRD for the cumulative incidence of transient flares between the intervention group (two [2%]) and control group (zero) was 2·60% (95% CI −0·93 to 6·13; p=0·15; figure 2). At week 48, patients in the intervention group were less likely to be in clinical and biochemical remission than patients in the control group (78 [72%] *vs* 55 [92%]; pooled aRD −16·1% [95% CI −31·3 to −0·91]; p=0·038; figure 2). More patients in the intervention group used escape medication (12 [11%]) than in the control group (one [2%]; pooled aRD 8·67% [95% CI 0·44 to 16·90]; p=0·039; figure 2). For the intervention group, this included budesonide (eight [67%] of 12), prednisone (four [33%]), thioguanine (one [8%]), and a switch to ustekinumab (one [8%]), while on adalimumab dose intervals of 2 weeks (three [25%]), 3 weeks (eight [67%]), and 4 weeks (three [25%]). For the control group, the escape medication was budesonide (one [100%] of one).

In the intervention group, 17 (16%) patients decreased their dose interval during the study period. Five (29%) of these 17 patients reduced the adalimumab dose interval from 3 weeks to 2 weeks, seven (41%) patients reduced the dose interval from 4 weeks to 2 weeks, and five (29%) patients reduced the dose interval from 4 weeks to 3 weeks. Of the 12 patients in the intervention group who received escape medication, four (33%) decreased the adalimumab dose interval, two (17%) stopped adalimumab, four (33%) continued on the increased dose interval, and two (17%) further increased their dose interval.

All patients in the control group continued adalimumab in a 2-weekly dose interval. At week 48 in the intervention group, 71 (65%) patients had increased their dose interval to 4 weeks, 18 (17%) had increased the dose interval to 3 weeks, and 12 (11%) had returned to a 2-weekly interval (figure 3). The mean cumulative dose of adalimumab over the study period was 595 mg (SD 69) for the intervention group and 960 mg for the control group.

During the study, six patients in the intervention group discontinued adalimumab. Three (50%) patients discontinued due to antibody titres (one of whom developed a lupus-like skin reaction treated with prednisone, one was in biochemical remission but had abdominal symptoms for which they continued budesonide, and one patient maintained remission during follow-up without therapy), one (17%) patient was pregnant (who was also lost to follow-up and thus deemed to have dropped out of the study), one (17%) had renal cell carcinoma, and one (17%) had loss of response and subsequent start of ustekinumab despite a therapeutic adalimumab drug level.

Change in quality of life over the study period in both groups is shown in the appendix (p 1). The results from the multivariate Wald test for the SIBDQ (pooled p-value 0·96), HBI (pooled p-value 0·58), PRO-2 (pooled p-value 0·76),

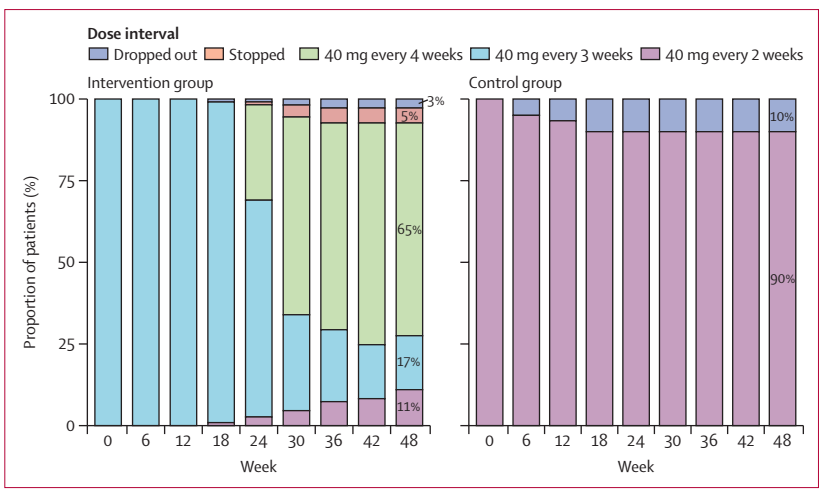

Figure 3: **Adalimumab dose intervals during follow-up**
Dropped out=participants who were lost to follow-up. Stopped=participants who stopped adalimumab but continued in the study.

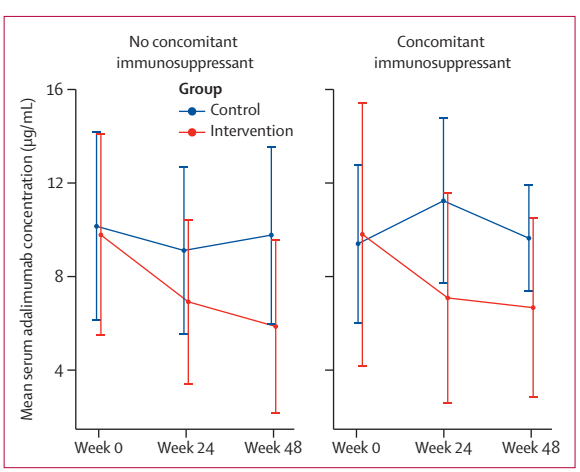

Figure 4: **Change in mean adalimumab serum concentration for both groups over the study period stratified by concomitant immunosuppressant use**
Whiskers show SD.

and faecal calprotectin (pooled p-value 0·052) showed no significant difference between groups. However, we found that faecal calprotectin was higher in the intervention group at week 24 (1·72 times higher [95% CI 1·07–2·77]) and week 36 (1·85 times higher [1·14–3·01]). The parameter estimates with corresponding 95% CIs are shown in the appendix (pp 5–6).

Mean adalimumab concentrations for both groups are shown in figure 4 and appendix p 12. No effect of concomitant immunosuppression on adalimumab drug concentrations was observed. Four (4%) patients in the intervention group developed anti-adalimumab antibodies during the study, which resulted in adalimumab discontinuation for three (75%) patients. One (1%) patient in the intervention group already had (in retrospect) detectable anti-adalimumab antibodies at baseline and stopped adalimumab after increasing the

	Intervention group			Control group		
	Mild	Moderate	Any	Mild	Moderate	Any
Total	103·52	64·82	168·35	73·11	61·56	134·67
Infections and infestations	28·06	31·93	59·99	28·86	46·17	75·03
Gastrointestinal disorders	31·93	10·64	42·57	5·77	0·00	5·77
Skin and subcutaneous tissue disorders	7·74	7·74	15·48	5·77	5·77	11·54
Respiratory, thoracic, and mediastinal disorders	5·81	0·97	6·77	13·47	1·92	15·39
General disorders	12·58	1·94	14·51	7·70	3·85	11·54
Musculoskeletal and connective tissue disorders	4·84	5·81	10·64	3·85	1·92	5·77
Injury, poisoning and procedural complications	0·97	2·90	3·87	3·85	0·00	3·85
Neoplasms benign, malignant, and unspecified	1·94	0·00	1·94	1·92	1·92	3·85
Blood and lymphatic system disorders	1·94	0·97	2·90	0·00	0·00	0·00
Eye disorders	2·90	0·00	2·90	1·92	0·00	1·92
Nervous system disorders	2·90	0·00	2·90	0·00	0·00	0·00
Immune system disorders	0·97	0·97	1·94	0·00	0·00	0·00
Renal and urinary disorders	0·97	0·97	1·94	0·00	0·00	0·00

Data are incidence rates per 100 person-years in the observed population.

Table 2: **Incidence of adverse events per system organ class and grade**

	Proportion of patients
Failed intervention	44·5%
Major failure	3·8%
Persistent flare	1·9%
Intervention-related serious adverse event	1·8%
Minor failure	44·5%
Transient flare	2·6%
Rescue medication	11·9%
Lost remission at week 48	31·0%
Did not increase dose interval at week 48	15·6%

Data are averaged over the imputed datasets.

Table 3: **Proportion of patients in the intervention group with intervention failure according to different outcomes**

dose interval to 3 weeks. All patients who developed antibodies were on adalimumab monotherapy. No patients in the control group developed anti-adalimumab antibodies during the study. Another three (3%) patients in the intervention group (and none in the control group) had undetectable adalimumab concentrations at single timepoints during the study (one at baseline, two at week 48) without detectable anti-adalimumab antibodies. In the intervention group, subtherapeutic concentrations were found for 13 (13%) of 98 patients at week 0, 31 (34%) of 92 patients at week 24, and 38 (44%) of 86 patients at week 48. In the control group, subtherapeutic concentrations were found for five (10%) of 52 patients at week 0, seven (16%) of 45 patients at week 24, and six (12%) of 49 patients at week 48. 132 (88%) of 150 patients had a therapeutic adalimumab concentration at baseline. Of the 85 patients in the intervention group with a therapeutic adalimumab concentration at baseline, 19 (22%) had subtherapeutic concentrations at week 24 and 28 (33%) had subtherapeutic concentrations at week 48. In the control group, two (4%) of 47 patients at week 24 and one (2%) of 47 patients at week 48 had subtherapeutic concentrations.

Seven serious adverse events occurred during the study follow-up, all in the intervention group (seven [6%] patients). Two (29%) patients were admitted to hospital for pneumonia, two (29%) patients had intestinal obstruction, one (14%) patient had obstructive symptoms due to an anastomotic stricture (history of two ileocolonic resections), one (14%) patient had a renal cell carcinoma (resulting in discontinuation of adalimumab), and one (14%) patient was admitted to hospital due to urolithiasis. No deaths occurred during follow-up.

The incidence of adverse events was slightly higher in the intervention group than the control group (table 2). The most common adverse events were infections, gastrointestinal disorders (including disease activity), and dermatological disorders (table 2 and appendix pp 7–8). The reduction in infections in the intervention group was mostly observed in the moderate category, while the increase in gastrointestinal disorders in the intervention group was both in the mild and moderate categories. 65·79 possibly intervention-related adverse events occurred per 100 person-years, of which gastrointestinal disorders, musculoskeletal disorders, and dermatological disorders were most reported (appendix p 9). The occurrence of possibly adalimumab-related adverse events was similar between the intervention group and the control group (appendix pp 10–11). We observed 3·85 injection site reactions per 100 person-years in the control group while none were reported in the intervention group.

Results from the best–worst (three [3%] in the intervention group *vs* six [10%] in the control group; aRD –7·41% [90% CI –14·41 to –0·41]) and worst–best sensitivity analyses (six [6%] *vs* zero; aRD 5·51% [90% CI 1·90 to 9·11]) for the primary outcome were similar to the main analysis. 12 (7%) patients had an endoscopy around week 48 (seven [6%] in the intervention group and five [8%] in the control group); sensitivity analyses of the secondary endpoint of clinical and biochemical remission without results of endoscopy was similar to the main analysis (77 [71%] *vs* 54 [90%]; pooled aRD –13·91% [95% CI –29·54 to 0·02]; p=0·080). Post-hoc analysis of corticosteroid-free clinical and biochemical remission showed that patients in the intervention group were less likely to be in corticosteroid-free clinical and biochemical remission at week 48 than patients in the control group (75 [69%] *vs* 55 [92%]; pooled aRD –19·16% [95% CI –34·53 to –3·78]; p=0·015). After 48 weeks, averaged over the imputed datasets, 44·5% of patients in the intervention group reached the

post-hoc composite outcome of intervention failure, meaning that 55·5% of patients had a successfully increased dose interval (table 3). Most patients with intervention failure were not in clinical and biochemical remission at week 48 or did not manage to extend their dose interval to 3 or 4 weeks. Few patients had major negative consequences of the intervention: a persistent flare or an intervention-related serious adverse event (table 3).

Apparent discriminative performance of the prediction model was moderate, with an area under the receiver operating characteristic curve (AUC) of 0·72 (appendix p 2). Calibration was adequate, with a calibration intercept of –0·04 and slope of 1·14 (appendix p 3). After the variable selection procedure, we included active smoking, longer remission duration, previous inflammatory bowel disease-related intra-abdominal surgery, proximal small bowel disease, and increased HBI and faecal calprotectin as risk factors for intervention failure. Previous exposure to adalimumab was predictive of intervention success. Patients with adalimumab concentrations between 10 and 11 µg/mL were more likely to successfully increase the adalimumab interval than patients with lower or higher drug concentrations. For odds ratios from the model, see the appendix (p 12). Internal validation showed that apparent performance estimates were too optimistic and the optimism-corrected AUC was 0·63. Optimism-corrected calibration estimates showed predicted risk estimates that were too extreme, indicating overfitting on the development data (appendix p 12). This means that external validity of the prediction model is low and that it is likely that these predictors are less useful to identify patients who can increase their dose interval.

Medication costs per patient were significantly lower (–€2545 [95% BCa –2780 to –2192]) in the intervention group than the control group, whereas non-medication health-care costs (€474 [95% BCa 149 to 952]) were higher in the intervention group than the control group (appendix p 12).

Post hoc, we found that a large proportion of patients lost clinical or biochemical remission at any point during the study. Averaged over the multiply imputed datasets, this was 77% in the intervention group and 64% in the control group. This was recaptured at week 48 for most patients, as 31% and 17% were not in clinical and biochemical remission at week 48 in the intervention and control group, respectively. Most patients in both groups did not undergo treatment changes after losing clinical and biochemical remission (intervention group: 72% and control group: 95%), and often spontaneously recaptured clinical and biochemical remission (63% and 74%). 17 (16%) patients in the intervention group decreased their adalimumab dose interval and lost clinical and biochemical remission; of whom 43% recaptured clinical and biochemical remission at the end of the study.

Discussion

In this multicentre, randomised controlled trial in patients with Crohn's disease in stable remission, an increased adalimumab dose interval was non-inferior compared with conventional dosing for the occurrence of persistent flares. Patients in both groups had low and similar rates of transient flares, but more patients on conventional dosing were in remission at the end of follow-up. Mean adalimumab drug concentrations in the intervention group decreased over time but remained detectable for nearly all patients. The proportion of infection-related adverse events was lower in the intervention group than the control group, whereas the incidence of gastrointestinal adverse events was higher in the intervention group. At the end of the trial, 89 (82%) patients in the intervention group continued an extended adalimumab dose interval.

Although dose de-escalation of anti-TNF therapy is frequently requested by patients, data from controlled trials are scarce. Studies investigating the increase of adalimumab dose intervals in patients with inflammatory bowel disease are retrospective in nature, with focus on the endpoints of clinical remission or relapse, rather than persistent flares.[30] We established non-inferiority for the primary endpoint of persistent flares because the 90% CI for the treatment difference fell within the prespecified margin; the pooled adjusted risk difference for persistent flares was 1·86% for the increased dose intervals group compared with the control group. A trial design similar to our study was applied in a non-inferiority, randomised controlled trial with persistent flares as the primary outcome in patients with rheumatoid arthritis. That study also showed that the intervention of increasing adalimumab dose intervals was non-inferior to conventional dosing for persistent rheumatoid arthritis flares.[7]

Although the occurrence of persistent flares was similar in both groups, we found more patients received escape therapy and fewer were in clinical and biochemical remission in the intervention group. The reduction in clinical and biochemical remission rates might reflect mild disease activity, without being an overt symptomatic disease flare. The clinical implication of this observation is that continued and strict monitoring for biochemical and clinical disease activity beyond 48 weeks using faecal calprotectin and progression of symptoms remains important. Our long-term extension study, in which patients are being followed up for a further 2 years, will address whether isolated biochemical disease activity at week 48 precedes a clinical flare and requires therapeutic adjustments. Half the patients receiving escape therapy could continue or even further extend their adalimumab dose interval, raising the question whether the rescue therapy was always necessary.

To our knowledge, no prospective studies are available with which to compare these results, but

three retrospective studies showed a successful increase of the adalimumab dosing interval to 3 weeks in 59–65% of patients,[8–10] whereas around 82% of the patients in our study were on an extended dose interval at week 48. Possible explanations of this difference are the strict inclusion criteria for the LADI trial and the longer follow-up of the retrospective studies. Patients in our study had to be in clinical and biochemical remission at baseline, whereas in the retrospective studies, all patients who increased their adalimumab dose interval were included with more lenient inclusion criteria. Indeed, these studies also showed that lower inflammatory parameters were associated with successful dose interval increase. Moreover, patients were followed-up for 48 weeks in our trial, whereas median follow-up time in the retrospective studies was between 15·9 and 34 months. As intervention failure could still occur on the increased dose interval beyond 1 year, the longer follow-up might have resulted in higher failure rates. We also extended most patients to adalimumab every 4 weeks, which could have led to higher failure rates compared with the retrospective studies that only increased adalimumab intervals to 3 weeks. Our long-term extension study beyond 48 weeks to assess the long-term sustainability of an increased adalimumab dose interval is ongoing.

The loss of clinical and biochemical remission in 31% of the patients after an increase of the dose interval is similar to the relapse rates observed after anti-TNF discontinuation (38%).[4] However, loss of clinical and biochemical remission was defined as an increase in either HBI, C-reactive protein, or faecal calprotectin, whereas the relapse rates from discontinuation studies were based on necessity of introduction or reintroduction of biologics, corticosteroids, immunosuppressants, or surgery.

The lower proportion of adalimumab-related infections in the intervention group compared with conventional dosing is a clinically relevant finding and consistent with results of previous studies.[8,31] The increased dose intervals mostly reduced moderate infections (necessitating non-invasive interventions, such as antibiotics). Furthermore, we observed a reduction in the incidence of reported injection site reactions in the intervention group compared with the control group.

Although these observations suggest benefit from increasing the adalimumab dose interval, we also observed an increased rate of gastrointestinal adverse events, in part due to recurrence of disease activity. Gastrointestinal adverse events were mostly mild and more frequently observed in the intervention group, whereas patient-reported disease activity and quality of life remained similar between the two groups. However, we found that faecal calcprotectin increased in the intervention group during the study, again showing the need for our long-term extension study. We also found that patients in both groups lost clinical and biochemical remission relatively often during the study period, but remission was in most cases recaptured without the need for intervention.

At week 48, around 82% of participants in the intervention group remained on an increased dose interval, including 65% every 4 weeks and 17% every 3 weeks, while 11% returned to the conventional dosing. These results differ from anti-TNF discontinuation studies showing that only between 38% and 66% of patients with inflammatory bowel disease maintained remission without anti-TNF after 1 year.[4,32,33] This difference might favour the strategy of increasing intervals as opposed to discontinuation of anti-TNF.

To estimate the clinical impact of the intervention, we evaluated the composite outcome of intervention failure. Although 44·5% of patients in the intervention group had intervention failure, only a small proportion of patients had major negative consequences from the intervention (ie, a persistent flare or intervention-related serious adverse event). Most intervention failures were due to lost remission at week 48 or failing to increase the dose interval. Although patients with a 2-weekly dose interval at week 48 might be considered to have intervention failure, it is important to realise that while searching for an individualised dose interval, it is inevitable that some patients fare best on the 2-weekly interval. With our stepwise strategy and 6-weekly follow-up schedule, we found an appropriate dose interval to maintain remission for most patients without major consequences. However, some patients did lose remission at week 48. These data on clinical outcomes might aid the discussion between patient and physician on adalimumab interval extension in daily practice.

Our prediction model had modest apparent discriminative performance for differentiating patients with a successfully increased dose interval and patients with failed interval extension. These results should be interpreted with caution. Internal validation showed that discriminative ability of the model was optimistic and that it suffered from overfitting, which would lead to biased risk predictions when the model is used in clinical practice. Interestingly, use of concomitant immunosuppressants was not predictive of successful interval increase, although it was a protective factor against relapse after cessation of anti-TNF therapy in Crohn's disease in previous studies.[4] Moreover, adalimumab drug concentrations were non-linearly related to the outcome, as patients with drug concentrations between 10 and 11 µg/mL were more likely to have a successfully increased dose interval compared with patients with lower and higher drug concentrations. Given the poor performance of the model in internal validation and absence of external validation, individualised risk estimates for disease recurrence following increasing adalimumab intervals remain an unmet need. A future direction for research

would be to develop and validate a clinical prediction model with more advanced methods to better inform health-care practitioners, patients, and policy makers on implementation of the strategy of increasing adalimumab dose intervals.

To our knowledge, no controlled data on anti-TNF dose de-escalation are available, while many patients are eager to reduce biological therapy once stable remission is achieved. This randomised controlled trial sheds light on this topic and provides important data on disease activity, safety, pharmacokinetics, and drug use following an increase of the adalimumab dose interval. The pragmatic trial design included routine measurements commonly used in daily practice, such as clinical disease activity, biochemistry, and adalimumab drug concentrations, resulting in high external validity of our results.

We also acknowledge several limitations. First, investigators, nurses, and patients were not masked to treatment allocation. Masking would have created many practical hurdles to implementing this trial. In addition, the goal of this pragmatic study was to provide high external validity, and masking would have lowered this. Second, systematic endoscopic evaluation of disease activity was not mandatory in this trial. Full endoscopic remission at baseline might have affected the number of patients in long-term remission after increasing the dose interval because endoscopic remission was also associated with a lower risk of relapse after full anti-TNF withdrawal.[34] Absence of endoscopic evaluation during the study could have potentially resulted in underestimation of disease activity despite the use of the combination of clinical and biochemical disease activity. Third, the relatively stringent primary endpoint might not have fully captured the effect of increasing adalimumab intervals on disease activity. We aimed to cover this by a broad range of secondary endpoints, elucidating the trade-off between increased intervals and different measures of disease activity. Fourth, there might remain some residual confounding as illustrated by the difference in median age between the intervention (40 years) and control group (44 years). Although we adjusted for this possible confounder in the generalised linear mixed models, this was not possible for the other outcomes in the prespecified analysis plan. Fifth, the adalimumab drug concentrations were measured at weeks 0, 24, and 48 and were not always true trough concentrations. Although this might potentially overestimate drug concentrations, a previous study found no correlation between time since last administration and adalimumab drug concentrations.[35] Last, the wide CIs for the secondary outcome measures of clinical and biochemical remission and escape medication should be considered. This is mostly likely due to the relatively small sample size, and these results should be interpreted with caution. Although these results show little compatibility with no difference between the intervention and control group; results are compatible with both a small and a large difference in remission and escape medication between groups. This compatibility issue should also be considered for the quality-of-life outcomes analysed with generalised linear mixed models because for most parameter estimates, CIs were relatively wide.

The cost-effectiveness of increased adalimumab dose intervals and selection of patient subgroups that would benefit most from this strategy remain gaps in knowledge. We found that health-care costs for the intervention group were significantly lower than for the control group. We are currently conducting a cost-utility analysis, which will be published separately, that should indicate whether this cost reduction outweighs possible differences in quality of life.

In conclusion, increasing adalimumab dose intervals was non-inferior to conventional dosing for persistent flares in patients with Crohn's disease in stable clinical and biochemical remission, while infection-related adverse events and health-care costs were reduced. These observations were counterbalanced by a lower rate of clinical remission and more gastrointestinal adverse events in the intervention group. Taken together, these outcomes provide a good basis to discuss increasing adalimumab dose intervals with patients who have had or want to lower risk of adverse events or want to reduce exposure to biologics in general. This should be discussed in a shared decision making process, taking into account the patient perspective on medication use, adverse events, and risk of a flare or loss of clinical and biochemical remission.

Contributors

CJvdW, FH, RWMP, LJTS, and WK contributed to the conception and design of the study. RCAvL, FMJ, RWMP, LJTS, DJdJ, ACdV, PJB, RLW, AGLB, IAMG, FHJW, TEHR, MWMDL, AAvB, BO, MJP, MGVMR, NKdB, RCM-H, PCJtB, AEvdM-dJ, JMJ, SVJ, ACITLT, CJvdW, and FH contributed to patient inclusion and data collection. RCAvL, FMJ, RWMP, and LJTS were responsible for project administration. CJvdW and FH were responsible for project supervision. RCAvL and FMJ accessed and verified the underlying data. RCAvL was responsible for the statistical analysis with supervision from WK and FA. All authors contributed to interpreting the data. RCAvL, FMJ, CJvdW, and FH wrote the first draft of the manuscript and all authors reviewed and approved the manuscript for submission. All authors had access to all data and shared final responsibility for the decision to submit for publication.

Declaration of interests

FMJ has received a research grant from ZonMW. DJdJ has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Galapagos and held leadership roles in the Dutch Initiative on Crohn and Colitis and the IBD workgroup of the Dutch Gastroenterology Society. ACdV has received research grants from Takeda, Janssen, and Pfizer. RLW has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Ferring, Pfizer, Galapagos, AbbVie, and Janssen. TEHR has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie and has participated in the advisory board for Galapagos. MWMDL has received a grant for podcasts from Pfizer; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Janssen-Cilag and Galapagos; participated in advisory boards of BMS and Galapagos; and held leadership roles in the Elisabeth Twee Steden Ziekenhuis. AAvB has received research grants from AbbVie, Celgene/BMS, Janssen, Pfizer, Teva, and ZonMW;

consulting fees from Ferring, Galapagos, AbbVie, and BMS; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Ferring, Galapagos, and Janssen; support for attending meetings from Janssen; and held leadership roles in committees of the Dutch Gastroenterology Society and National Federation of Medical Specialists. BO has received research grants from Galapagos, Takeda, Ferring, and Celltrion; received consulting fees from AbbVie, Galapagos, Pfizer, Ferring, Takeda, and Janssen; received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Takeda, Galapagos, AbbVie, and Ferring; and was chairman of the IBD Committee of the Dutch Association of Gastroenterology. MJP has received consulting fees from Takeda, Janssen, Galapagos, and AbbVie; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Janssen. NKdB has received research grants from Teva, Takeda, and the Dutch Gastroenterology and Hepatology Patient Association (MLDS); and has received consulting fees from Teva. RCM-H has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Janssen-Cilag and is a member of the national IBD Committee of the Dutch Association for Gastroenterology and Hepatology. AEvdM-dJ has received research grants from Galapagos, Nestle, Cablon, and Norgine; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Galapagos, Tramedico, and Janssen-Cilag; and has participated in an advisory board for Ferring. FH has received research grants from Janssen, AbbVie, Pfizer, and Takeda; and has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie, Janssen, Takeda, and Pfizer. CJvdW has received research grants from ZonMW, Falk, and Pfizer; has received consulting fees from Janssen, Galapagos, and Pfizer; has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Ferring and AbbVie; and had leadership roles in the European Crohn's and Colitis Organisation, United European Gastroenterology Council, and the Dutch Association for Gastroenterology. All other authors declare no competing interests.

Data sharing

Requests for sharing of de-identified data by third parties will, after written request to the corresponding author, be considered. If the request is approved and a data access agreement is signed only de-identified data will be shared.

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