Mechanisms and management of loss of response to anti-TNF therapy for patients with Crohn's disease: 3-year data from the prospective, multicentre PANTS cohort study

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Summary

Background We sought to report the effectiveness of infliximab and adalimumab over the first 3 years of treatment and to define the factors that predict anti-TNF treatment failure and the strategies that prevent or mitigate loss of response.

Methods Personalised Anti-TNF therapy in Crohn's disease (PANTS) is a UK-wide, multicentre, prospective observational cohort study reporting the rates of effectiveness of infliximab and adalimumab in anti-TNF-naive patients with active luminal Crohn's disease aged 6 years and older. At the end of the first year, sites were invited to enrol participants still receiving study drug into the 2-year PANTS-extension study. We estimated rates of remission across the whole cohort at the end of years 1, 2, and 3 of the study using a modified survival technique with permutation testing. Multivariable regression and survival analyses were used to identify factors associated with loss of response in patients who had initially responded to anti-TNF therapy and with immunogenicity. Loss of response was defined in patients who initially responded to anti-TNF therapy at the end of induction and who subsequently developed symptomatic activity that warranted an escalation of steroid, immunomodulatory, or anti-TNF therapy, resectional surgery, or exit from study due to treatment failure. This study was registered with ClinicalTrials.gov, NCT03088449, and is now complete.

Findings Between March 19, 2014, and Sept 21, 2017, 389 (41%) of 955 patients treated with infliximab and 209 (32%) of 655 treated with adalimumab in the PANTS study entered the PANTS-extension study (median age 32·5 years [IQR 22·1–46·8], 307 [51%] of 598 were female, and 291 [49%] were male). The estimated proportion of patients in remission at the end of years 1, 2, and 3 were, for infliximab 40·2% (95% CI 36·7–43·7), 34·4% (29·9–39·0), and 34·7% (29·8–39·5), and for adalimumab 35·9% (95% CI 31·2–40·5), 32·9% (26·8–39·2), and 28·9% (21·9–36·3), respectively. Optimal drug concentrations at week 14 to predict remission at any later timepoints were 6·1–10·0 mg/L for infliximab and 10·1–12·0 mg/L for adalimumab. After excluding patients who had primary non-response, the estimated proportions of patients who had loss of response by years 1, 2, and 3 were, for infliximab 34·4% (95% CI 30·4–38·2), 54·5% (49·4–59·0), and 60·0% (54·1–65·2), and for adalimumab 32·1% (26·7–37·1), 47·2% (40·2–53·4), and 68·4% (50·9–79·7), respectively. In multivariable analysis, loss of response at year 2 and 3 for patients treated with infliximab and adalimumab was predicted by low anti-TNF drug concentrations at week 14 (infliximab: hazard ratio [HR] for each ten-fold increase in drug concentration 0·45 [95% CI 0·30–0·67], adalimumab: 0·39 [0·22–0·70]). For patients treated with infliximab, loss of response was also associated with female sex (*vs* male sex; HR 1·47 [95% CI 1·11–1·95]), obesity (*vs* not obese 1·62 [1·08–2·42]), baseline white cell count (1·06 [1·02–1·11] per 1×10^9 increase in cells per L), and thiopurine dose quartile. Among patients treated with adalimumab, carriage of the *HLA-DQA1*05* risk variant was associated with loss of response (HR 1·95 [95% CI 1·17–3·25]). By the end of year 3, the estimated proportion of patients who developed anti-drug antibodies associated with undetectable drug concentrations was 44·0% (95% CI 38·1–49·4) among patients treated with infliximab and 20·3% (13·8–26·2) among those treated with adalimumab. The development of anti-drug antibodies associated with undetectable drug concentrations was significantly associated with treatment without concomitant immunomodulator use for both groups (HR for immunomodulator use: infliximab 0·40 [95% CI 0·31–0·52], adalimumab 0·42 [95% CI 0·24–0·75]), and with carriage of *HLA-DQA1*05* risk variant for infliximab (HR for carriage of risk variant: infliximab 1·46 [1·13–1·88]) but not for adalimumab (HR 1·60 [0·92–2·77]). Concomitant use of an immunomodulator before or on the day of starting infliximab was associated with increased time without the development of anti-drug antibodies associated with undetectable drug concentrations compared with use of infliximab alone (HR 2·87 [95% CI 2·20–3·74]) or introduction of an immunomodulator after anti-TNF initiation (1·70 [1·11–2·59]). In years 2 and 3, 16 (4%) of 389 patients treated with infliximab and 11 (5%) of 209 treated with adalimumab had adverse events leading to treatment withdrawal. Nine (2%) patients treated with infliximab and two (1%) of those treated with adalimumab had serious infections in years 2 and 3.

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Interpretation Only around a third of patients with active luminal Crohn's disease treated with an anti-TNF drug were in remission at the end of 3 years of treatment. Low drug concentrations at the end of the induction period predict loss of response by year 3 of treatment, suggesting higher drug concentrations during the first year of treatment, particularly during induction, might lead to better long-term outcomes. Anti-drug antibodies associated with undetectable drug concentrations of infliximab, but not adalimumab, can be predicted by carriage of *HLA-DQA1*05* and mitigated by concomitant immunomodulator use for both drugs.

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Introduction

Anti-TNF treatment failure is common, with a quarter of patients having primary non-response and a third of initial responders losing response by the end of the first year. In the first year of the Personalising Anti-TNF therapy in Crohn's disease (PANTS) study, we observed a complex multi-directional relationship between disease activity, anti-TNF drug concentrations, and the development of anti-drug antibodies (appendix p 14).[1] Individuals with the most active disease had the

See Online for appendix

Research in context

Evidence before this study

The patient, disease, and pharmacokinetic factors implicated in anti-TNF treatment failure and loss of response remain poorly elucidated, in particular over the longer term. Findings from the first year of the Personalising Anti-TNF therapy in Crohn's disease (PANTS) study were published in 2019; in this study, we found that anti-TNF treatment failure is common in the first year of treatment and is predicted by low drug concentrations, mediated in part by immunogenicity. In a separate genome wide association study, we found that carriage of the *HLA-DQA1*05* haplotype was associated with a doubling in immunogenicity to infliximab and adalimumab therapies. We conducted a comprehensive, updated search of PubMed for publications from database inception to Dec 21, 2023, using the terms "Crohn's disease" AND "antitumor necrosis factor" OR "anti-tumour necrosis factor" OR "infliximab" OR "adalimumab" OR "anti TNF" OR "anti-TNF" OR "anti-tumour necrosis factor" AND "clinical response" OR "efficacy" OR "treatment failure" OR " loss of response" OR "immunogenicity". We did not identify any prospective cohorts of patients with inflammatory bowel disease (IBD) newly initiating anti-TNF therapy for whom data, including drug and anti-drug antibody concentrations, were systematically collected long term. We aimed to report the effectiveness of infliximab and adalimumab up to 3 years of treatment, the factors associated with anti-TNF treatment failure, and the effective strategies to prevent and mitigate loss of response.

Added value of this study

To our knowledge, the PANTS-extension study is the largest and longest prospective study of anti-TNF therapy in IBD to date. Patients were recruited from 120 UK hospitals, reflecting real-life practice in specialist and non-specialist IBD centres. We estimated that only about a third of patients with active luminal Crohn's disease who commenced treatment with an anti-TNF drug at the beginning of the PANTS study were in remission at the end of 3 years of treatment. We estimated that approximately two-thirds of patients enrolled in the PANTS study who initially responded to anti-TNF therapy subsequently lost response, and episodes of loss of response were associated with female sex, low drug concentrations, and the development of anti-drug antibodies associated with undetectable drug concentrations. The development of anti-drug antibodies associated with undetectable drug concentrations was associated with carriage of the *HLA-DQA1*05* risk variant (for infliximab, but not for adalimumab) and treatment without concomitant immunomodulator. In patients treated with infliximab, those who received the highest thiopurine drug quartile were least likely to experience loss of response, and those that started a an immunomodulator before or at the time of starting infliximab were least likely to develop anti-drug antibodies associated with undetectable drug concentrations. Patients treated with infliximab who were dose intensified in the setting of immune-mediated pharmacokinetic failure had low rates of drug persistence thereafter. Compared with year 1, when infusion and injection site reactions were common, adverse events were uncommon in years 2 and 3 of treatment.

Implications of all the available evidence

Our observations support the current practice of dose intensification in the setting of low drug concentrations without immunogenicity. For some patients who develop treatment failure despite adequate infliximab concentrations after dose intensification, our observations suggest targeting even higher drug concentrations to reach remission. In patients in whom immunomodulators are contraindicated or not tolerated, clinicians might decide against the use of anti-TNF drugs, particularly infliximab, in those who carry *HLA-DQA1*05*. Adalimumab monotherapy could be considered in patients who do not carry the risk allele.

highest risk of suboptimal drug blood concentrations and subsequent immunogenicity, leading to drug clearance and treatment failure. Moreover, carriage of the *HLA-DQA1*05* haplotype was associated with a doubling of immunogenicity.[2,3] The major modifiable factor in this disease–drug–immune response relationship was drug concentration.

Data relating to the efficacy of anti-TNF therapies beyond 1 year of treatment are scarce.[4–6] However, these data are increasingly important when weighing up the long-term risks and benefits of multiple new medical and surgical options.[7,8] Observational studies have mostly been from single centres, retrospective in design, and have infrequently reported pharmacokinetic data or explored the use of therapeutic drug monitoring (TDM) in the setting of loss of response.[9,10] Consequently, the factors associated with longer-term anti-TNF treatment failure remain poorly elucidated.

Specialty guidelines recommend strategies to manage loss of response informed by TDM, but data to support these actions are scarce.[11,12] Clinicians stratify loss-of-response episodes on the basis of clinical symptoms, anti-TNF drug concentration, and the development of anti-drug antibodies to adjust anti-TNF dose or frequency, optimise concomitant immunomodulator use, or to inform whether patients should be switched to another targeted therapy.

Here we report data from the 2-year extension to the PANTS study, including the effectiveness of infliximab and adalimumab at 2 and 3 years, factors associated with anti-TNF treatment failure, and suggest effective strategies to prevent and mitigate loss of response.

Methods

Study design and participants

PANTS is a UK-wide, multicentre, prospective, observational, cohort study reporting the rates of treatment failure of the anti-TNF drugs infliximab (originator [Merck Sharp & Dohme, Hertfordshire, UK] and biosimilar CT-P13 [Celltrion Healthcare, Incheon, South Korea]) and adalimumab (AbbVie, Chicago, IL, USA) in Crohn's disease.[1,2,13–15]

Patients were recruited at the time of first anti-TNF exposure from 120 National Health Service (NHS) trusts across the UK between March 7, 2013, and July 15, 2016 (appendix pp 3–13).[1] Patients were evaluated for 12 months or until drug withdrawal. At the end of first year, sites were invited to take part in the PANTS-extension (PANTS-E) study that extended follow-up to 3 years.

Patients were screened for inclusion 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 inclusion criteria were as follows: age 6 years or older; diagnosis of Crohn's disease involving the colon or the small intestine, or both; and active luminal disease supported by a C-reactive protein (CRP) concentration of more than 3 mg/L 90 days before the first dose or 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 contraindication for the use of, anti-TNF therapy. All eligibility criteria are provided in the protocol.

For the **PANTS study protocol** see https://www.ibdresearch.co.uk/pants/

The South West Research Ethics committee approved the study (REC reference: 12/SW/0323) in January, 2013. Patients were included after providing written informed consent. This study was registered with ClinicalTrials.gov, NCT03088449.

Procedures

The choice of anti-TNF drug, infliximab or adalimumab, was at the discretion of the treating physician and prescribed according to the UK licensed dosing schedule (infliximab via intravenous infusion: initially 5 mg/kg at baseline and then at weeks 2, 6, and 14, and then every 8 weeks; adalimumab via subcutaneous injection: adults aged 18 years and older 160 mg at baseline, then 80 mg at week 2, and then 40 mg every 2 weeks, and dosing in children aged 6–17 years was based on bodyweight above or below 40 kg).

Study visits were aligned to infliximab infusion dosing, and scheduled at first dose, post-induction (week 14), and at weeks 30 and 54. In PANTS-E the visits occurred once every 6 months and at treatment failure or exit. Exit occurred when patients stopped anti-TNF therapy or had an intestinal resection. In cases where the visit did not exactly occur on the day delineated by the protocol, the following windows of eligibility were specified: week 0 (week –4 to 0), week 14 (week 10 to 20), week 30 (week 22 to 38), week 54 (week 42 to 66), week 78 (week 66 to 90), week 102 (week 90 to 114), week 126 (week 114 to 138), and week 150 (week 138 to 162; each visit was only allocated to a single window; appendix p 15).

Variables recorded at baseline by sites were demographics (age, self-reported sex and ethnicity, comorbidities, height and bodyweight, and smoking status), Crohn's disease phenotype (age at diagnosis, disease duration, and Montreal classification), previous medical history and previous treatments received for Crohn's disease (drug history and previous Crohn's disease-related surgeries).

Blood samples were collected at every visit and stool samples were collected every 8 weeks. Blood and stool samples were processed through the central laboratory at the Royal Devon University Healthcare NHS Foundation Trust (Exeter, UK) for haemoglobin, white cell count, platelets, serum albumin, CRP, anti-TNF drug and anti-TNF antibody concentrations, and faecal calprotectin. For all patients treated with infliximab, we measured trough drug concentrations.

We used the Immundiagnostik (IDK) AG (Bensheim, Germany) IDKmonitor free infliximab (K9655) and adalimumab (K9657) drug concentration assays, which permit quantitative measurement of a free therapeutic

drug in serum. The assays follow a standard ELISA format using a specific monoclonal anti-drug antibody fragment as a capture antibody and peroxidase-labelled anti-human IgG antibody as a detection antibody. Since our previous publication reporting immunogenicity outcomes to the end of first year of PANTS,[1] the infliximab drug concentration assay has been recalibrated to an international standard. The measuring range for infliximab is now 1·9–45·0 mg/L, with absence of drug defined using a cutoff of less than 1·9 mg/L. For adalimumab, the measuring range remains at 0·8–45·0 mg/L, with absence of drug defined using a cutoff of less than 0·8 mg/L.

We used the IDKmonitor infliximab (K9654) and adalimumab (K9651) total anti-drug antibody assays, which allow semi-quantitative measurement of both free and bound anti-drug antibodies. A pre-treatment acid dissociation step is used to separate anti-drug antibodies from the therapeutic antibody. The assay then follows a standard ELISA format using recombinant therapeutic antibody as a capture and detection antibody. The positivity threshold for anti-infliximab antibodies is 9 AU/mL and for anti-adalimumab antibodies is 6 AU/mL.[13]

As previously reported, DNA was extracted from pretreatment blood samples from individuals in the PANTS cohort and genotyping was undertaken using the Illumina CoreExome microarray (Illumina, San Diego, CA, USA).[2] *HLA* types were imputed at 2-digit and 4-digit resolution for the following loci: *HLA-A*, *HLA-C*, *HLA-B*, *HLA-DRB1*, *HLA-DQA1*, *HLA-DQB1*, and *HLA-DPB1*. Long-read sequencing of these *HLA* alleles was undertaken to assess the accuracy of our imputation.

Results of TDM tests were made available to clinicians in real time once participants had completed 12 months in the study. Management of treatment failure was decided by the treating clinicians and not mandated by TDM results.

Outcomes

Treatment failure endpoints were primary non-response at week 14, non-remission at weeks 54, 102, and 150, and adverse events leading to drug withdrawal. We used composite endpoints using the Harvey Bradshaw Index (HBI) in adults and the short paediatric Crohn's disease activity index (sPCDAI) in children, corticosteroid use, and serum CRP concentration (appendix p 16). For endpoint assessment, children were defined as participants younger than 18 years, and adults as participants aged 18 years or older.

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 concentration 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 (with the same CRP concentration criteria as adults). The term grey zone was used to denote an intermediate response between primary non-response and response, defined as CRP concentration decreasing to 3 mg/L or less or by 50% or more from baseline (week 0), or an 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 concentration 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 concentration of 3 mg/L or less and an HBI score of 4 points or less for adults and a sPCDAI score of 15 points or less for children, no corticosteroid therapy at the study visit, and no exit due to treatment failure. Non-remission was defined as a CRP concentration of more than 3 mg/L or an HBI score of more than 4 points for adults or sPCDAI score of more than 15 points for children, ongoing corticosteroid therapy, or exit due to treatment failure.

Loss of response was defined in patients who initially responded to anti-TNF therapy at the end of induction and who subsequently developed symptomatic activity that warranted an escalation of steroid, immunomodulatory, or anti-TNF therapy, resectional surgery, or exit from study due to treatment failure, which has been defined earlier. Anti-TNF dose intensification was defined as an increase in anti-TNF dose or shortening of the time interval between anti-TNF doses, or both. Timing of loss of response was defined as the time of treatment escalation, drug withdrawal, or surgery. For the purposes of non-remission and primary non-response, we defined corticosteroid therapy as any systemic therapy, either oral or intravenous (including use of steroids for other conditions), but not including single pre-infusion dosing with hydrocortisone. Drug persistence was defined as the length of time from initiation of anti-TNF therapy to discontinuation of therapy.[16]

Adverse events were coded centrally according to the Medical Dictionary for Regulatory Activities version 23.1. 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' by the local research sites.[1,17] We collected data on adverse events of interest, including infection, malignancy, and infusion and injection reactions.

We evaluated the effect of drug and antidrug antibody concentrations at the timing of loss of response using

internationally-recommended definitions, and selected drug concentration thresholds on the basis of the limit of detection of our assay, as well as optimal week 14 drug concentration, to predict treatment failure throughout the study period.[12,16,18,19]

Immune-mediated pharmacokinetic failure was defined as treatment failure with undetectable anti-TNF drug concentrations (infliximab <1·88 mg/L, adalimumab <0·8 mg/L), and the presence of anti-TNF antibodies (infliximab ≥9 AU/mL, adalimumab ≥6 AU/mL). Non-immune-mediated pharmacokinetic failure was defined as treatment failure with undetectable or subtherapeutic anti-TNF drug concentrations (infliximab ≤10·25 mg/L, adalimumab ≤12 mg/L) and the absence of anti-TNF antibodies (infliximab <9 AU/mL, adalimumab <6 AU/mL). Pharmacodynamic failure in the presence of antibodies (known as double positive status) was defined as treatment failure with detectable anti-TNF drug concentrations (infliximab ≥1·88 mg/L, adalimumab ≥0·8 mg/L) and the presence of anti-TNF antibodies (infliximab ≥9 AU/mL, adalimumab ≥6 AU/mL). Pharmacodynamic failure in the absence of antibodies was defined as treatment failure with adequate anti-TNF drug concentrations (infliximab >10·25 mg/L, adalimumab >12 mg/L) and the absence of anti-TNF antibodies (infliximab <9 AU/mL, adalimumab <6 AU/mL).

Statistical analysis

At cohort inception, sample size was based on the design of a genetic study that aimed to identify a genetic predictor of primary non-response.[1,2] 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 calculator, that we needed to recruit 240 non-responders to yield 99% power to detect a genome-wide significant association ($p<5\times10^{-8}$) 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 patients treated with the biosimilar would permit a comparison of non-inferiority of biosimilar and originator infliximab on the basis of 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 patients treated with biosimilar to originator infliximab of 1:4.

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 scores were 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 immunogenicity and safety analyses because they had received one of the drugs.

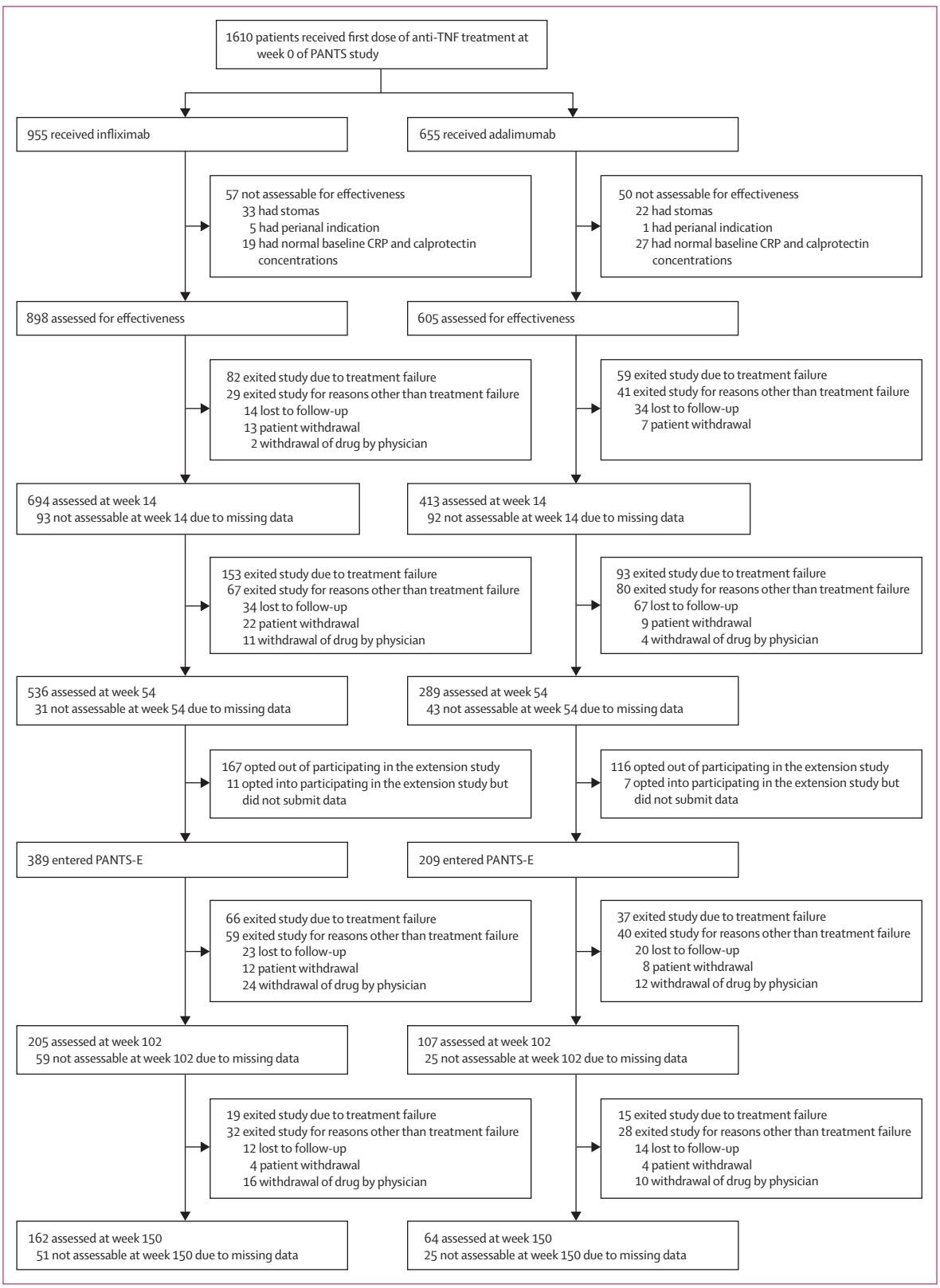
Because of differences in drug formulation, route of delivery, dosing interval, and potential for inducing immune response, infliximab and adalimumab treatment outcomes were analysed separately. Outcomes were assigned using an algorithm written in R (version 4.3.2). All analyses were two-tailed, and p values of less than 0·05 were considered significant.

We included patients with missing clinical variables in analyses for which they had data and have specified the denominator for each variable. We report continuous data as median (IQR) and discrete data as numbers and percentages. We performed univariable analyses using Fisher's exact test and the Mann-Whitney *U* test to identify differences in characteristics between patients treated with infliximab and adalimumab and those who entered the extension phase of the study and those who opted out.

We included the whole cohort to estimate remission over the course of the first 3 years of treatment. 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, including declining to participate in PANTS-E, withdrawal of consent at any point throughout the study, 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.

To account for variable length of follow up, including the requirement to consent separately for the extension phase, we used a modified survival technique to estimate remission rates at later timepoints. We estimated the proportion of patients who had exited due to treatment failure by any given timepoint using a standard Kaplan–Meier approach, stratified by any specific covariates of interest. For the proportion of patients who were estimated not to have exited due to treatment failure, we used the observed remission rates among those with assessable data. Hence, we present these data as proportions (rather than absolute numbers) and split participants into groups defined as exited due to treatment failure, remission while being treated with drug, and non-remission while being treated with drug. We used permutation testing to determine statistical significance for comparisons using estimates of remission. We did this by permuting the values for the independent covariate of interest and determining the proportion of repetitions in which we observed results at least as extreme as the one we observed in the real data. We used the comparisons of the absolute of the log odds ratio (OR), and therefore p values are two-tailed. We used bootstrapping to calculate 95% CIs for the estimates.

Only patients who had responded to anti-TNF treatment at week 14 were included in the assessment of rates of


1610 patients received first dose of anti-TNF treatment at week 0 of PANTS study
955 received infliximab
655 received adalimumab
57 not assessable for effectiveness
33 had stomas
5 had perianal indication
19 had normal baseline CRP and calprotectin concentrations
50 not assessable for effectiveness
22 had stomas
1 had perianal indication
27 had normal baseline CRP and calprotectin concentrations
898 assessed for effectiveness
605 assessed for effectiveness
82 exited study due to treatment failure
29 exited study for reasons other than treatment failure
14 lost to follow-up
13 patient withdrawal
2 withdrawal of drug by physician
59 exited study due to treatment failure
41 exited study for reasons other than treatment failure
34 lost to follow-up
7 patient withdrawal
694 assessed at week 14
93 not assessable at week 14 due to missing data
413 assessed at week 14
92 not assessable at week 14 due to missing data
153 exited study due to treatment failure
67 exited study for reasons other than treatment failure
34 lost to follow-up
22 patient withdrawal
11 withdrawal of drug by physician
93 exited study due to treatment failure
80 exited study for reasons other than treatment failure
67 lost to follow-up
9 patient withdrawal
4 withdrawal of drug by physician
536 assessed at week 54
31 not assessable at week 54 due to missing data
289 assessed at week 54
43 not assessable at week 54 due to missing data
167 opted out of participating in the extension study
11 opted into participating in the extension study but did not submit data
116 opted out of participating in the extension study
7 opted into participating in the extension study but did not submit data
389 entered PANTS-E
209 entered PANTS-E
66 exited study due to treatment failure
59 exited study for reasons other than treatment failure
23 lost to follow-up
12 patient withdrawal
24 withdrawal of drug by physician
37 exited study due to treatment failure
40 exited study for reasons other than treatment failure
20 lost to follow-up
8 patient withdrawal
12 withdrawal of drug by physician
205 assessed at week 102
59 not assessable at week 102 due to missing data
107 assessed at week 102
25 not assessable at week 102 due to missing data
19 exited study due to treatment failure
32 exited study for reasons other than treatment failure
12 lost to follow-up
4 patient withdrawal
16 withdrawal of drug by physician
15 exited study due to treatment failure
28 exited study for reasons other than treatment failure
14 lost to follow-up
4 patient withdrawal
10 withdrawal of drug by physician
162 assessed at week 150
51 not assessable at week 150 due to missing data
64 assessed at week 150
25 not assessable at week 150 due to missing data

and the factors predictive of loss of response thereafter. We estimated rates of loss of response, exit due to treatment failure, and immunogenicity using the Kaplan–Meier method, and we did comparative analyses using univariable and multivariable Cox proportional hazards regression. Variables assessed were baseline BMI (obese [≥30 kg/m²] *vs* not obese [<30 kg/m²]), week 14 status (remission *vs* response *vs* grey zone), week 14 and week 54 anti-TNF drug concentration quartile, week 14 and week 54 immunogenicity (immunogenic *vs* not immunogenic), white blood cell count (1·55–6·22 *vs* 6·23–7·90 *vs* 7·91–10·13 *vs* 10·14–22·90×10⁹ cells per L) baseline thiopurine dose quartile, sex (male *vs* female), presence of the *HLA-DQA1*05* risk variant (not present *vs* present, smoking status (never or former smoker *vs* current smoker), immunomodulator use (no immunomodulator *vs* immunomodulator), and timing of starting immunomodulator (>14 days before *vs* <14 days before and <14 days after *vs* >14 days after starting anti-TNF therapy). The Cox proportional hazards assumption was checked using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals, and was met. In our analyses of time to loss of response and immunogenicity, patients were censored if they exited for reasons other than treatment failure, after their last drug and antibody measurement, or at week 150.

We used multivariable Cox proportional hazards analyses to identify which factors were independently associated with loss of response. We included variables with univariable p values of less than 0·05 in the model and used Akaike Information Criterion (AIC) and backward stepwise variable selection. We also built predictive models, using backwards stepwise model selection starting from the null model, again using AIC. We used leave-one-out cross-validation to test the model, first to ensure the model was not overfitted, and second to estimate the diagnostic accuracy of the model. For prediction testing, a probability threshold was determined by maximising the sum of sensitivity and specificity. We explored associations with drug concentration using linear regression, using the same variable selection methods as those detailed earlier for logistic regression.

We determined optimal thresholds for drug concentrations by plotting outcome against intervals of drug concentration and looking for the threshold beyond which further increases were not associated with improvement in outcome. We calculated the rate of remission at week 54 for patients at or above each possible threshold of drug concentration at week 14. We wanted to find the threshold above which further increases in drug concentration were not associated with any incremental gain in remission rates, and so we did not use a receiver-operating characteristic approach because we would trade sensitivity against specificity.

The number and rates of adverse events per 100 patient-years of follow-up were summarised by anti-TNF and immunomodulator treatment groups

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.

Results

Of 1610 patients recruited to the PANTS study, 955 (59%) were treated with infliximab (753 [79%] received the originator and 202 [21%] received the biosimilar) and 655 (41%) were treated with adalimumab. Between March 19, 2014, and Sept 21, 2017, 598 patients were enrolled into the PANTS-E study, of whom 389 (65%) were treated with infliximab (262 [67%] received originator infliximab, 78 [20%] received the biosimilar, and 49 [13%] switched to the biosimilar in the first year of study) and 209 (35%) were treated with adalimumab (figure 1). Baseline demographic and clinical characteristics of patients who entered PANTS-E and those who did not are shown in the appendix (p 36). Among patients enrolled in PANTS-E, median age was 32·5 years (IQR 22·1–46·8), 307 (51%) of 598 were female, 291 (49%) were male, 558 (93%) were White, 19 (3%) were south Asian, and 21 (3%) were other ethnicities. By year 3, most participants had switched from infliximab originator to the biosimilar (appendix p 17).

At entry into PANTS-E, several baseline characteristics were significantly different between patients treated with infliximab and adalimumab, including age, BMI, disease duration, disease behaviour, and presence of perianal disease (appendix p 37). Compared with patients treated with adalimumab, those treated with infliximab had higher rates of immunogenicity in the first year (infliximab: 219 [56%] of 389; adalimumab: 65 [31%] of 209), higher baseline faecal calprotectin concentrations (infliximab: median 441 µg/g [IQR 202–949] adalimumab: 292 µg/g [138–620]), and increased rates of immunomodulator use (infliximab: 261 [67%]; adalimumab: 111 [53%]; all p<0·001).

Across all patients recruited to the PANTS study, the estimated proportions of patients treated with infliximab who were in remission at the end of years 1, 2, and 3 were 40·2% (95% CI 36·7–43·7), 34·4% (29·9–39·0), and 34·7% (29·8–39·5), respectively (figure 2). For patients treated with adalimumab, the estimated proportion in remission at years 1, 2, and 3 were 35·9% (95% CI 31·2–40·5), 32·9% (26·8–39·2), and 28·9% (21·9–36·3), respectively (figure 2). Estimated proportions for patients treated with originator infliximab and the biosimilar were similar to each other (appendix p 18).

Figure 1: **Study profile**
Patients who exited for reasons other than treatment failure were censored from that timepoint onwards. Patients who exited for treatment failure were regarded as being in non-remission from that timepoint onwards. At each study visit, we noted the number of patients who had not exited but were missing data at that timepoint and were therefore not assessable. CRP=C-reactive protein.

Of patients treated with infliximab and estimated to be in remission at week 14, the estimated proportion who were in remission at years 1, 2, and 3 were 63·4% (95% CI 57·8–69·0), 54·1% (46·7–61·8), and 54·4% (46·3–62·3), respectively. Of patients treated with adalimumab estimated to be in remission at week 14, the estimated proportion who were in remission at years 1, 2, and 3 were 60·1% (95% CI 52·0–67·8), 47·1% (36·6–57·5), and 49·0% (36·3–61·7), respectively.

Of patients treated with infliximab who were estimated to be in remission at year 1, the estimated proportion who were in remission at years 2 and 3 were 70·6% (95% CI 63·2–77·6) and 62·9% (54·7–70·8), respectively. Of patients treated with adalimumab who were estimated to be in remission at year 1, the estimated proportion who were in remission at years 2 and 3 were 70·1% (95% CI 59·3–80·5) and 66·9% (50·1–81·8), respectively.

Among patients treated with infliximab, a lower proportion of female patients than male patients were in remission at years 2 and 3 (appendix p 19). A dose–response association was seen for week 14 drug concentration and remission rates at year 2 and 3 (figure 3; appendix p 20). Determined graphically, optimal drug concentration thresholds at week 14 to predict remission at years 1, 2, and 3 were approximately 6·1–10·0 mg/L for infliximab and 10·1–12·0 mg/L for adalimumab. For both infliximab and adalimumab, these optimal week 14 drug concentrations were associated with increased remission rates at year 2 (infliximab: OR 2·20 [95% CI 1·38–3·56]; adalimumab: 3·65 [1·83–8·67]) and year 3 (infliximab: 1·89 [1·16–3·11]; adalimumab: 6·15 [2·50–23·19]). Additionally, presence of anti-drug antibodies at week 14 was associated with decreased remission rates at year 2 (infliximab: OR 0·44 [95% CI 0·21–0·81]; adalimumab: 0·16 [0·00–0·46]) and year 3 (infliximab: 0·37 [0·15–0·72]; adalimumab: 0·21 [0·08–0·71]; appendix pp 21–22).

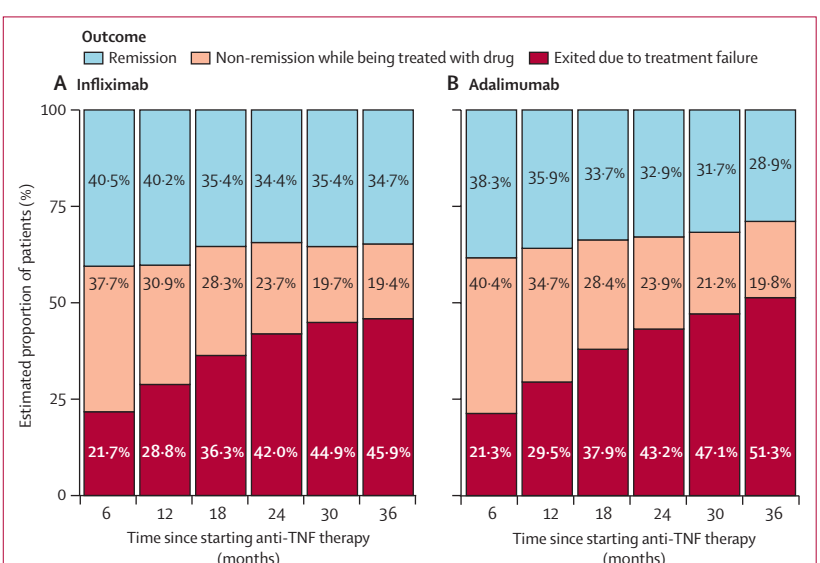


Figure 2: **Estimated proportions of patients in remission, non-remission, and who exited due to treatment failure at the end of years 1, 2, and 3 of the study, by anti-TNF therapy**
Proportions might not add up to 100% due to rounding.

The optimal minimal week 54 drug concentration to ensure remission at subsequent timepoints was estimated to be lower than the optimal week 14 concentration to ensure remission at week 54 for infliximab, but not for adalimumab. At week 54, for infliximab, we estimated that maintaining drug concentrations of 3·6–4·5 mg/L was sufficient, whereas for adalimumab the drug concentration needed to be maintained at more than 10 mg/L (appendix p 23).

For loss of response assessment, after excluding patients who had primary non-response, the estimated proportion of patients treated with infliximab who had loss of response by years 1, 2, and 3 were 34·4% (95% CI 30·4–38·2), 54·5% (49·4–59·0), and 60·0% (54·1–65·2), respectively (appendix p 24). For patients treated with adalimumab, the estimated proportions of patients who had loss of response by years 1, 2, and 3 were 32·1% (95% CI 26·7–37·1), 47·2% (40·2–53·4), and 68·4% (50·9–79·7), respectively. Estimated median time to loss of response for patients treated with infliximab was 1·9 years (95% CI 1·7–2·4) and for those treated with adalimumab was 2·3 years (1·9–2·8). Estimated rates for loss of response events for patients treated with the infliximab originator and biosimilar were similar to one another (appendix p 24).

The univariable analysis of factors associated with time to loss of response or exit due to treatment failure are shown in figure 4. For patients treated with infliximab and adalimumab, associations were found with BMI, response status at week 14, anti-TNF drug concentration at week 14, immunogenicity at week 14, anti-TNF drug concentration at week 54, and immunogenicity at week 54. Baseline thiopurine drug concentration quartile and sex were associated with loss of response or exit due to treatment failure for patients treated with infliximab but not for those treated with adalimumab, and carriage of *HLA-DQA1*05* risk variant was associated with loss of response or exit due to treatment failure in patients treated with adalimumab and not those treated with infliximab. Factors that had no association with either drug were smoking status, use of immunomodulator, and timing of starting immunomodulator (data not shown).

Multivariable analyses showed that drug concentration at week 14 was the major independent risk factor associated with loss of response or exit due to treatment failure for both drugs at year 2 and 3 (infliximab: hazard ratio [HR] for each ten-fold increase in drug concentration 0·45 [95% CI 0·30–0·67], adalimumab: 0·39 [0·22–0·70]; appendix pp 25–32). For patients treated with infliximab, loss of response or exit due to treatment failure was also associated with female sex (*vs* male sex; 1·47 [1·11–1·95], obesity (*vs* not obese; 1·62 [1·08–2·42]), and baseline white cell count (1·06 [1·02–1·11) per 1×10^9

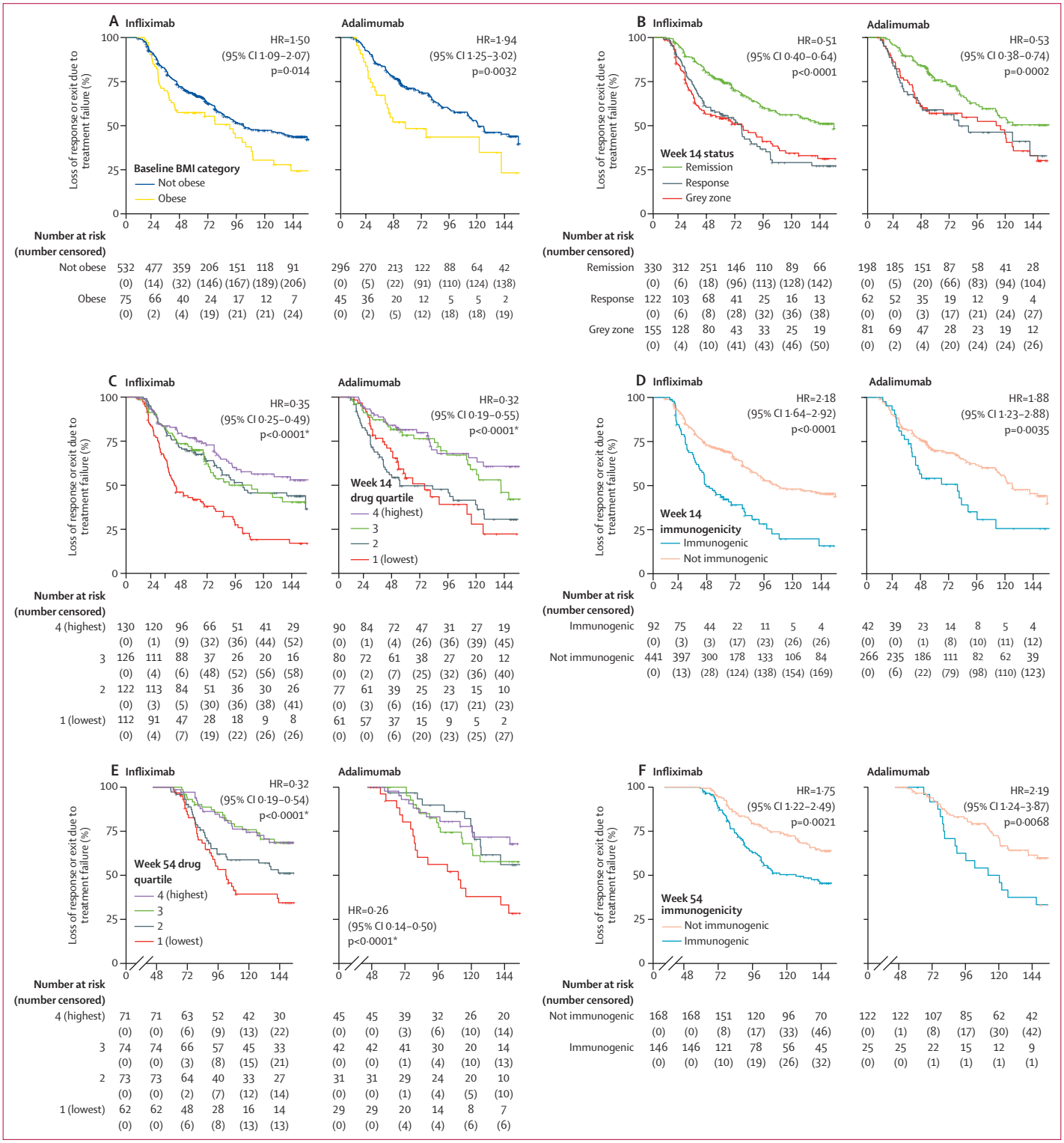
Figure 3: **Estimated proportions of patients in remission, non-remission, and who exited due to treatment failure at the end of years 1, 2, and 3 of study, by week 14 drug concentration of infliximab (A) and adalimumab (B)**

The numbers of patients in each bin were selected to approximately balance the number of patients in each dose group, while preferring thresholds with multiples of 0·5 and whole numbers.

increase in cells per L), but not carriage of the *HLA-DQA1*05* risk variant (HR 1·55 [0·97–2·48]). Furthermore, in multivariable analysis, once controlling for variables predictive of loss of response, including week 14 drug and antibody concentrations and interaction between baseline immunomodulator and *HLA-DQA1*05* risk variant, lower doses of thiopurine were associated with higher risk of loss of response or exit for treatment failure, even when compared against no thiopurine, although no association was found for the highest dose of thiopurine (appendix pp 25–32). Among patients treated with adalimumab, carriage of the *HLA-DQA1*05* risk variant was associated with loss of response or exit due to treatment failure (HR 1·95 [95% CI 1·17–3·25]). This association was not observed in patients who carried the risk variant who were taking concomitant immunomodulatory therapy (0·48 [0·24–0·97]; appendix p 25).

For patients treated with infliximab, the estimated proportion who developed of anti-drug antibodies associated with undetectable drug concentrations at years 1, 2, and 3 were 31·3% (95% CI 27·7–34·7), 37·0% (32·8–40·8), and 44·0% (38·1–49·4), respectively. For patients treated with adalimumab, the estimated proportions at years 1, 2, and 3 were 12·5% (95% CI 9·0–15·8), 15·5% (11·2–19·6), and 20·3% (13·8–26·2),

respectively (appendix p 33). Estimated rates for immunogenicity for patients treated with the infliximab originator and biosimilar were similar to each other (appendix p 33). Concomitant use of an immunomodulator, before or on the day of starting infliximab, was associated with increased time without the development



(Figure 4 continues on next page)

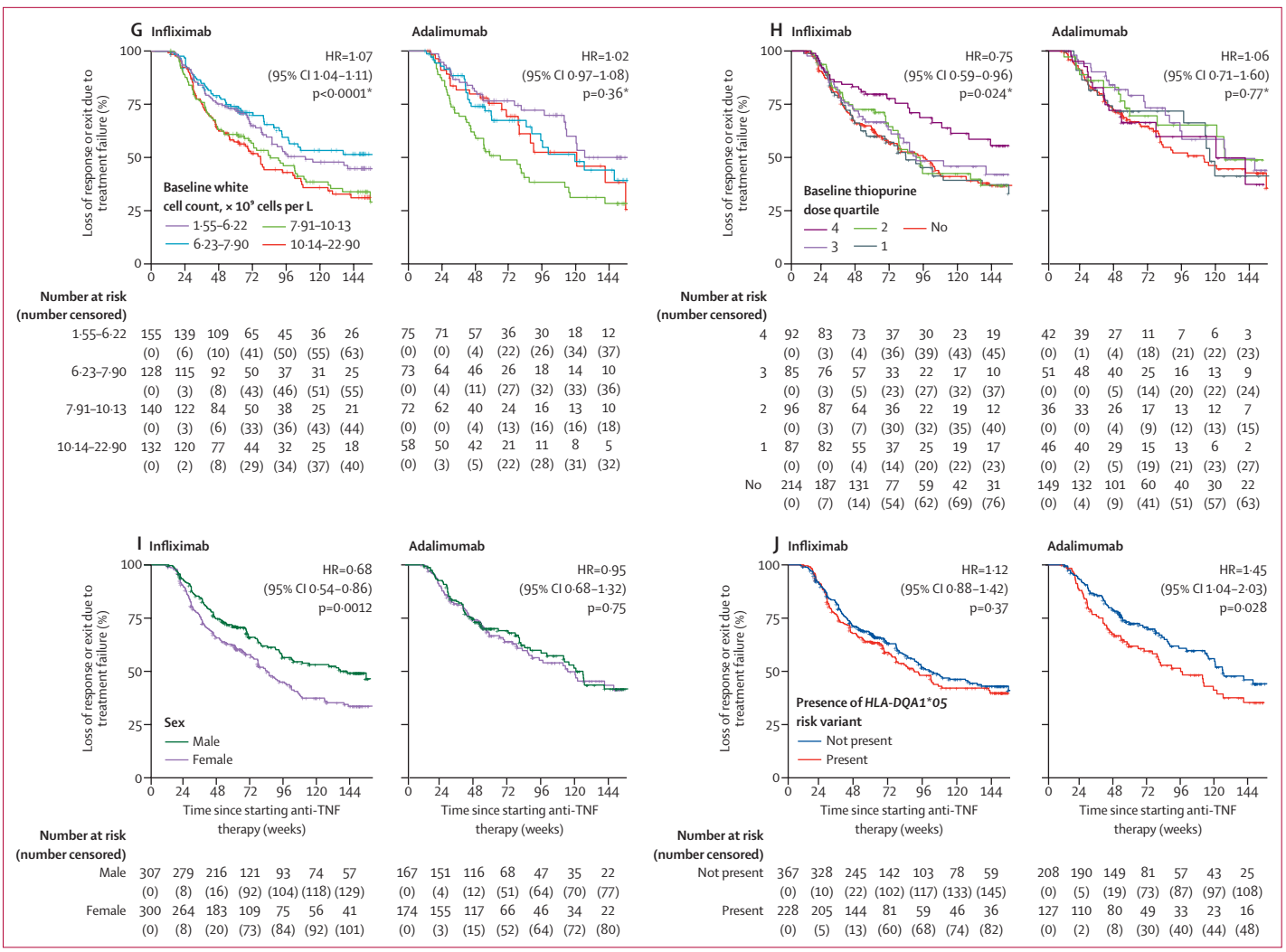


***Figure 4*: Univariable associations of time to loss of response or exit due to treatment failure using Kaplan-Meier and Cox proportional hazards methods, by BMI (A); week 14 remission status (B), anti-TNF drug concentration (C), and immunogenicity status (D); week 54 anti-TNF drug concentration (E) and immunogenicity status (F); baseline white blood cell count (G), baseline thiopurine dose (H), sex (I), and *HLA-DQA1*05* risk variant (J) for patients treated with infliximab and adalimumab**

Kaplan-Meier graphs for survival without loss of response or exit due to treatment failure from study according to BMI (not obese <30·0 kg/m² *vs* obese ≥30·0 kg/m²; A), week 14 status (remission *vs* response *vs* grey zone; B), week 14 anti-TNF drug concentration (quartile 1: infliximab <1·9 to 3·1 mg/L, adalimumab <0·8 to 7·5 mg/L; quartile 2: infliximab 3·2 to 5·9 mg/L, adalimumab 7·6 to 10·8 mg/L; quartile 3: infliximab 6·0 to 10·5 mg/L, adalimumab 10·9 to 14·4 mg/L; and quartile 4: infliximab >10·5 mg/L, adalimumab >14·4 mg/L; C), week 14 immunogenicity (presence of anti-TNF antibodies: infliximab ≥9 AU/mL, adalimumab ≥6 AU/mL *vs* not immunogenic: absence of anti-TNF antibodies; D), week 54 anti-TNF drug concentration (quartile 1: infliximab <1·9 to 2·3 mg/L, adalimumab <0·8 to 5·7 mg/L; quartile 2: infliximab 2·4 to 4·3 mg/L, adalimumab 5·8 to 10·0 mg/L; quartile 3: infliximab 4·4 to 7·7 mg/L, adalimumab 10·1 to 14·1 mg/L; and quartile 4: infliximab >7·7 mg/L, adalimumab >14·1 mg/L; E), week 54 immunogenicity (presence of anti-TNF antibodies: infliximab ≥9 AU/mL, adalimumab ≥6 AU/mL *vs* not immunogenic: absence of anti-TNF antibodies); F), baseline white blood cell count (1·55–6·22 *vs* 6·23–7·90 *vs* 7·91–10·13 *vs* 10·14–22·90 × 10^9 cells per L; G), baseline thiopurine dose quartile (no: no thiopurine; quartile 1: azathioprine 0·18 to 1·39 mg/kg, mercaptopurine 0·17 to 0·66 mg/kg; quartile 2: azathioprine 1·40 to 1·85 mg/kg, mercaptopurine 0·67 to 0·89 mg/kg; quartile 3: azathioprine 1·86 to 2·19 mg/kg, mercaptopurine 0·90 to 1·05 mg/kg; and quartile 4: azathioprine 2·20 to 4·15 mg/kg, mercaptopurine 1·06 to 2·95 mg/kg; H), sex (male *vs* female; I), and presence of the *HLA-DQA1*05* risk variant (not present *vs* present; J). p values and HRs are derived from Cox proportional hazards models for each individual variable. The data for week 14 drug concentrations and immunogenicity (panels C and D) and week 54 drug concentrations and immunogenicity (panels E and F) exclude any patients who exited the study before week 14 and 54 visits, respectively. All plots based on drug concentration are based on the $\log_{10}$ of the drug concentration; therefore, the data show the HR for each ten-fold increase in concentration. For baseline thiopurine concentration association (panel H), the HR calculation was based on per unit increase of mg/kg of thiopurine dosing, in azathioprine-equivalent dosing. HR=hazard ratio. *p value based on continuous analysis.

of anti-drug antibodies associated with undetectable drug concentrations compared with use of infliximab alone (HR 2·87 [95% CI 2·20–3·74]), or introduction of an immunomodulator after anti-TNF therapy initiation (1·70 [1·11–2·59]; figure 5A). Concomitant use of an immunomodulator, before or on the day of starting adalimumab was associated with increased time without the development of anti-drug antibodies associated with undetectable drug concentrations compared with use of infliximab alone (HR 2·62 [95% CI 1·48–4·64]) but not introduction of an immunomodulator after anti-TNF therapy initiation (1·10 [0·26–4·76]; figure 5B). Carriage of the *HLA-DQA1*05* risk variant, stratified by immunomodulator use, was associated with decreased

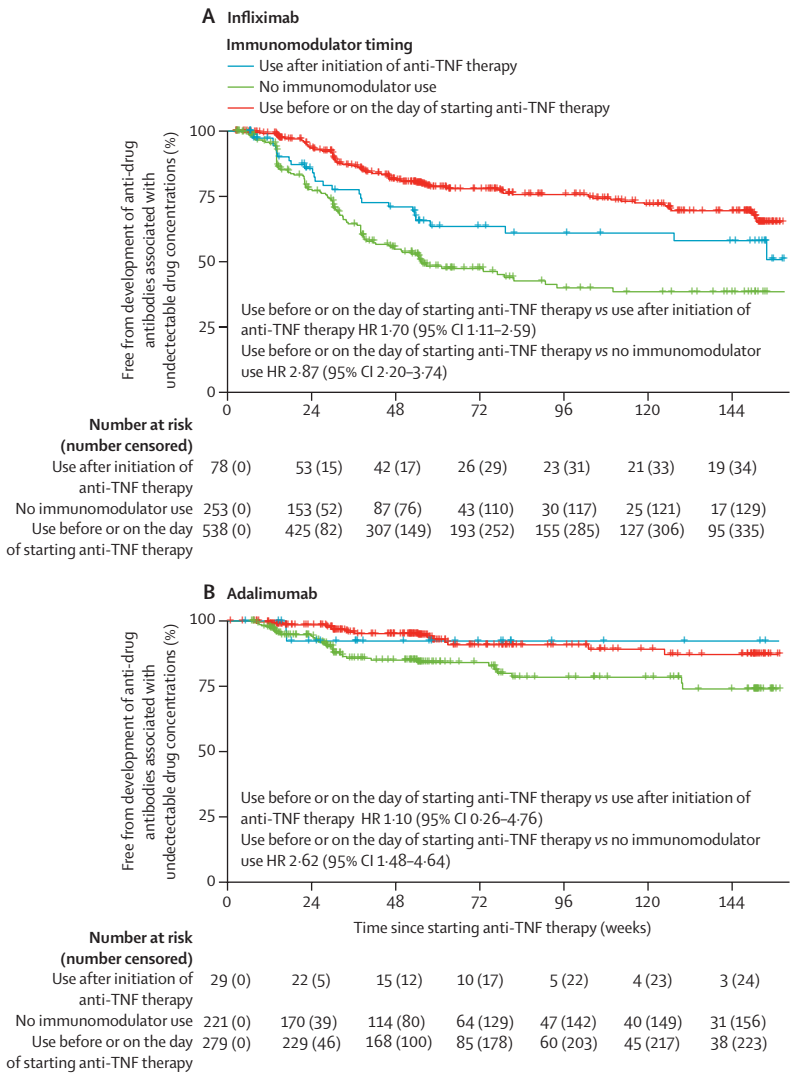


Figure 5: **Time to development of anti-drug antibodies associated with undetectable drug concentrations, using Kaplan-Meier and Cox proportional hazards methods, stratified by timing of immunomodulator use, for patients treated with infliximab (A) and adalimumab (B)**

time without the development of anti-drug antibodies associated with undetectable drug concentrations in patients treated with infliximab, but not those treated with adalimumab (appendix p 34). The HR for development of anti-drug antibodies associated with undetectable drug concentrations in the presence of immunomodulators for patients treated with infliximab was 0·40 (95% CI 0·31–0·52), and for those treated with adalimumab was 0·42 (0·24–0·75). The HR for development of anti-drug antibodies associated with undetectable drug concentrations with carriage of *HLA-DQA1*05* risk variant was 1·46 (1·13–1·88) for patients treated with infliximab and 1·60 (0·92–2·77) for those treated with adalimumab.

Using a Cox proportional hazards model, we found that low anti-TNF drug concentration at week 14 was associated with a shorter time to development of anti-drug antibodies associated with undetectable drug concentrations (ie, positive for antibodies, and negative for drug; infliximab: HR 0·15 [95% CI 0·09–0·25], adalimumab: 0·02 [0·01–0·04] for each ten-fold increase in drug concentration). Using a time-varying approach to account for individual changes in antibody status throughout PANTS-E, compared with patients who had not developed immunogenicity at a specific timepoint, the presence of anti-drug antibodies associated with undetectable drug concentration was associated with an increased risk of loss of response or exit due to treatment failure (infliximab: HR 2·91 [95% CI 2·11–4·00], adalimumab: 4·04 [1·97–8·30]); however, the detection of antibodies in the presence of drug was not associated with increased risk of loss of response or exit due to treatment failure (infliximab: HR 1·26 [0·92–1·73], adalimumab: 1·51 [0·93–2·46]).

Of the 522 patients treated with infliximab who had a positive anti-drug antibody test at any timepoint, 442 (85%) were re-tested at least 4 weeks later. 76 (17%) of 442 patients' repeat antibody tests were negative and 366 (83%) were positive. The median anti-drug antibody concentration of the initial test was 11·0 AU/mL (IQR 9·0–17·3) for patients who subsequently tested negative and 18 AU/mL (12·0–34·0) for those who subsequently tested positive. Of 191 patients treated with adalimumab with a positive anti-drug antibody test, 126 (66%) were re-tested at least 4 weeks later. 34 (27%) of 126 patients' repeat antibody tests were negative and 92 (73%) were positive. The median anti-drug antibody concentration of the initial positive test was 8·4 AU/mL (IQR 6·0–15·0) for patients who subsequently tested negative and 15 AU/mL (7·0–54·0) for those who subsequently tested positive. Only one patient treated with adalimumab and two treated with infliximab started on an immunomodulator between first positive antibody reading and next antibody reading. Estimated proportions of patients with anti-drug antibodies associated with undetectable drug concentrations 1 year after the second positive antibody, inclusive of those who remained positive for drug only, were 35·3% (95% CI 26·5–43·0) for those treated with infliximab and 23·7% (8·7–36·2) for those treated with adalimumab.

Over the study period, there were 686 episodes of loss of response. 188 (48%) of 392 patients treated with infliximab and 70 (30%) of 231 treated with adalimumab had anti-drug antibodies at the time of loss of response.

Of the 188 patients treated with infliximab who had a positive anti-drug antibody test at the time of loss of response, 70 (37%) were re-tested at least 4 weeks after the loss of response event. 13 (19%) of 70 patients' repeat antibody tests were negative and 57 (81%) were positive. The median anti-drug antibody concentration of the initial positive test was 13·0 AU/mL (IQR 11·0–17·0) for patients who subsequently tested negative and 45·0 AU/mL (25·0–85·0) those who subsequently tested positive. Of the 70 patients treated with adalimumab who

had a positive anti-drug antibody test at the time of loss of response, 29 (41%) were re-tested at least 4 weeks after the loss of response event. Nine (31%) of 29 patients' repeat antibody tests were negative and 20 (69%) were positive. The median anti-drug antibody concentration of the initial positive test was 7·0 AU/mL (IQR 6·0–8·0) for patients who subsequently tested negative and 112·5 AU/mL (22·3–172·5) for those who subsequently tested positive.

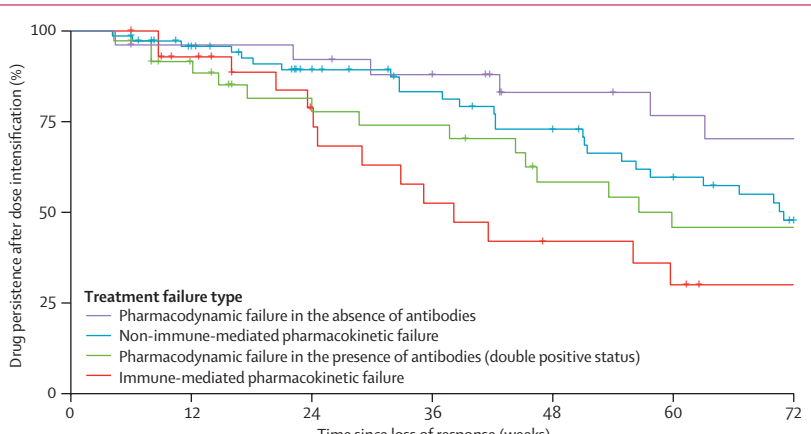
Across 686 loss of response episodes, 732 clinician actions were taken to manage loss of response. 288 (39%) of 732 actions intensified the anti-TNF dose, 50 (7%) started the patient on or increased their dose of an immunomodulator, 114 (16%) started the patient on a course of steroids, 24 (3%) recommended surgery, and 256 (35%) stopped the drug (appendix p 35). Among patients treated with infliximab who received intensified anti-TNF therapy at the point of loss of response, those who had immune-mediated pharmacokinetic failure had the lowest estimated rates of drug persistence throughout the remainder of the study compared with patients who had non-immune-mediated pharmacokinetic failure (HR 0·44 [95% CI 0·23–0·83]), pharmacodynamic failure in the absence of antibodies (0·35 [0·16–0·77]), and pharmacodynamic failure in the presence of antibodies (0·65 [0·33–1·29]; figure 6). This association was not seen for patients treated with adalimumab (data not shown).

The risk of adverse events at any point during the 3-year study were similar between patients treated with infliximab and adalimumab (appendix p 38) and those who were treated with an immunomodulator compared with those who were not (appendix p 39).

In year 1, adverse events leading to treatment withdrawal were reported for 84 (9%) of 955 patients treated with infliximab and 42 (6%) of 655 patients treated with adalimumab. Adverse events leading to treatment withdrawal in years 2 and 3 occurred for 16 (4%) of 389 patients treated with infliximab and 11 (5%) of 209 patients treated with adalimumab (appendix p 40).

Eight patients died during the course of the 3-year study period; five (1%) of 955 who had been treated with infliximab and three (<1%) of 655 treated with adalimumab. The median age at the time of death was 66·0 years (IQR 51·5–69·0). Five of eight patients died within the first year of the study, none of whom responded to anti-TNF treatment for their Crohn's disease by the time of death; two died of pneumonia, two died of intra-abdominal sepsis, and one of Crohn's disease-related malnutrition. Four of five who died during the first year were taking concomitant corticosteroids at the time of death, and one was taking azathiopurine.[1] Three died during years 2 and 3, while in the PANTS-E study: one of bowel perforation, one by suicide, and one of metastatic malignant melanoma malnutrition. One of the three patients was taking concomitant corticosteroids at the time of death and two were taking azathioprine.

In addition to the serious infections reported in the first year of study (infliximab: 38 [4%] of 955, adalimumab 21 [3%] of 655),[1] a further nine (2%) of 389 patients treated with infliximab and two (1%) of 209 treated with adalimumab reported serious infections during years 2 and 3, including active tuberculosis in one patient treated with adalimumab (appendix p 40). In years 2 and 3, infusion reactions occurred in four (1%) of patients treated with infliximab and injection-site reactions occurred in in two (1%) patients treated with adalimumab.



Number at risk (number censored)							
Pharmacodynamic failure in the absence of antibodies	26 (0)	24 (1)	23 (1)	21 (3)	15 (7)	12 (9)	11 (9)
Non-immune-mediated pharmacokinetic failure	73 (0)	64 (8)	51 (18)	41 (22)	35 (24)	27 (26)	19 (29)
Pharmacodynamic failure in the presence of antibodies (double positive status)	37 (0)	29 (5)	22 (9)	20 (9)	14 (11)	11 (11)	11 (11)
Immune-mediated pharmacokinetic failure	29 (0)	24 (3)	15 (9)	10 (9)	7 (10)	5 (10)	3 (12)

Figure 6: **Drug persistence in patients who received dose intensification of infliximab after loss of response event, stratified by drug level and antibody status at time of loss of response**

Discussion

Approximately a third of patients with active luminal Crohn's disease who commenced treatment with an anti-TNF drug at the beginning of the PANTS study were estimated to be in remission at the end of 2 and 3 years of treatment. This was predicted by remission status at the end of treatment induction and year 1. For both infliximab and adalimumab, low week 14 anti-TNF drug blood concentrations and presence of immunogenicity were predictive of lower year 2 and year 3 remission rates. Approximately two-thirds of patients who enrolled in the PANTS study who initially responded to anti-TNF therapy subsequently lost response by the end of year 3. Loss of response or exit due to treatment failure, for both patients treated with infliximab and adalimumab, was predicted by low anti-TNF drug concentrations at week 14. Further, for those treated with infliximab, loss of response was predicted by lower thiopurine dose quartiles, female sex, and obesity, and for those treated with adalimumab, was predicted by carriage of *HLA-DQA1*05* risk variant.

Anti-drug antibodies associated with undetectable drug concentrations, detected in an estimated 44·0% of patients treated with infliximab and 20·3% treated with adalimumab by year 3, were associated with low drug concentrations at week 14. Concomitant use of an immunomodulator, started before or on the day of the first infliximab infusion, was associated with increased time without the development of anti-drug antibodies associated with undetectable drug concentrations. Infliximab dose intensification in the setting of immune-mediated pharmacokinetic failure was associated with low rates of drug persistence.

Most previous studies of anti-TNF therapy have been limited to estimating rates of treatment failure up to 1 year.[5,6] At the end of 1 year of treatment with infliximab, we previously found that female patients had lower remission rates than did male patients.[1] Consistent with this finding, during PANTS-E, female sex was associated with both loss of response or exit due to treatment failure through years 2 and 3. Similar findings were reported in a single-centre retrospective cohort analysis of 210 patients with Crohn's disease treated with infliximab[20] and in patients with other immune-mediated diseases including psoriasis[21] and rheumatoid arthritis.[22] The biological basis for this association is not known but it does not appear to be mediated by sex differences in rates of immunogenicity. However, this association might be explained by increased reporting of adverse events and increased rates of non-adherence and treatment discontinuation reported in female patients.[23]

We previously reported that obesity was associated with decreased remission rates at week 54 only in patients treated with adalimumab and we attributed this finding to the fixed dosing schedule. Herein, we report a similar association for patients treated with infliximab after years 2 and 3 of treatment, despite the weight-based dosing schedule. Similar findings have been reported in a single-centre retrospective cohort of 124 patients initiating infliximab therapy,[24] and a meta-analysis of anti-TNF treatment failure in several rheumatic diseases.[25] By contrast, no difference in clinical remission or response rates based on BMI were observed in a pooled data analysis of 1205 patients with inflammatory bowel disease (IBD) treated with infliximab from four pivotal randomised controlled trials.[26] The association between obesity and loss of response to anti-TNF drugs might be explained by a larger body surface area, enhanced proteolysis, and TNF stored in adipose tissue.[27]

We found clear dose–response relationships between low anti-TNF drug concentrations at weeks 14 and 54 and estimated rates of treatment failure across 3 years of treatment. We previously reported that the optimal week 14 drug concentration associated with remission at week 54 was 7 mg/L for infliximab and 12 mg/L for adalimumab.[1] These suggested cutoffs lie within the range of drug concentrations associated with remission at years 1, 2, and 3 (infliximab: 6·1–10·0 mg/L and adalimumab: 10·1–12·0 mg/L) reported here. These concentrations are considerably higher than the target drug concentrations derived from previous observational studies.[28] Arguably, based on our data, most patients were under-dosed in routine clinical care between 2013 to 2016, suggesting that true pharmacodynamic treatment failure might be more uncommon than observed in this study.

While inter-individual differences in the pharmacokinetics of the anti-TNF drugs clearly influence the heterogeneity in response to treatment,[29–31] a role for proactive TDM driven dosing—particularly during induction—remains controversial. Most, but not all, prospective studies have not found improved clinical outcomes compared with conventional care.[32] This might reflect facets of study design, including the timing of dose optimisation and the target drug concentration used. Crucially, these studies used substantially lower target drug concentrations (0·5–8·0 mg/L) than the optimal cutoffs observed in the current study.[33–36] However, the pivotal TDM agnostic dose finding studies, including most recently the SERENE trials, did not show additional benefit of high dose induction when offered to all patients.[4,37,38] Whether selective high-dose induction targeting a higher drug concentration leads to improved outcomes is worthy of further study. Because we found similar clinical and pharmacokinetic outcomes between biosimilar and originator infliximab, any additional drug costs associated with dose intensification should be offset by use of increasingly inexpensive biosimilar preparations.

In the PANTS-E study, we used a drug tolerant anti-drug antibody assay and found that only anti-drug antibodies associated with undetectable drug concentrations were associated with loss of response or exit due to treatment failure. Antibodies to the anti-TNF drugs were most likely to be detected in the first year of treatment;

only an estimated 13% of patients treated with infliximab and 8% treated with adalimumab developed anti-drug antibodies associated with undetectable drug concentrations after year 1. While this finding might suggest little benefit of using a drug-tolerant over a drug-sensitive assay, the drug-tolerant assay does allow for earlier detection of immunogenicity and a window of opportunity to add an immunomodulator to reduce the risk of subsequent drug clearance and treatment failure.[39,40]

Loss of response and non-remission in years 2 and 3 of anti-TNF treatment are predicted by low drug concentrations at week 14 and week 54. While the direction of this dose–response association is uncertain, it is plausible that achieving higher drug concentrations during year 1, particularly during induction, might lead to improved long-term outcomes. Because most loss of response events occurred in the first year of treatment, the benefit of proactive TDM is likely to be small after year 1,[33] and reactive TDM in the setting of treatment failure is then likely to be more cost-effective.[34] Further prospective studies of early dose optimisation using proactive TDM are underway.[41,42]

Data are scarce regarding the optimal dose of thiopurines when used in combination with anti-TNF therapy. Most studies have suggested that the 6-thioguanine nucleotide (6-TGN) concentrations required to mitigate immunogenicity to anti-TNF therapy are lower than the therapeutic concentration targeted when thiopurines are used as monotherapy; however, these studies have been limited by retrospective design, small sample size, and short-term follow-up.[43–45] The prospective COMBO-IBD study found that reaching a 6-TGN concentrations of at least 146 pmol per 8×10^8 red blood cells in patients treated with infliximab and azathioprine was sufficient to augment infliximab concentrations.[46] However, this study was underpowered to define the optimal cutoff of 6-TGN at higher doses. Like Kariyawasam and colleagues,[47] who studied the effect of 6-TGN concentrations on adalimumab-related treatment failure, we found that patients in the highest weight-based quartile of thiopurine dosing were least likely to have loss of response. Once we controlled for factors associated for loss of response or exit due to treatment failure, including obesity, week 14 drug and antibody concentrations, and interaction between baseline immunomodulator and *HLA-DQA1*05* risk variant, lower doses of thiopurine were associated with loss of response or exit for treatment failure compared with no treatment with a thiopurine. The reasons for this finding remain unclear. This finding does not suggest that treatment with thiopurines should be avoided, because thiopurines are still associated with improved pharmacokinetics and reduced rates of immunogenicity in infliximab therapy; however, these data do support the use of at least 2·2 mg/kg of azathioprine and at least 1·1 mg/kg of mercaptopurine, when used alongside infliximab therapy, rather than lower doses.

We found that use of a concomitant immunomodulator reduces the risk of developing anti-drug antibodies associated with undetectable drug concentrations to both infliximab and adalimumab. We and others have shown that for infliximab, concomitant treatment with an immunomodulator translates to improved outcomes.[1,6] With the increasingly early introduction of infliximab, commencement of a concomitant thiopurine might be delayed while waiting on a thiopurine methyltransferase laboratory result, or to allow steroid taper to minimise the risks of triple immunosuppression. Our data from patients who started a thiopurine after initiation of infliximab suggest this delay might be associated with an increased risk of immunogenicity and should be avoided. However, too few patients had a short delay (less than 2 weeks) before starting a thiopurine (data not shown), and therefore our analyses were underpowered to ascertain their risk compared with patients who had longer delays.

In the setting of loss of response, 39% of episodes were managed through anti-TNF dose intensification, and 35% of patients had their anti-TNF treatment withdrawn by their clinician. This low rate of dose intensification is probably reflective of clinical practice at the time the study was conducted. We looked at the outcome of dose intensification, stratified by drug and antibody concentrations at the time of loss of response. In patients treated with infliximab who developed immune-mediated pharmacokinetic failure (undetectable drug concentration with antibodies), dose intensification resulted in shorter drug persistence than in patients with non-immune mediated pharmacokinetic failure (undetectable or subtherapeutic drug concentration without antibodies). These observations support the current practice of dose intensification in the setting of low drug concentrations without immunogenicity.[11,12] Our observation that dose intensification was associated with increased drug persistence in patients who had treatment failure despite adequate infliximab concentrations could imply that even higher drug concentrations are required to achieve remission for some individuals.[28,48] In the setting of loss of response, the primary purpose of TDM is to identify patients with immunogenic-pharmacokinetic failure in whom dose intensification is likely to be unsuccessful.

Although some, but not all, data support the use of *HLA-DQA1*05* testing to guide the choice of anti-TNF monotherapy and combination therapy, estimates of the positive and negative predictive values are modest.[49] Arguably, all patients treated with an anti-TNF therapy should be prescribed an immunomodulator to reduce the risk of loss of response and immunogenicity. In patients in whom immunomodulators are contraindicated or not tolerated, clinicians could decide against the use of anti-TNF drugs, particularly infliximab for those who carry *HLA-DQA1*05*. Adalimumab monotherapy could be considered in patients who do not carry the risk allele. Alternatively,

recent meta-analyses suggest that the effect of *HLA-DQA1*05* in patients treated with infliximab might be overcome by proactive TDM.[49,50]

Our study has several limitations. First, consistent with registration trials and other real-world prospective cohort studies, about a third of patients who completed the first year of PANTS did not enter the extension phase. There were few differences between patients who continued into the second year and those who did not; however, the slightly higher proportion of male patients who did not continue at that point might have had a small effect on our results. To mitigate possible observation bias, we used a modified survival technique and permutation testing to estimate the number of patients in remission throughout the entire study. Second, in the absence of standardised definitions of treatment response and loss of response, we used pragmatic definitions combining corticosteroid use, clinical and biochemical markers of disease activity, and clinician action. We did not use endoscopic outcomes or obtain 6-TGN concentrations, which we acknowledge would have strengthened our data. Finally, the effect of treatment intensification anti-drug antibody concentrations is difficult to evaluate because very high drug concentrations following dose intensification interfered with our drug tolerant anti-drug antibody assay. Moreover, with 6-monthly study visits in years 2 and 3, we had insufficient drug and antibody concentration data immediately after dose optimisation to assess this further.

We collected data from more than 120 sites from across the UK. Our findings are likely to be generalisable to patients with Crohn's disease, and to similar patient cohorts from other high-income countries. However, whether our results are generalisable to other anti-TNF drugs , including certolizumab and golimumab, or when used in patients with ulcerative colitis, remains unknown.

In conclusion, we estimated that only around a third of patients with active luminal Crohn's disease treated with an anti-TNF drug were in remission at the end of 3 years of treatment. Low drug concentrations at the end of induction predicted loss of response up to year 3 of treatment, suggesting higher drug concentrations during the first year of treatment, particularly during induction, could lead to improved long-term outcomes. Anti-drug antibodies associated with undetectable drug concentrations of infliximab, but not adalimumab, can be predicted by carriage of *HLA-DQA1*05* and mitigated by concomitant immunomodulator use for both drugs.

Contributors

NC, SL, CB, CWL, SS, PMI, RKR, JRG, TA, and NAK participated in the conception and design of this study. CB was the project manager and coordinated patient recruitment. RN and TJM coordinated all biochemical analysis and central laboratory aspects of the project. NC, SL, BH, AT, RS, CR, MB, and NAK were involved in the acquisition, analysis, or interpretation of data. Data analysis was done by NC, SL, and NAK. Drafting of the manuscript was done by NC, SL, RS, CR, MB, CWL, SS, PMI, RKR, JRG, TA, and NAK. TA obtained the funding for the study. All the authors contributed to the critical review and final approval of the manuscript. NAK, SL, and NC accessed and verified the underlying study data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The authors were not precluded from accessing data in the study and they accept responsibility to submit for publication.

Declaration of interests

CR reports receiving salary from the National Institute of Health Research outside the submitted work. RN reports receiving non-financial support from Immunodiagnostik. CWL has received consulting fees from AbbVie, Galapagos, Takeda, Janssen, Novartis, Pfizer, GSK, BMS, Boehringer Ingelheim, Celltrion, Amgen, and Iterative Health and payment or honoraria from AbbVie, Galapagos, Takeda, Janssen, Novartis, Pfizer, GSK, BMS, Boehringer Ingelheim, Celltrion Healthcare, Amgen, and Fresnius Kabi. SS has received consulting fees from Takeda, AbbVie, Merck, Ferring, Pharmacosmos, Warner Chilcott, Janssen, Falk Pharma, Biohit, TriGenix, Celgene, and Tillots Pharma; payment or honoraria from AbbVie, Takeda, Celltrion Healthcare, Pfizer, Biogen, AbbVie, Janssen, Merck, Warner Chilcott, Falk Pharma, and Janssen; is chair of the Research Committee of the British Society of Gastroenterology; is chair of the Clinical Research Committee of the European Colitis and Crohns Organisation; and is co-director of research for the South Asian IBD Alliance. PMI reports research grants from Celltrion Healthcare, Takeda, Pfizer, and Galapagos; personal payments from AbbVie, Arena, Boehringer Ingelheim, BMS, Celltrion Healthcare, Elasmogen, Endpoint Health, Gilead, Janssen, Lilly, Pfizer, Sandoz, and Takeda; and travel support from Takeda, AbbVie, and Tillotts Pharma, outside the submitted work. RKR has received grants from Nestle, consulting fees from AbbVie, payment or honoraria from Tillotts Pharma and Janssen, and support for attending meetings or travel from Celltrion Healthcare. JRG reports grants from F Hoffmann-La Roche, Biogen, Celltrion Healthcare, and Galapagos and non-financial support from Immundiagnostik outside the submitted work. TA reports grants or contracts from MSD, AbbVie, Hospira (Pfizer), Napp Pharmaceuticals, Celgene, Celltrion, F Hoffmann-La Roche, Biogen, Nova Pharmaceuticals, Galapagos, Takeda, and Pfizer; consulting fees from Amgen, Celltrion, Janssen, and Eli Lilly; payment or honoraria from F Hoffmann-La Roche, Pfizer, and Takeda; and support for attending meetings or travel from Tillotts Pharma and Celltrion Healthcare. NAK reports institutional grants or contracts from AbbVie, Biogen, Celgene, Celltrion Healthcare, Galapagos, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Roche, and Takeda; personal consulting fees from Amgen, Bristol Myers Squibb, Celltrion Healthcare, Falk Pharma, Galapagos, Janssen, Pfizer, Pharmacosmos, Takeda, and Tillotts Pharma; personal payments or honoraria from Amgen, Celltrion Healthcare, Falk Pharma, Galapagos, Janssen, Pharmacosmos, Galapagos, Takeda, and Tillotts Pharma; support for attending meetings or travel from AbbVie, Falk Pharma, Janssen, and Pharmacosmos; participation in the Data Monitoring Committee for BEACON study; and is chair of the British Society of Gastroenterology IBD Clinical Research Group. NC, SL, CB, BH, AT, RS, MB, and TJM decare no competing interests.

Data sharing

Individual participant de-identified raw data and a data dictionary defining each field in the set that underlie the results reported in this Article will be available immediately after publication for a period of 5 years. The data will be made available to investigators whose proposed use of the data has been approved by an independent review committee. Analyses will be restricted to the aims in the approved proposal. Proposals should be directed to Tariq Ahmad (tariq.ahmad1@nhs.net). To gain access data, requestors will need to sign a data access agreement.

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