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Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study

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Summary

Background Anti-TNF drugs are effective treatments for the management of Crohn's disease but treatment failure is common. We aimed to identify clinical and pharmacokinetic factors that predict primary non-response at week 14 after starting treatment, non-remission at week 54, and adverse events leading to drug withdrawal.

Methods The personalised anti-TNF therapy in Crohn's disease study (PANTS) is a prospective observational UK-wide study. We enrolled anti-TNF-naive patients (aged ≥6 years) with active luminal Crohn's disease at the time of first exposure to infliximab or adalimumab between March 7, 2013, and July 15, 2016. Patients were evaluated for 12 months or until drug withdrawal. Demographic data, smoking status, age at diagnosis, disease duration, location, and behaviour, previous medical and drug history, and previous Crohn's disease-related surgeries were recorded at baseline. At every visit, disease activity score, weight, therapy, and adverse events were recorded; drug and total anti-drug antibody concentrations were also measured. Treatment failure endpoints were primary non-response at week 14 ,non-remission at week 54, and adverse events leading to drug withdrawal. We used regression analyses to identify which factors were associated with treatment failure.

Findings We enrolled 955 patients treated with infliximab (753 with originator; 202 with biosimilar) and 655 treated with adalimumab. Primary non-response occurred in 295 (23·8%, 95% CI 21·4–26·2) of 1241 patients who were assessable at week 14. Non-remission at week 54 occurred in 764 (63·1%, 60·3–65·8) of 1211 patients who were assessable, and adverse events curtailed treatment in 126 (7·8%, 6·6–9·2) of 1610 patients. In multivariable analysis, the only factor independently associated with primary non-response was low drug concentration at week 14 (infliximab: odds ratio 0·35 [95% CI 0·20–0·62], p=0·00038; adalimumab: 0·13 [0·06–0·28], p<0·0001); the optimal week 14 drug concentrations associated with remission at both week 14 and week 54 were 7 mg/L for infliximab and 12 mg/L for adalimumab. Continuing standard dosing regimens after primary non-response was rarely helpful; only 14 (12·4% [95% CI 6·9–19·9]) of 113 patients entered remission by week 54. Similarly, week 14 drug concentration was also independently associated with non-remission at week 54 (0·29 [0·16–0·52] for infliximab; 0·03 [0·01–0·12] for adalimumab; p<0·0001 for both). The proportion of patients who developed anti-drug antibodies (immunogenicity) was 62·8% (95% CI 59·0–66·3) for infliximab and 28·5% (24·0–32·7) for adalimumab. For both drugs, suboptimal week 14 drug concentrations predicted immunogenicity, and the development of anti-drug antibodies predicted subsequent low drug concentrations. Combination immuno-modulator (thiopurine or methotrexate) therapy mitigated the risk of developing anti-drug antibodies (hazard ratio 0·39 [95% CI 0·32–0·46] for infliximab; 0·44 [0·31–0·64] for adalimumab; p<0·0001 for both). For infliximab, multivariable analysis of immunododulator use, and week 14 drug and anti-drug antibody concentrations showed an independent effect of immunomodulator use on week 54 non-remission (odds ratio 0·56 [95% CI 0·38–0·83], p=0·004).

Interpretation Anti-TNF treatment failure is common and is predicted by low drug concentrations, mediated in part by immunogenicity. Clinical trials are required to investigate whether personalised induction regimens and treatment-to-target dose intensification improve outcomes.

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Introduction

The anti-TNF monoclonal antibodies infliximab and adalimumab are effective treatments for patients with Crohn's disease refractory to conventional therapies. Successful treatment leads to mucosal healing, reduced hospitalisations (ie, admissions to hospital) and sur-geries, and improvement in quality of life.[1–5]

Unfortunately, anti-TNF treatment failure is common: 10–40% of patients do not respond to induction therapy (primary non-response),[6–8] 24–46% of patients have secondary loss of response in the first year of treatment,[9] and approximately 10% have an adverse drug reaction that curtails treatment.[10]

Multiple patient, disease, and drug related factors have been implicated in anti-TNF treatment failure,[11] but their relative effects, interactions, and effect on drug and anti-drug antibody concentrations have not been explored in an adequately powered prospective study. Early identi-fication of patients at risk of treatment failure might help facilitate direct monitoring, early dose optimisation, and use of strategies to mitigate the development of anti-drug antibodies, allowing these drugs to be used in a safer, more cost-effective manner.

The main aim of the personalised anti-TNF therapy in Crohn's disease study (PANTS) was to build a bio-repository to investigate the genetic and other factors associated with anti-TNF treatment failure in patients with active luminal Crohn's disease. In this Article, we report the

clinical and pharmacokinetic factors associated with and predictive of anti-TNF failure in the first year of treatment.

Methods

Study design and participants

PANTS is a UK-wide, multicentre, prospective obser-vational cohort reporting on treatment failure of the anti-TNF drugs infliximab (originator, Remicade [Merck Sharp and Dohme, Hertforshire, UK] and biosimilar, CT-P13 [Celltrion, Incheon, South Korea]) and adalimumab (Humira [AbbVie, Chicago, IL, USA]) in anti-TNF-naive patients with active luminal Crohn's disease.

Patients were recruited at the time of first anti-TNF exposure from 120 National Health Service trusts across the UK (appendix pp 3–10) between March 7, 2013, and July 15, 2016. Patients were evaluated for 12 months or until drug withdrawal.

Patients were screened for inclusion in our cohort at the time of decision to treat with an anti-TNF drug and no more than 4 weeks before starting to receive the drug. The eligibility criteria were as follows: age 6 years or older; diagnosis of Crohn's disease involving the colon, the small intestine, or both; and active luminal disease supported by a C-reactive protein (CRP) of more than 3 mg/L 90 days before the first dose, faecal calprotectin of more than 50 μg/g between 90 days before and 28 days after first dose, or both. Exclusion criteria included previous exposure to, or contraindications for the use of, anti-TNF therapy (all criteria available in the protocol).

The South West Research Ethics committee approved the study (REC reference: 12/SW/0323) in January, 2013. Patients were included after providing informed, written consent. The protocol is available online.

Procedures

The choice of anti-TNF was at the discretion of the treating physician and prescribed according to the licensed dosing schedule.

Study visits were scheduled at first dose (week 0), post-induction (week 14), and at weeks 30 and 54 after first dose. Additional visits were planned for infliximab-treated patients at each infusion, and for both groups at the time of treatment failure or treatment discontinuation. In cases in which the visit did not occur on the exact day delineated by the protocol, the following windows of eligibility were specified: week 0 (week −4 to 0), week 14 (week 10–20), week 30 (week 22–38), and week 54 (week 42–66; appendix pp 12–13).

At baseline, sites recorded demographic data, smoking status, age at diagnosis, disease duration, Montreal classification of disease location and behaviour,[12] previous medical and drug history, and previous Crohn's disease-related surgeries. At every visit, disease activity score, weight, therapy, and adverse events were recorded.

Blood and stool samples were processed through the central laboratory at the Royal Devon and Exeter National Health Service Foundation Trust. Drug and total anti-drug antibody concentrations were measured with IDKmonitor ELISA assays (Immundiagnostik AG, Bensheim, Germany) done on the Dynex DS2 ELISA robot (Dynex technologies, Worthing, UK; appendix p 11). For all infliximab-treated patients, we used trough drug concentrations, excluding concentrations measured at other timepoints. For adalimumab-treated patients, we asked research sites to take blood samples as near as possible to trough while minimising inconvenience to patients.

We chose a drug tolerant anti-drug antibody assay that allowed us to identify all patients with immunogenicity irrespective of circulating drug concentration. Based upon manufacturer's recommendation we defined immunogenicity as an anti-drug antibody titre of 10 arbitrary units per mL or more, and stratified immunogenicity by the presence or absence of detectable drug (<0·8 mg/L). Investigators were masked to these data until week 54.

Outcomes

Treatment failure endpoints were primary non-response at week 14, non-remission at week 54, and adverse events leading to drug withdrawal. We used composite endpoints defined using symptom scores (Harvey Bradshaw index [HBI] in adults[13] and the HBI or Short Paediatric Crohn's Disease Activity Index [sPCDAI] in children),[14] corticosteroid use, and CRP (appendix p 14).

Primary non-response was defined as exit before week 14 because of treatment failure (including resectional inflammatory bowel disease surgery) or corticosteroid use at week 14 (new prescriptions or if previous dose had not been stopped). Patients whose CRP did not decrease to 3 mg/L or less or by 50% or more from baseline (week 0), and whose HBI score did not decrease to 4 points or less or by 3 points or more from baseline, were also classified as having a primary non-response. Children were defined as having a primary non-response when their sPCDAI score did not decrease to 15 points or less or by more than 12·5 points from baseline (besides same CRP criteria as adults). Grey zone denoted an intermediate response between primary non-response and response, defined as CRP decreasing to 3 mg/L or less or by 50% or more from baseline (week 0), or HBI score decreasing to 4 points or less or by 3 points or more from baseline, but not both. Treatment response was defined as a decrease in CRP to 3 mg/L or less or by 50% or more from baseline (week 0) and a decrease in HBI to 4 points or less or by 3 points or more from baseline for adults, or a decrease in sPCDAI to 15 points or less or by 12·5 points from baseline (week 0) for children. Remission was defined as CRP of 3 mg/L or less and HBI score of 4 points or less (sPCDAI score ≤15 points), no ongoing steroid therapy, and no exit due to treatment failure. Loss of response in patients who did not have primary non-response was defined as symptomatic inflammatory bowel disease activity that warranted an escalation of steroid, immunomodulatory or anti-TNF therapy, resectional surgery, or exit from study due to treatment failure.[9] Timing of loss of response was defined as the time of treatment escalation, drug withdrawal, or surgery.

Non-remission was assessed at week 54 and defined as CRP of more than 3 mg/L or an HBI score of more 4 points (sPCDAI 15< points for children), ongoing steroid therapy, or exit due to treatment failure. Patients exited the study when they stopped anti-TNF therapy or had an intestinal resection. We defined steroid therapy for the purposes of non-remission and primary non-response as any systemic therapy, either oral or intravenous (includ-ing use of steroids for other conditions), but not including single pre-infusion dosing with hydrocortisone.

Adverse events were coded centrally according to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. Serious adverse events included those that required hospitalisation, were life-threatening, or resulted in persistent, permanent, or substantial disability or incapacity. Causality was graded according to the Good Clinical Practice framework guidelines as not related, unlikely, possibly, probably, or definitely related to treatment by the local research sites.[15]

Statistical analysis

At cohort inception, sample size was based on the design of a genetic study aimed at identifying a genetic predictor of primary non-response, the results of which will be reported elsewhere. Assuming that 20% of patients would have a primary non-response, and assuming a perfectly tagged risk allele frequency of 25%, we calculated, using Purcell's genetic power calcul-ator, that we needed to recruit 240 non-responders to yield 99% power to detect a genome-wide significant association ($p<5 \times 10^{-8}$) for a relative risk of 2, and 30% power for a relative risk of 1·5. We anticipated that the proportion of patients lost due to attrition would be 20%, so our recruitment target was 1600 patients.

In February, 2015, the infliximab biosimilar CT-P13 became available in the UK. We calculated that a sample size of 180 biosimilar-treated patients would permit a comparison of non-inferiority of biosimilar and originator infliximab based on a power of 80%, our observation that 25% of patients had a primary non-response, a non-inferiority margin of 10%, attrition rate of 20%, and a ratio of biosimilar-treated to originator infliximab-treated patients of 1:4.[12]

Following central monitoring, we identified three groups of patients who we subsequently excluded from the effectiveness analyses: patients with stomas because the HBI and sPCDAI are not validated for this patient group; patients that were recruited into the study with normal calprotectin and CRP concentrations at prescreening and during the first visit; and patients for whom the only indication for anti-TNF treatment was perianal disease. However, we included these patients in our immuno-genicity and safety analyses, because they had received one of the drugs.

Because of differences in drug formulation, route of delivery, dosing interval, and potential for inducing immune response, infliximab and adalimumab treatment outcomes were analysed separately.[16] Outcomes were assigned using an algorithm written in R version 3.5.1. All analyses were two-tailed, and p values of less than 0·05 were considered significant.

Patients who exited the study because of treatment failure were deemed to be in non-remission for every subsequent timepoint. Patients who exited the study because of loss to follow-up, patient withdrawal of consent, or elective withdrawal of drug by their physician, including for pregnancy, were censored at the time of study exit and were excluded from the denominator for subsequent analyses.

We did univariable analyses using Fisher's exact and Mann-Whitney *U* tests to identify differences in baseline characteristics between infliximab-treated and adalimumab-treated patients, and to determine categori-cal and continuous factors associated with predefined outcomes. We used multivariable logistic regression analyses to identify which factors were independently associated with treatment failure. We included variables with a univariable p value of less than 0·05 in the model and used the Akaike information criterion (AIC) and backward stepwise variable selection. We also built predictive models, using forwards and backwards stepwise model selection starting from the null model (ie, with no covariates, just an intercept term), with AIC. We used leave-one-out cross-validation to test the model, firstly to ensure the model was not overfitted, and secondly to estimate the diagnostic accuracy of the model. For prediction testing, a probability threshold was deter-mined by maximising the sum of sensitivity and specificity.

We explored associations with trough drug con-centration using linear regression, using the same variable selection methods as those detailed for the logistic regression analyses. Proportions of patients with immuno-genicity and loss or response were estimated using the Kaplan-Meier method, and com-parative analyses were done by the use of univariable and multivariable Cox proportional hazards regression. For immunogenicity, patients were censored after their last drug and antibody measurement or at week 54. For loss of response, patients were censored if they exited for reasons other than treatment failure or at week 54.

Optimal thresholds for drug concentrations were determined graphically by plotting outcome against intervals of drug concentration and looking for the threshold beyond which further increases were not associated with improvement in outcome.

Non-inferiority for biosimilar infliximab was assessed by determining whether the one-sided 95% CI of the absolute difference in proportions was 10% or more. The confidence interval was calculated using the prop.test function in R software.

This study was registered with ClinicalTrials.gov, number NCT03088449.

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final res-ponsibility for the decision to submit for publication.

Results

Between March 7, 2013, and July 15, 2016, 1610 patients were included in this prospective study; 955 (59%) patients were treated with infliximab (753 [47%] with originator infliximab, and 202 [13%] with biosimilar) and 655 (41%) were treated with adalimumab (figure 1). Differences between demographic and clinical characteristics of infliximab-treated and adalimumab-treated patients are shown in table 1 and the appendix (pp 34–35).

Several baseline characteristics were significantly different between the infliximab-treated and adalimumab-treated patients, including age, smoking, body-mass index, disease duration, disease location, and disease behaviour. Patients treated with infliximab had more active disease at baseline than did patients treated with adalimumab, as evidenced by higher serum CRP and faecal calprotectin concentra-tions (table 1). Most differences persisted when the 219 paediatric patients (aged <18 years at time of first dose) were excluded, almost all of whom were treated with infliximab (appendix p 34). At initiation of anti-TNF treatment, immunomodulator use was higher in patients treated with infliximab than those treated with adalimumab (589 [62%] of 955 *vs* 344 [53%] of 655; p<0·0001), but no differences were seen in the proportions of patients treated with corticosteroids (table 1).

1241 patients were assessable at week 14. Primary non-response occurred in 170 (21·9%, 95% CI 19·1–25·0) of 775 patients treated with infliximab and 125 (26·8%, 22·9–31·1) of 466 patients treated with adalimumab (table 2). After excluding primary non-responders, the estimated proportion of infliximab-treated patients who had loss of response by week 54 was 36·9% (32·7–40·9), and for adalimumab was 34·1% (28·4–39·4; appendix pp 15–16). At week 54, 469 (60·9%; 57·4–64·0) of 770 infliximab-treated patients were classified as being in non-remission, compared with 295 (66·9%; 62·3–71·3) of 441 adalimumab-treated patients (table 2).

Univariable analyses showed the strongest associ-ations with primary non-response to infliximab and adalimumab were with week 14 drug and anti-drug antibody concentrations (table 3; appendix p 17). Primary non-response to infliximab was also associated with older age at first dose, smoking at baseline, non-use of an immunomodulator at baseline, lower baseline albumin concentrations, and higher baseline white cell count. Primary non-response to adalimumab was associated with a higher body-mass index at baseline.

Univariable analysis showed, for both drugs, that the most significant determinant of non-remission at week 54 was clinical status at week 14 (table 4; appendix pp 21–22). Despite meeting primary non-response criteria, 76 (44·7%, 95% CI 37·1–52·5) of 170 infliximab-treated patients and 61 (48·8%, 39·8–57·9) of 125 adalimumab-treated patients continued drug beyond week 20. Of these, only ten (14·9%, 7·4–25·7) of 67 patients treated with infliximab (data for nine patients continuing infliximab after primary non-response not available) and four (8·7%, 2·4–20·8) of 46 patients treated with adalimumab (data for 15 patients continuing adalimumab after primary non-response not available) were in remission at week 54 (14 [12·4%, 95% CI 6·9–19·9] of 113 patients overall). Body-mass index, baseline smoking status, week 14 drug con-centration, week 14 antibody concentration, and immunogenicity in first year were also associated with non-remission at week 54 for both drugs. In addition, among patients treated with infliximab, but not those treated with adalimumab, non-remission at week 54 was associated with older age, female sex, non-use of an immuno-modulator at baseline, and higher baseline white cell count.

Multivariable analyses showed that, for both drugs, only week 14 drug concentration was independently associated with primary non-response (table 5). A dose–response association was seen for week 14 drug concentration and remission up to 7 mg/L for infliximab and 12 mg/L for adalimumab (appendix p 18). In infliximab-treated pa-tients for whom we measured drug concentrations at week 6, a dose–response association was seen between week 6 drug concentrations up to 30–35 mg/L and increasing week 14 remission (appendix p 19). Our predictive models of primary non-response to infliximab and adalimumab, however, were not clinically useful (appendix pp 20, 37). For infliximab, the area under the curve (AUC) was 0·53 (95% CI 0·46–0·59) with a sensitivity of 0·35, specificity of 0·75, positive predictive value of 0·27, and negative predictive value of 0·81, whereas for adalimumab the AUC was 0·54 (0·46–0·62) with a sensitivity of 0·35, specificity of 0·95, positive predictive value of 0·56, and negative predictive value of 07·8.

Among patients who continued treatment beyond week 14, multivariable analyses (table 5) showed, inde-p-endent associations between drug concentrations at week 14 and non-remission at week 54 for both drugs. The optimal drug concentration at week 14 that was associated with remission at week 54 was 7 mg/L for infliximab and 12 mg/L for adalimumab (appendix p 18). Obesity at baseline was associated with non-remission at week 54 only in patients treated with adalimumab. Smoking at baseline and no previous history of perianal disease were associated with poorer outcomes at week 54 for both drugs on univariable analyses, but only for adalimumab on multivariable analyses (data not shown for infliximab because smoking at baseline dropped out of the model during backwards stepwise regression).

We devised two diagnostic models informed by significant uni-variable factors to predict non-remission to infliximab and adalimumab at week 54. Our first model attempted to predict non-remission using baseline variables only and had low diagnostic value. Our second model using baseline variables and week 14 pharmacokinetic data had greater predictive power: for infliximab, the AUC was 0·814 (95% CI 0·76–08·7) and for adalimumab 0·75 (0·68–08·3; appendix pp 20, 39–41).

Serious adverse events, excluding worsening of Crohn's disease activity, were observed in 171 (17·9%, 95% CI 15·5–20·5) of 955 infliximab-treated patients and 96 (14·7%, 12·0–17·6) of 655 adalimumab-treated patients. Adverse events leading to treatment withdrawal occurred in 84 (8·8%, 7·1–10·8) of 955 patients treated with infliximab and 42 (6·4%, 4·7–8·6) of 655 patients treated with adalimumab (appendix p 42).

Five patients died (three treated with infliximab and two with adalimumab), all of whom were in the upper quartile for age. None of those who died had responded to treatment by the time of death: four died from sepsis (two from pneumonia, two from intra-abdominal sepsis), and one of Crohn's disease-related malnutrition. Four of the five patients were taking concomitant corticosteroids at the time of death and one was taking azathioprine.

Serious infections were reported in 38 (4·0%, 95% CI 2·8–5·4) of 955 infliximab-treated patients, includ-ing active tuberculosis in three patients, and 21 (3·2%, 2·0–4·9) of 655 adalimumab-treated patients, none of whom had tuberculosis (appendix p 42). Concomitant immunomodulatory therapy was not associated with an increased risk of infections, even when stratified by age (appendix p 43).

Infusion reactions within 24 h of infliximab, which occurred after a median of 5 weeks (IQR 1–14) of starting treatment, were observed in 31 (3·2%, 95% CI 2·3–4·6) of 955 patients (appendix p 42) and were associated with anti-drug antibody titre (median peak antibody 96 arbitrary units per mL [IQR 5–313] in patients with an infusion reaction *vs* 8 arbitrary units per mL [5–45] in patients without an infusion reaction; p=0·0037). Injection site reactions to adalimumab, which occurred after a median of 14 weeks (IQR 3·5–27·2), were observed in 28 (4·3% [95% CI 2·9–6·2]) of 655 patients (appendix p 42) but were not associated with immuno-genicity (p=0·58).

Univariable factors associated with low drug con-centrations at weeks 14 and 54 are shown in the appendix (pp 23, 24, 44, 45). In multivariable analyses, for both drugs, low drug concentrations at both week 14 and week 54 were significantly associated with week 14 anti-drug antibody formation and markers of active disease (table 5). Lower albumin concentrations at week 14 were independently associated with week 14 drug concentration for infliximab, whereas obesity at baseline was in-dependently associated with week 14 and week 54 drug concentrations for adalimumab. In patients treated with infliximab but not those treated with adalimumab, use of an immunomodulator at baseline was associated with higher week 54 drug concentrations (table 5).

The estimated proportion of patients with immuno-genicity by week 54 was 62·8% (95% CI 59·0–66·3) for infliximab-treated patients and 28·5% (24·0–32·7) for adalimumab-treated patients (appendix p 25). 31·2% (95% CI 27·6–34·6) of patients treated with infliximab, and 12·3% (8·9–15·6) of those treated with adalim-umab had anti-drug antibody concentrations of 10 arbitrary units per mL or more and undetectable drug concentrations at week 54 (appendix p 27).

Among infliximab-treated patients for whom early anti-drug antibody concentrations were available, the Kaplan-Meier estimate of anti-drug antibody positivity was 1·6% (95% CI 0·8–2·4) at 2 weeks, 3·3% (2·2–4·5) at 6 weeks, and 17·2% (14·6–19·7) at 14 weeks.

The univariable factors associated with time to immunogenicity are shown in figure 2 and the appendix (p 46), respectively. Multivariable analyses showed that drug concentration at week 14 was the major independent risk factor associated with time to immunogenicity for both drugs after that timepoint. In addition, time to immunogenicity was associated with obesity for adalimumab-treated patients and smoking for infliximab-treated patients (figure 2, table 5).

Immunomodulator use was the main protective factor against immunogenicity, with similar effect sizes for infliximab (hazard ratio [HR] 0·39 [95% CI 0·32–0·46], p<0.0001) and adalimumab (HR 0·44 [0·31–0·64], p<0.0001) (appendix p 46). No difference was measured in time to immunogeni-city between thiopurine medications or methotrexate (appendix pp 29–30). Thiopurines reduced immuno-genicity to infliximab in a dose-dependent manner with the lowest immunogenicity observed in patients treated with the highest thiopurine doses (appendix p 31).

Sensitivity analyses exploring the effect of combination immunomodulator use on clinical outcomes showed that immunomodulator use was associated with a lower proportion of infliximab-treated patients in non-remission at week 54 than was monotherapy (combin-ation 52·6% [95% CI 47·9–57·1] *vs* monotherapy 74·0% [68·6–78·9]), but this association was not seen in adalimumab-treated patients (64·2% [57·6–70·4] *vs* 69·8% [63·1–75·9]). Further sensitivity analyses of infliximab-treated patients, limited to the modifiable factors of immunomodulator use and drug and anti-drug antibody concentrations, showed that the benefit of immuno-modulators (odds ratio [OR] 0·56 [95% CI 0·38–0·83]) was independent of $\log_{10}$ drug concentra-tion (0·30 [0·18–0·49]) or $\log_{10}$ anti-drug antibody concentration (1·61 [1·02–2·63]) status at week 14 (appendix p 47).

No differences were measured in baseline demographic or clinical characteristics between patients treated with biosimilar and originator infliximab (appendix p 48). Of 955 patients treated with originator infliximab, 79 (8%) changed to biosimilar during the first year of treatment and were excluded from analyses comparing originator and biosimilar infliximab after the switch date. At week 14, biosimilar was non-inferior to originator infliximab for primary non-response (difference in proportions –3·9% [one-sided 95% CI upper bound 2·4]). At week 54, biosimilar was non-inferior to originator infliximab for non-remission (–2·2% [one-sided 95% CI upper bound 5·6]; appendix p 32). Among patients who

started on originator infliximab and did not switch during the first year, 64 (9%) of 674 exited the study because of adverse events; among patients treated with biosimilar infliximab, 16 (8%) of 202 exited for adverse events (one-sided 95% CI upper bound of difference 5·5%). The estimated proportion of patients with immunogenicity by week 54 was 62·1% (95% CI 57·4–66·2) for patients treated with originator infliximab and 64·5% (55·4–71·7) for patients treated with biosimilar infliximab (appendix p 25). 31·3% (27·0–35·4) of patients treated with originator infliximab and 33·5% (25·0–41·0) of those treated with biosimilar had anti-drug antibody concentrations of 10 arbitrary units per mL or more and undetectable drug con-centrations at week 54 (appendix p 27).

Discussion

Our cohort study of 1610 anti-TNF-naive patients with active luminal Crohn's disease showed that primary non-response occurred in 24% and non-remission in 63% of patients, and that adverse events curtailed treatment in 8% of patients. Obesity, smoking, low albumin concentra-tions, higher baseline markers of disease activity, and develop-ment of immunogenicity were all associated with low drug concentrations, which mediated non-remission.

Numerous studies have reported an association between drug concentration and clinical outcome, although the therapeutic thresholds, particularly for adalimumab, are poorly defined.[17] In our study, low drug concentrations during induction were associated with primary non-response at week 14 and non-remission at week 54. Patients with primary non-response who continued standard dosing regimens rarely entered remission. Dose intensification might improve outcomes for patients with suboptimal drug concentrations at week 14, whereas an early switch out-of-class might be more appropriate for patients with optimal drug concentrations. Despite variation in drug concentration among patients in remission, our data suggest that a higher target drug concentration might be required during induction than those reported in previous studies,[18] probably reflecting our more stringent definition of remission. The optimal week 14 drug concentrations associated with remission at both week 14 and 54 were 7 mg/L for infliximab and 12 mg/L for adalimumab. The importance of drug concentration is further shown by our predictive models, which were only clinically useful when week 14 pharmacokinetic data were included.

Previous prospective randomised studies of proactive dose increases based on drug concentrations did not show improved clinical outcomes. For both the TAXIT[19] and TAILORIX[20] studies, this absence of improvement might in part be explained by inclusion of patients after the crucial induction period and use of infliximab thresholds of 3 mg/L. Further adequately powered clinical trials are required to investigate whether optimising drug concentra-tion on a treat-to-target basis during the induction period improves outcomes.[21]

Using analytical platforms that differed only by target antibody, we have shown that immunogenicity is more common in patients treated with infliximab than adalimumab: an observation frequently attributed to the chimeric formulation of infliximab. For both drugs, however, we observed a bidirectional negative relation-ship between drug concentration and immunogenicity. The lowest drug concentrations were measured in patients with high titre anti-drug antibody concentrations, in keeping with the known effect of the antibodies on drug clearance. Conversely, low drug concentrations at week 14 were associated with an increased risk of immunogenicity by week 54. This association is con-sistent with the discontinuity theory of the immune response, which proposes that intermittent exposure to antigen promotes a persistent immune reaction, whereas exposure at constant concentrations, observed with adalimumab delivered subcutaneously every 2 weeks, induces an immune tolerance.[22] Immuno-genicity, which we have shown might occur earlier than previously suggested by other studies, might be mitigated by early dose optimisation, minimising loss of response.[23] We accept, however, that this observation might be explained by the formation of anti-drug antibodies at concentra-tions sufficient to lower the drug concentration but not detectable by our assay.

Immunomodulator use was associated with lower immunogenicity to both drugs and higher drug con-centrations for infliximab-treated patients com-pared with no immunomodulator use. Methotrexate exerted a similar effect to thiopurine drugs on immuno-genicity. In contrast to previous reports,[24,25] we showed that thiopurines reduced immunogenicity in infliximab-treated patients in a dose-dependent manner without an obvious threshold effect. Post-hoc analyses of the SONIC study suggested that the primary benefit of azathioprine was on pharmacokinetics of infliximab.[26] Conversely, in our study, we showed that concomitant immunomodulator use in infliximab-treated patients was associated with higher week 54 remission compared with no immuno-modulator use, independently of week 54 drug concentration or immuno-genicity status, suggest-ing that the addition of immunosuppression to anti-TNF therapy might have additional benefits. Consistent with previous studies,[27] immunomodulator use was not associated with increased remission for adalimumab treatment; however, this finding might have been in-fluenced by low rates of immunogenicity, short duration of follow-up, or both.

We have shown that obesity is independently associated with low drug concentrations and non-remission at week 54 for adalimumab. Our data suggest that the previously reported associations of obesity and primary non-response are likely to be mediated by low drug concentrations.[28] For adalimumab-treated patients, fixed dosing was probably a major contributing factor. Obesity was also associated with immunogenicity to adalimumab; further clinical trials of dose optimisation are needed to clarify if this finding was because of suboptimal dosing during in-duction or whether obesity contributes to immuno-genicity directly.

Our observation that cigarette smoking was inde-pendently associated with an increased risk of immuno-genicity to infliximab might explain the poorer, less dur-able anti-TNF response reported in patients with Crohn's disease who smoke than in non-smokers.[29]

Previous studies investigating the association between baseline markers of inflammation and anti-TNF response are conflicting.[2,30] In our study, higher baseline markers of inflammation predicted lower drug concentrations at week 14, suggesting that higher inflammatory load might contribute to faster drug elimi-nation. We have shown that lower baseline albumin concentrations predict sub-optimal week 14 infliximab concentrations, similarly to other studies.[31] This association might reflect increased drug clearance as well as higher faecal protein losses.

Data from a nationwide population-based study sug-gest that benefits of anti-TNF and immunomodulatory com-bination treatment need to be considered against the additional risks of serious and opportunistic infection.[32] In this study, while acknowledging our smaller sample size and shorter duration of follow-up, combination therapy was not associated with an increased risk of infection in the first year of treatment, even among older patients (>50 years). However, sepsis was the cause of death in four of the five patients who died in the first year: all were older than 50 years, all but one was prescribed concomitant corticosteroids, and none had responded to anti-TNF.

Our study had some limitations. We used pragmatic definitions of treatment ineffectiveness combining cortico-steroid use with clinical and biochemical mark-ers of disease activity that are closely aligned with routine treatment targets. Although we accept that our data would have been strengthened by endoscopic outcomes, we observed a significant association between clinical outcomes at weeks 14 and week 54 and faecal calprotectin (appendix p 33). We are likely to have underestimated the rate of loss of response because our definition required an increase in therapy that was not always initiated. In addition, we used a pragmatic schedule of visits to mini-mise inconvenience to patients, and fewer

assess-ments were undertaken for adalimumab-treated than infliximab-treated patients. We acknowledge that because CRP is elevated in obesity we might have overestimated the effect of body-mass index on treatment ineffectiveness. Finally, we did not do real-time monitoring; therefore, the proportion of missing data is higher in this study than in registration trials.[6–8]

To our knowledge, this study is the largest prospective study of anti-TNF therapy in inflammatory bowel disease. We have shown that the major modifiable factors associated with treatment ineffectiveness were low drug concentrations and immunogenicity. Con-comitant im-muno-modulator use and dose intensification in at-risk individuals during induction might improve the effective-ness and durability of treatment. Reassuringly, treatment ineffectiveness, safety, and immunogenicity of origina-tor infliximab are no different to the biosimilar, which removes some of the cost constraints of dose intensi-fication. Further clinical trials are required to better understand whether these strategies can allow us to improve the effectiveness and durability of anti-TNF therapy.

Contributors

TA, CB, GAH, JRFC, ALH, MP, JCM, PMI, JL, RKR, and CWL participated in the conception and design of this study. CB was the project manager and coordinated patient recruitment. TJM, MHP, and RN coordinated all biochemical analysis and central laboratory aspects of the project. NAK, JRG, TA, GAH, JRFC, CPS, CWL, ALH, MP, SS, JCM, PMI, JL, RKR, PH, NMH, DM, AT, GJW, NC, SL, SB, and DRG were involved in the acquisition, analysis, or interpretation of data. Data analysis was done by NAK, GAH, HDG, and BH. Drafting of the manuscript was done by TA, JRG, NAK, DM, GAH, TM, CB, NC, and SL. TA obtained the funding for the study. All the authors contributed to the critical review and final approval of the manuscript.

Declaration of Interests

NAK declares personal fees from Falk, Takeda, and Pharmacosmos; other fees from Janssen; and non-financial support from Janssen, AbbVie, and Celltrion outside the submitted work. GAH reports non-financial support from AbbVie, outside the submitted work, and is now an employee of AbbVie and owns stock in the company. GJW reports grants from Crohn's Colitis UK; and personal fees from AbbVie, Janssen, Tillotts, and Falk, outside the submitted work. AH has served as consultant, advisory board member, or speaker for AbbVie, Atlantic, Bristol-Myers Squibb, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire, and Takeda; and also serves on the Global Steering Committee for Genentech, all outside the submitted work. SS reports personal fees from AbbVie, Merck, and Takeda; and grants from Takeda, Tillotts, AbbVie, and Merck, outside the submitted work. PMI reports personal fees from AbbVie, Janssen, Pfizer, Sandoz, VH squared, Samsung Bioepis, and Ferring; grants from MSD; grants and personal fees from Takeda; and non-financial support from Falk, outside the submitted work. DM reports grants from the US National Institutes of Health and Helmsley Charitable Trust, during this study; and grants and personal fees from Janssen, Precision IBD Inc, Second Genome, Qu Biologics, Pfizer, Gilead, and Takeda, outside the submitted work. CWL reports grants and personal fees from AbbVie, GlaxoSmithKline, Janssen, Takeda, Amgen, Pfizer, Samsung Bioepis, and Cellgene; and grants and personal fees from Gilead, outside the submitted work. JRFC reports personal fees from AbbVie, Janssen, MSD, Celltrion, Napp Pharmaceuticals, and Sandoz; and grants and personal fees from Takeda, Biogen, and Hospira, outside the submitted work. CPS received grants from Warner Chilcott and Abbvie; has provided consultancy to Warner Chilcott, Dr Falk, AbbVie, Takeda, and Janssen; and had speaker arrangements with Warner Chilcott, Dr Falk, AbbVie, MSD, and Takeda. JL has served as advisory board member for Atlantic Health, AbbVie, MSD, Shire, Ferring International, Celltrion, Takeda, Pfizer, Janssen, GlaxoSmithKline; has served as a consultant for AbbVie UK, Takeda, Bristol-Myers Squibb; has received grants from Takeda, Hospira (Pfizer), AbbVie, Global, Ferring, MSD, Allergen, Shire, Cornerstone US, and Janssen; fees for educational presentations from AbbVie International and Cornerstone UK; travel and accommodation expenses from AbbVie, Warner Chilcot UK, and Takeda; and has received travel support from AbbVie, Warner Chilcot, Takeda, and Pfizer, outside the submitted work. RKR reports honoraria from Abbvie, Ferring, Therakos, and Celltrion; and grants from Nestec, outside the submitted work. JRG received honoraria from Falk, AbbVie, and Shield therapeutics, outside the submitted work for unrelated topics. TA reports grants from AbbVie, MSD, Napp Pharmaceuticals, Celltrion, Pfizer, Janssen, and Celgene during this study; personal fees and non-financial support from Immunodiagnostik; personal fees and non-financial support from Napp Pharmaceuticals, AbbVie, and MSD; personal fees from Celltrion and Pfizer; grants and personal fees from Takeda; and grants and non-financial support from Tillotts, outside the submitted work. All other authors declare no competing interests.

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References

1 Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology* 2005; **128:** 862–69.

2 Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010; **362:** 1383–95.

3 D'haens G, Van Deventer S, Van Hogezand R, et al. Endoscopic and histological healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: a European multicenter trial. *Gastroenterology* 1999; **116:** 1029–34.

4 Louis E, Löfberg R, Reinisch W, et al. Adalimumab improves patient-reported outcomes and reduces indirect costs in patients with moderate to severe Crohn's disease: results from the CARE trial. *J Crohns Colitis* 2013; **7:** 34–43.

5 Loftus E V, Feagan BG, Colombel J-F, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol* 2008; **103:** 3132–41.

6 Rutgeerts P, D'Haens G, Targan S, et al. Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; **117:** 761–69.

7 Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130:** 323–33.

8 Colombel J-F, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132:** 52–65.

9 Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther* 2011; **33:** 987–95.

10 Sprakes MB, Ford AC, Warren L, Greer D, Hamlin J. Efficacy, tolerability, and predictors of response to infliximab therapy for Crohn's disease: a large single centre experience. *J Crohns Colitis* 2012; **6:** 143–53.

11 Naviglio S, Giuffrida P, Stocco G, et al. How to predict response to anti-tumour necrosis factor agents in inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol* 2018; **12:** 797–810.

12 Chow S-C, Shao J, Wang H. Sample size calculations in clinical research. New York, NY: Marcel Dekker, 2003.

13 Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980; **1:** 514.

14 Kappelman MD, Crandall W V, Colletti RB, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. *Inflamm Bowel Dis* 2011; **17:** 112–17.

15 WHO. The use of the WHO-UMC system for standardised case causality assessment-1-The use of the WHO-UMC system for standardised case causality assessment. https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf (accessed Dec 18, 2018).

16 Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet* 2017; **389:** 1710–18.

17 Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel diseases. *Gastroenterology* 2017; **153:** 835–57.e6.

18 Cornillie F, Hanauer SB, Diamond RH, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. *Gut* 2014; **63:** 1721–27.

19 Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015; **148:** 1320–29.e3.

20 D'Haens G, Vermeire S, Lambrecht G, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. *Gastroenterology* 2018; **154:** 1343–51.e1.

21 Van Stappen T, Bollen L, Vande Casteele N, et al. Rapid test for infliximab drug concentration allows immediate dose adaptation. *Clin Transl Gastroenterol* 2016; **7:** e206.

22 Pradeu T, Jaeger S, Vivier E. The speed of change: towards a discontinuity theory of immunity? *Nat Rev Immunol* 2013; **13:** 764–69.

23 Ungar B, Engel T, Yablecovitch D, et al. Prospective observational evaluation of time-dependency of adalimumab immunogenicity and drug concentrations: the Poetic study. *Am J Gastroenterol* 2018; **113:** 890–98.

24 Yarur AJ, Kubiliun MJ, Czul F, et al. Concentrations of 6-thioguanine nucleotide correlate with trough levels of infliximab in patients with inflammatory bowel disease on combination therapy. *Clin Gastroenterol Hepatol* 2015; **13:** 1118–24.e3.

25 Roblin X, Boschetti G, Williet N, et al. Azathioprine dose reduction in inflammatory bowel disease patients on combination therapy: an open-label, prospective and randomised clinical trial. *Aliment Pharmacol Ther* 2017; **46:** 142–49.

26 Colombel J-F, Reinisch W, Mantzaris GJ, et al. Randomised clinical trial: deep remission in biologic and immunomodulator naïve patients with Crohn's disease—a SONIC post hoc analysis. *Aliment Pharmacol Ther* 2015; **41:** 734–46.

27 Chalhoub JM, Rimmani HH, Gumaste VV, Sharara AI. Systematic review and meta-analysis: adalimumab monotherapy versus combination therapy with immunomodulators for induction and maintenance of remission and response in patients with Crohn's disease. *Inflamm Bowel Dis* 2017; **23:** 1316–27.

28 Singh S, Facciorusso A, Singh AG, et al. Obesity and response to anti-tumor necrosis factor-α agents in patients with select immune-mediated inflammatory diseases: a systematic review and meta-analysis. *PLoS One* 2018; **13:** e0195123.

29 Juillerat P, Sokol H, Froehlich F, et al. Factors associated with durable response to infliximab in Crohn's disease 5 years and beyond: a multicenter international cohort. *Inflamm Bowel Dis* 2015; **21:** 60–70.

30 Magro F, Rodrigues-Pinto E, Santos-Antunes J, et al. High C-reactive protein in Crohn's disease patients predicts nonresponse to infliximab treatment. *J Crohns Colitis* 2014; **8:** 129–36.

31 Fasanmade AA, Adedokun OJ, Olson A, Strauss R, Davis HM. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. *Int J Clin Pharmacol Ther* 2010; **48**: 297–308.

32 Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018; **155:** 337–46.e10.