Author/s:
Doecke, JD;Hartnell, F;Bampton, P;Bell, S;Mahy, G;Grover, Z;Lewindon, P;Jones, LV;Sewell, K;Krishnaprasad, K;Prosser, R;Marr, D;Fischer, J;R Thomas, G;Tehan, JV;Ding, NS;Cooke, SE;Moss, K;Sechi, A;De Cruz, P;Grafton, R;Connor, SJ;Lawrance, IC;Gearry, RB;Andrews, JM;Radford-Smith, GL

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Infliximab versus Adalimumab in Crohn's disease: results from 327 patients in an Australian and New Zealand observational cohort study.

Short title: Infliximab versus Adalimumab in Crohn's disease.

James D Doecke [1,2*], Felicity Hartnell [3*], Peter Bampton[4], Sally Bell[5], Gillian Mahy[6], Zubin Grover[7], Peter Lewindon[8], Lee V Jones [9], Karen Sewell[3], Krupa Krishnaprasad[10], Ruth Prosser[4], Debra Marr[11], Jesse Fischer[12], Gareth R Thomas[12], Jane V Tehan[5], Nik S Ding[5], Sharon E Cooke[6], Kerrie Moss[4], Alexandra Sechi[13], Peter De Cruz[5], Rachel Grafton[14], Susan J Connor[13], Ian C Lawrance[11], Richard B Gearry[12], Jane M Andrews[14], Graham L Radford-Smith[3,8,10].

[1]CSIRO Preventative Health Flagship, Parkville, Australia.
[2]CSIRO Computational Informatics/Australian e-Health Research Centre, Brisbane, Australia.
[3]Royal Brisbane and Women's Hospital, Brisbane, Australia.
[4]Flinders Medical Centre, Bedford Park, Australia.
[5]St Vincent's Hospital, Melbourne, Australia.
[6]Townsville Hospital, Townsville, Australia.
[7]Princess Margaret Hospital for Children, Perth, Australia
[8]University of Queensland, Brisbane, Australia
[9]Queensland University of Technology, Brisbane, Australia.
[10]QIMR Berghofer Medical Research Institute, Brisbane, Australia.
[11]University of Western Australia, Harry Perkins Institute for Medical Research, Murdoch, Australia.
[12]University of Otago, Christchurch, New Zealand.
[13]Liverpool Hospital, Sydney, Australia.
[14]Royal Adelaide Hospital, Adelaide, Australia

On behalf of the Australian and New Zealand Inflammatory Bowel Disease Consortium.

*These authors contributed equally to the work.

Corresponding author:

Graham L Radford-Smith

IBD Program

QIMR Berghofer Medical Research Institute

Brisbane, QLD, Australia.

Email: Graham.radford-smith@qimrberghofer.edu.au

Phone: 61736461754

Fax: 61736464336

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ABSTRACT

Background: Maintenance anti-tumour necrosis factor-α (anti-TNFα) treatment for Crohn's disease is standard of care for patients with an inadequate response to corticosteroids and immunomodulators.

Aim: To compare the efficacy and safety of infliximab and adalimumab in clinical practice and assess the value of concomitant immunomodulator therapy.

Methods: We performed an observational cohort study in consecutive patients with Crohn's disease qualifying for anti-TNFα treatment in Australia and New Zealand between 2007 and 2011. Demographic and clinical data were prospectively recorded to identify independent factors associated with induction and maintenance of response to infliximab or adalimumab, or to either anti-TNFα therapy.

Results: Three hundred and twenty-seven patients (183 infliximab, 144 adalimumab) successfully applied for treatment. Eighty-nine percent responded in all groups and median maintenance of response was similar for the two agents. Concomitant immunomodulator with infliximab, but not adalimumab, demonstrated a significantly longer response overall (P=0.002), and significantly fewer disease and treatment-related complications (P=0.017). Corticosteroids at baseline, and/or in the preceding 12 months, was associated with a nine to thirteen times greater risk of disease flare during maintenance treatment as compared to no corticosteroids (P<0.0001). Maintenance of response was similar in the anti-TNF naïve and anti-TNF experienced subgroups.

Conclusions: In this large, real life study, we demonstrate infliximab and adalimumab to have similar response characteristics. However, infliximab requires concomitant immunomodulator to achieve optimal

maintenance of response comparable to adalimumab monotherapy. The results of this study will assist clinicians in further optimizing patient care in their day-to-day clinical practice.

INTRODUCTION

Scheduled anti-TNFα therapy with infliximab *(Remicade (Janssen Biotech, Malvern, PA, USA))* or adalimumab *(Humira (Abbvie, North Chicago, IL, USA))* has long been established as an effective treatment for patients with refractory Crohn's disease (CD) *[1-7]*. The decision to use infliximab or adalimumab in clinical practice is usually determined by the attending physician or the patient. Factors that may be considered in this decision include prior history of anti-TNF therapy and any associated adverse events, the ability to attend a day therapy unit for intravenous (i.v.) infusions, the willingness to consider (self-administered) subcutaneous (s.c.) injections and the patient's history of adherence to previous treatment and management strategies. Clinical data taken from large, observational cohorts comparing the long term efficacy of infliximab and adalimumab are limited *[8]*. A single centre study, which assessed 93 patients (44 infliximab, 49 adalimumab), demonstrated no difference in the remission rates *[9]*. A matched cohort study of 200 anti-TNF naïve CD patients also demonstrated similar response rates at 1 and 2 years between infliximab and adalimumab, but with a significantly better response rate in the subgroup of infliximab patients treated with concomitant immunomodulator therapy *[10]*. A recent Austrian study combining data from 4 tertiary care centres in anti-TNF naïve CD patients demonstrated equivalence for infliximab and adalimumab following induction and at 12 months, but did not replicate the benefits of concomitant immunomodulator with infliximab *[11]*. The majority of published studies have also set inclusion and exclusion criteria for their study populations, and thus do not include *all consecutive CD patients* offered, and treated with, either infliximab or adalimumab *[12]*.

The efficacy of infliximab and adalimumab decreases over time, and it is widely postulated that this is due to the development of antibodies *[13-14]*. There is also increasing evidence that concomitant immunomodulator therapy (IM) with azathioprine, mercaptopurine or methotrexate, reduces the development of anti-drug antibodies, and thus optimises maintenance of response to infliximab. [*15-17*]. Furthermore, concomitant immunomodulators may reduce the risk of infusion reactions and IBD flares. There is mixed evidence regarding the usefulness of immunomodulator co-treatment with adalimumab. An early study identified no benefit *[18]*, while more recent work suggests that immunomodulators during the first semester, or induction period, may reduce treatment failure *[19]*.

Given the paucity of real world clinical data comparing infliximab and adalimumab together with the role of concurrent immunomodulators, the current study addressed three practical questions that face clinicians who wish to use anti-TNF therapy for refractory CD:

1. What factors determine longer term maintenance of response to anti-TNFα therapy?
2. How does the therapeutic efficacy of infliximab compare with adalimumab in day-to-day, non-randomised clinical practice over the longer term? And
3. Are there real world measurable effects of concomitant immunomodulators on treatment durability, and adverse event outcomes, for either biologic agent?

METHODS

Patients and study design

This was an observational cohort study performed across collaborating centres using a prospectively designed and standardised assessment and treatment schedule. Patients with CD refractory to conventional therapy have been able to access either infliximab (since 2007) or adalimumab (since 2008) through government-funded schemes within Australia and in New Zealand. Nine hospitals within the ANZ IBD Consortium *[20]*, and each with a dedicated IBD team, took part in the study. Consecutive patients at each centre with a confirmed diagnosis of CD based upon established criteria *[21]*, and who had successfully applied to receive scheduled anti-TNF therapy with either infliximab or adalimumab were included. The infliximab regime included induction (5mg/kg) at 0, 2 and 6 weeks followed by eight weekly IV infusions. For adalimumab, patients underwent induction with 160mg at week 0, 80mg at week 2 and 40mg at week 6, followed by fortnightly subcutaneous injection of 40mg. The decision to commence either infliximab or adalimumab was based upon a discussion between each clinician and patient. Specific information relating to each selection was not available.

The study included anti-TNF naïve (n=199) and anti-TNF experienced (n=122) patients during the period from October 2007 to December 2011. A retrospective review of ANZ IBD databases containing prospectively entered biologics data, together with chart review, identified baseline demographic and clinical characteristics, including: CDAI; CRP (mg/L); a Montreal classification for each case; smoking data; surgical history; and both previous and current corticosteroid, immunomodulator and biologic drug therapy. For refractory luminal CD, both government schemes require that all patients have been optimized on standard therapy, including therapeutic immunomodulator therapy and at least one course of corticosteroid therapy since diagnosis, but still have active disease at the time of the application. Specifically, the schemes' eligibility criteria mandated that all patients without clinically significant drug intolerances had received a minimum of 3 months of immunomodulator therapy prior to biologic commencement, using either azathioprine (≥ 2 mg/kg), mercaptopurine (≥ 1.0 mg/kg), or methotrexate (≥ 15 mg/week). The perianal disease indication requires ≥ 1 draining perineal fistula, which has not responded to standard therapy including immunomodulators and antibiotics. Patients with documented previous intolerances or allergies to either corticosteroids and/or immunomodulators can successfully apply in the

absence of these drug classes.

Evaluation of induction and maintenance phases

Induction

For the luminal disease indication, induction success was defined as a CD activity index (CDAI) of ≤ 150 or a Paediatric CDAI (PCDAI) in children 6-17 years of age that had fallen by 15 or more and to less than 30. Patients who had a CDAI > 150 or PCDAI ≥30, who required surgery, or had an anti-TNF-related adverse event necessitating treatment withdrawal, were classified as primary non-responders. For the perianal disease indication, induction success was defined as cessation or substantial reduction in fistula output, tenderness and erythema as judged by the treating clinician.

Corticosteroid therapy was classified into the following four subgroups: no corticosteroids at baseline (first dose of anti-TNF therapy) or during 12 months prior to commencing anti-TNF therapy; completing course of corticosteroids at baseline but no additional corticosteroid courses in the 12 months prior to commencing anti-TNF therapy; corticosteroids in the 12 months prior to commencing anti-TNF therapy but not at baseline; corticosteroids in the 12 months prior to commencing anti-TNF therapy and on corticosteroids at baseline.

Given that treatment with either adalimumab or infliximab was un-interrupted from baseline through to maintenance for patients who achieved a CDAI of ≤ 150, the induction phase was analyzed together with the maintenance phase in terms of the effects of concomitant immunomodulator therapy and the potential effects of additional clinical characteristics on long-term treatment response.

Maintenance semesters

For each six-month semester during the maintenance phase, data were gathered pertaining to co-treatment with immunomodulator therapy, adverse anti-TNF events, and disease flares (IBD flares). An IBD flare (‘flare semester’) was defined as an escalation in symptoms requiring commencement, or increase, in corticosteroids, and/or hospitalisation, and/or resective surgery, and/or a new perianal complication (perianal event). Treatment changes not related to a disease flare (e.g. tapering of corticosteroids, cessation of immunomodulators) were recorded separately. Disease remission and hence a “remission semester” was defined by a CDAI of ≤ 150.

A ‘failure semester’ was defined as cessation of either infliximab or adalimumab due to an inability to attain or maintain, remission (CDAI of ≤ 150 or PCDAI<30) when assessed at the end of each six-month semester, or development of an anti-TNF adverse event that prevented ongoing treatment. Any semester that required

a switch to the alternative anti-TNF agent, and/or re-induction, and/or dose intensification due to inability to achieve or maintain remission was also classified as a 'failure semester'. Data pertaining to switching and/or re-induction were not included in this study. Temporary cessation was classified separately, and defined as cessation for a period of ≥ 3 months, as a result of pregnancy, infection, patient choice, or a joint decision by the treating gastroenterologist and the patient.

Flare semesters and failure semesters were compared separately with remission semesters for a range of demographic and clinical factors including: gender, age at diagnosis, disease duration, location, and behavior, smoking history, corticosteroid use, and immunomodulator therapy. To capture the effect of concomitant immunomodulator therapy, analyses were defined by two methods:

a. Concomitant immunomodulator therapy defined as ≥ 3 months of treatment prior to the commencement of anti-TNF therapy, followed by either no concomitant immunotherapy or at least one dose of concomitant immunotherapy during the study period or,
b. Concomitant immunomodulator therapy defined as ≥ 3 months of treatment prior to the commencement of anti-TNF therapy, followed by one of four regimes: 1) no concomitant immunomodulators during anti-TNF therapy, 2) less than 50% of the time on concomitant immunomodulators during anti-TNF therapy, 3) between 50 and 100% of the time on concomitant immunomodulators during anti-TNF therapy, and 4) 100% of the time on concomitant immunomodulators.

Semesters were analysed as a complete collection, with the primary endpoint being cessation of the biologic drug, and secondary endpoints being a disease flare or an anti-TNF adverse event within a semester, whilst still continuing the drug. Survival was defined as time in weeks to either primary non-response or secondary loss of response resulting in cessation of either infliximab or adalimumab and equates with ongoing anti-TNFα treatment free of a failure semester. Infliximab and adalimumab were also compared directly for success at induction, maintenance of response, and the frequency of disease flares and anti-TNF-related adverse events.

Statistical analysis

Data pertinent to each patient's first course of either adalimumab or infliximab from initiation to either last infusion within the study timeframe or failure were included for the purposes of these analyses. Continuous variables were described using mean and standard deviation and analysed using un-paired t-tests. Categorical variables were described using frequencies and percentages and analysed using chi-square. Kaplan-Meier survival analyses were used to analyse individual predictors and display survival curves. Cox proportional hazards regression was used to analyse multivariate survival data. Purposeful selection was

used to create a multivariable model by including variables from the univariate analysis with a p-value <0.10. Variables were then excluded from this model that did not reach significance (p<0.05). Excluded variables were added back to the model one at a time to check for confounding. Hazard ratios and 95% confidence intervals were reported. Logistic regression, adjusting for relevant covariates was used to define odds ratio's (95% confidence intervals (CI)) to assess flare risk.

RESULTS

Patient characteristics

A total of 327 consecutive CD patients at the nine IBD centres were studied after commencing eitherinfliximab (183) or adalimumab (144). Of these, all 327 patients were available for analysis of anti-TNF induction, and 294 patients were available for analysis of ongoing maintenance. By far the most frequent indication for either infliximab or adalimumab was for refractory luminal CD (n=289) followed by refractory paediatric luminal disease (n=23) followed by perianal fistulising disease (n=15). Two hundred and seventy-five patients were infliximab-naïve (75%) and 281 (86%) were adalimumab-naïve.

Patient demographics and clinical features stratified by biologic treatment are given in Table 1, while demographic and clinical features stratified by induction/maintenance phase are given in Supplementary Table 1. Patients treated with adalimumab were older (ADA: 37.4 ±12.2 vs IFX: 33.2 ±12.9, P=0.002), with greater disease duration (adalimumab: 69% >5 years vs infliximab: 54% > 5 years, P=0.019), and a higher frequency of ileal disease (adalimumab: 29% Ileal vs infliximab: 19% Ileal, P=0.034). Paediatric patients with refractory luminal disease were limited to infliximab therapy through the government scheme. The difference in disease duration between treatment groups was no longer significant when this small subgroup was excluded (P=0.206). Median baseline CDAI was marginally higher for the infliximab treatment group as compared with the adalimumab treatment group (adalimumab: 343 vs infliximab: 357, P = 0.046). Median CRP at baseline was not different between treatment groups (adalimumab: 8.9 (IQR: 22.8) vs infliximab: 6.6 (IQR:16.8), P=0.385). Those receiving adalimumab were more likely to have received compassionate adalimumab (25%) prior to entry into the government-subsidized scheme as compared to those receiving infliximab through this scheme (4%)*(P<0.0001)*. Sixty-three patients (19%) did not take concomitant immunomodulators during either the induction or maintenance phases due to drug intolerances or allergies. Of those on concomitant immunomodulators, the most frequently used was azathioprine (148, 45%) followed by mercaptopurine (62, 19%).

Response to induction

From 327 induction periods available for analysis, 163 patients receiving infliximab achieved CDAI/PCDAI/Perianal fistula remission (89%), as did 128 receiving adalimumab (89%). Hence, thirty-six

patients (20 infliximab (11%) and 16 adalimumab (11%)), were classified as primary non-responders and did not continue into maintenance. There were no identifiable clinical differences in those who failed induction as compared to those who remitted (Supplementary Table 1, P>0.05). Concomitant immunomodulator therapy did not significantly influence the rate of primary non-response overall or for either agent (flare: P=0.75 & P=0.37 for infliximab and adalimumab respectively).

Long term treatment response

Induction and maintenance were analysed together given that these 2 phases were part of the same treatment algorithm. There were 1274 semesters available for analysis, including 730 with infliximab (597 infliximab plus immunomodulators (infliximab+immunomodulators) and 133 infliximab monotherapy) and 544 with adalimumab (342 adalimumab plus immunomodulators (adalimumab+immunomodulators) & 202 adalimumab monotherapy). Overall, an IBD flare occurred in approximately one in three semesters (34.3%). The proportion of disease-related flare semesters was similar for adalimumab (35.1%) as compared to infliximab (33.7%) (P=0.15).

The only clinical parameter associated with a flare semester was prior corticosteroid treatment (P<0.0001). Thus, patients who were completing a course of corticosteroids at baseline (but who had not received additional courses of corticosteroids in the 12 months prior to commencing anti-TNF therapy) were nearly nine times more likely to have a subsequent flare (and hence a flare semester) as compared to the reference group (no corticosteroids at baseline nor in previous 12 months) (OR 8.9, 95% CI 3.3 – 27.2). Patients receiving corticosteroids at baseline and during the 12 months prior were at the highest risk of disease flare as compared to the reference group (OR 13.3, 95% CI 6.9 - 27.0, P<0.0001). Gender, age, current smoking, previous bowel resection, disease duration, and concomitant perianal disease did not influence the rate of flares. To further investigate the subgroup of patients who were receiving steroids at baseline and/or in the 12 months prior to commencement of anti-TNF therapy, we compared multiple baseline clinical variables (age, gender, disease location and behaviour, disease duration, presence of perianal disease, smoking, need for surgical resection, CDAI, weight) together with baseline CRP with the above reference group (no corticosteroids at baseline nor in previous 12 months). We did not identify any significant differences between these subgroups.

The effect of concomitant immunomodulator therapy

Concomitant immunomodulator therapy was analyzed in three ways: 1. Effect on flares across semesters; 2. Effect on overall maintenance of response and hence prevention of a failure semester and 3. Effect with adalimumab, as compared to infliximab, therapy. Frequencies of flare semesters, both split for treatment alone, and concomitant immunomodulator therapy within treatment, are shown in Table 2. Overall, IBD

flare semesters were significantly less common in those patients on concomitant immunomodulators (P=0.003). In subgroup analysis, this remained significant for infliximab (0.004) but not for adalimumab (P=0.19). When looking at all adverse events across all semesters, combining all IBD flares with anti-TNF-related adverse events, adverse event frequency was significantly lower in patients on any immunomodulator (P=0.004), however this effect was diluted when we stratified by treatment type, infliximab+immunomodulators (P=0.017) and adalimumab+immunomodulators (P=0.12) as compared to patients on monotherapy. Perianal complications were seen most frequently in those individuals on adalimumab plus immunomodulators, and this reached statistical significance when compared to patients on adalimumab monotherapy (26% versus 10%, P=0.05). Anti-TNF related adverse events were more frequent in those patients receiving infliximab as compared to adalimumab (10% versus 5%, P=0.05).

Maintenance of response, based upon a survival analysis, for the whole anti-TNF population was also significantly influenced by concomitant immunomodulator therapy [(with/without concomitant immunomodulator therapy) P=0.006, Figure 1b]. This remained significant after adjustment for demographic and clinical characteristics including age at commencement of anti-TNF therapy, gender, disease location and behavior and previous treatment with steroids (P=0.025). Analysis of each drug separately demonstrated that maintenance of response was enhanced by concomitant immunomodulators for infliximab (P=0.002, Figure 1c), but not for adalimumab (P=0.332, Figure 1d). There was no significant difference in maintenance of response time between the two treatment groups overall (P=0.97, Figure 1a) or in the minority of patients on either monotherapy (P=0.11, Supplementary Figure-1).

Overall, median survival time between treatments was similar for those treated with adalimumab monotherapy and concomitant therapy (adalimumab monotherapy: 61.8 weeks, adalimumab with concomitant immunomodulator therapy 59.8 weeks), while for those treated with infliximab, the median survival time was 19 weeks longer for those treated with infliximab and concomitant immunomodulator therapy. Patients with a secondary loss-of-response treated with infliximab plus immunomodulators had a longer median survival time as compared with those on infliximab monotherapy, while the secondary loss-of-response subgroup treated with adalimumab plus immunomodulators had a shorter median survival time as compared with those who had been on adalimumab monotherapy.

Assessing changes in survival time for those patients with prior use of either anti-TNFα treatment (Figures 1E & 1F) showed no significant differences using the univariate model. However adjusting for age, gender, disease location, disease behavior and use of immunomodulators, we found that those patients with prior use of infliximab had significantly longer survival time than those patients who had no prior history of treatment with infliximab (P=0.028). The same was not true for adalimumab (P=0.300). Sensitivity analyses to define

model performance for anti-TNF naïve and anti-TNF experienced subgroups, showed very similar results, with c-indices of 0.53 and 0.55 respectively, confirming no bias in assessing survival time when assessing both anti-TNF naïve and anti-TNF experienced subgroups together.

Assessing maintenance of response by differential levels of concomitant immunomodulator therapy identified that in the cohort as a whole, those participants without any concomitant immunomodulator therapy had the shortest survival time compared with those taking concomitant immunomodulator therapy <50% of the time, >50% but less than 100% of the time, and lastly those taking concomitant immunomodulator therapy 100% of the time (Figure 1d, P=0.015). These relationships were strengthened for those taking infliximab (Figure 1e, P=0.007), but were not present for those taking adalimumab (Figure 1f, P=0.663).

DISCUSSION

This large real world study provides a unique insight into what the treating clinician can expect from the step up use of anti-TNF agents in patients with CD refractory to traditional medical management. In particular, there is no major efficacy difference between infliximab and adalimumab but infliximab requires concomitant immunomodulators to achieve optimal maintenance of response. Those patients who receive oral corticosteroids in the 12 months prior to and/or at commencement of anti-TNF are much more likely to lose response.

There are limited detailed, clinical data on the real world durability of anti-TNFα therapy, specifically head-to-head studies comparing the relative efficacy of infliximab as compared to adalimumab for refractory CD, the role of concomitant immunomodulator therapy with each agent, and the frequency of disease and treatment-related adverse events while on anti-TNF therapy. We performed a thorough retrospective observational cohort study based upon prospectively designed government access schemes in Australia and New Zealand. Our data demonstrate similar levels of overall efficacy for infliximab and adalimumab as assessed by the median length of clinical remission (infliximab, 63 weeks versus adalimumab, 61 weeks, P=0.311) and a low overall early failure rate following induction of 11% (36/327). We also confirmed the clinical benefit of concomitant immunomodulator therapy in patients treated with infliximab as measured by a clinically relevant extension in maintenance of response (infliximab with concomitant immunomodulator therapy median weeks = 64 compared with infliximab without concomitant immunomodulator therapy median weeks = 45, P=0.002), but did not observe the same effect for patients treated with adalimumab and immunomodulators (adalimumab with concomitant immunomodulator therapy median weeks = 60 compared with adalimumab without concomitant immunomodulator therapy median weeks = 62, P=0.332). Across all semesters for both agents, concomitant immunomodulator therapy was associated with

significantly fewer disease and anti-TNF related complications (P=0.003). However, immunomodulator therapy in combination with adalimumab was associated with a higher risk of perianal complications (P=0.04). We did not identify any clinical predictors that significantly associated with a primary non-response to anti-TNFα therapy.

Studies directly comparing infliximab with adalimumab in the context of refractory CD are limited to a single centre retrospective series of 93 cases (infliximab 44, adalimumab 49) *[9]*, a retrospective matched cohort study (n=200) *[10]*, and an observational cohort study *[11]*. While the first included all consecutive patients who satisfied standard local criteria, the matched cohort study, by definition, had to select patients who were also anti-TNF naïve. The study by Narula and colleagues similarly excluded anti-TNF experienced subjects and utilized a Harvey-Bradshaw threshold score, which correlates with mild-to-moderate CD *[11]*. The rates of induction success, and maintenance of response, across these two studies are comparable to the current study, both overall and for the individual anti-TNF agents. The figures are also higher than those reported in randomised clinical trials (RCT), as previously noted, in part related to prior anti-TNF exposure (for adalimumab trials), higher rates of concomitant immunomodulator therapy seen in cohort studies , the clinical heterogeneity introduced by large numbers of recruiting sites to large RCT, and the enrollment of patients without active disease *[14]*.

The current study benefits from the use of a standard application process, which necessitates treatment optimisation, including use of immunomodulators, prior to considering any refractory CD patient for anti-TNF therapy. This includes the prospective collection and detailed recording of CDAI data and perianal fistulising data for each case. Detailed recording of concomitant immunomodulator therapy throughout the study period allowed subgroup analysis, comparing the outcomes of patients on no immunomodulators with different levels of immunomodulator use, and thus determining whether there was a dose-response relationship. Furthermore, utilizing two separate categorizations of concomitant therapy enabled the dissection of survival times for those treated either with or without immunosuppression for both adalimumab and infliximab.

Our findings for concomitant immunomodulator therapy in patients receiving infliximab are consistent with data generated by both recent cohort studies, and by RCT, and with the earliest report on concomitant therapy from 2001 *[22]*. The data, differ from the initial RCT and early clinical studies that demonstrated no benefit. The current dataset explored the relationship between infliximab and immunomodulator use across a range of dose intensities (Figure 1d) with those individuals on no concomitant immunomodulators experiencing the shortest maintenance of response times. We also observed that individuals taking immunomodulators 100% of the time did not demonstrate the longest maintenance of response time. Factors

contributing to this include disease severity and small numbers in each of the immunomodulator subgroups.

In contrast to infliximab, we did not find a benefit for adalimumab and immunomodulator therapy. While a recent retrospective study indicates that the use of immunomodulator therapy over the first three months of induction may lower adalimumab failure rates independent of ongoing immunomodulator use *[19]*, our study could not replicate this finding. Factors that may influence these different outcomes include the larger fraction of patients with B1 (non stricturing, non penetrating) disease in the European study (59% with B1 disease in Reenaers et al *[19]* versus 46% with B1 disease in current study, P=0.015) and the definitions of drug failure and clinical response/remission in each study. The use of adalimumab with concomitant immunomodulators was associated with a higher risk of new perianal complications at 23% as compared to adalimumab monotherapy with a rate of 9% (P=0.04). However, the numbers in these subgroups were small (Table 2) and hence caution should be used in any interpretation of these analyses.

The current study benefits from detailed data on the use of corticosteroids both prior to, and during, treatment with either anti-TNFα. We identify a dose-response relationship between corticosteroid use and the risk of IBD flares. Hence, individuals with the greatest corticosteroid exposure prior to first anti-TNFα treatment were up to thirteen times more likely to experience a disease flare (P<0.0001). Importantly, this survived multivariate analysis of gender, age, current smoking, previous bowel resection, CDAI score, disease duration, and concomitant perianal disease. Although this may in part reflect greater disease burden, and hence a greater requirement for ongoing corticosteroids, we further addressed this by analysis of disease characteristics in the corticosteroid and no corticosteroid subgroups and found no significant differences. These data also provide further support for the concept of a top-down approach to treatment in patients with CD, thus reducing corticosteroid exposure and improving both short and long term outcomes *[23]*.

Potential limitations of the current study include its retrospective nature (although the data pertaining to each application for anti-TNF therapy was collected prospectively), patients were not randomised to infliximab versus adalimumab, nor to mono- or combination therapy, and no serum was prospectively collected for either measurement of trough drug levels or anti-drug antibodies.

This real world study of refractory CD will reassure clinicians in terms of the short and long-term treatment outcomes for infliximab and adalimumab. The results will assist them in making decisions concerning concomitant immunomodulator use and providing explanations to their patients in terms of the need to try to withdraw corticosteroids. Individuals with extensive disease, including perianal disease, together with those who have a history of poor adherence to therapy, may benefit from infliximab with immunomodulators, while older patients with no issues around adherence but with additional co-morbidities such as sun-related

skin damage may benefit from adalimumab monotherapy. Further real-life cohort studies will benefit from the addition of therapeutic drug monitoring of anti-TNFα therapy and the impact of drug levels on response and hence long-term outcomes.

AUTHORSHIP:

Guarantor of the article: A/Prof Graham Radford-Smith

Author contributions: GR-S was responsible for the study concept and design, data acquisition, analysis and interpretation, funding, drafting and revision of the manuscript. JD was responsible for analysis and interpretation of data, drafting and revision of manuscript. FH was responsible for data acquisition, drafting of the manuscript. PB, SB, GM, ZG, PL, SJC, ICL, RBG and JMA were responsible for acquisition of data, critical review of the manuscript. LVJ assisted with statistical analysis. KS, KK, RP, DM, JF, GRT, JVT, NSD, SEC, KM, AS, PDC and RG were responsible for data acquisition.

All authors approved the final version of the manuscript.

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TABLE AND FIGURE LEGENDS

Table 1. Demographic and clinical characteristics of study population.

Footnote: Statistics are presented for the comparison between treatment groups. P-values are presented from the use of either Independent Samples T-test or Mann-Whitney U test for continuous data, and Chi-square test for analysis of frequencies.

Supplementary Table 1: Demographic and clinical characteristics of the primary non-response (≤3 months) as compared to the maintenance of response (>3 months) groups.

Footnote: Statistics are presented for the comparison between treatment groups. P-values are presented from the use of either Independent Samples T-test or Mann-Whitney U test for continuous data, and Chi-square test for analysis of frequencies.

Table 2. Adverse event frequencies within the different treatment groups.

Footnote: Frequencies of adverse events are shown for each of the adverse events that occurred over the treatment period. Percentages for the All AE line are in proportion to the total number of semesters. Percentages for IBD flare represent the total number of IBD related flares in proportion to the total number

of adverse events recorded. All other line percentages represent the proportion that each flare occurred within the left heading. For example all flare types under the heading "All AE" are proportional to the total number of adverse events, while the flare types that fall under the IBD flares heading are proportional to the total number of IBD flares.

Figure 1: Survival curves between treatments and with or without concomitant immunomodulator.
Survival time is defined as time in weeks to either primary non-response or secondary loss of response to either Infliximab or Adalimumab. A) Infliximab vs adalimumab; B) Use of concomitant immunomodulators, yes/no; C) Use of concomitant immunomodulators, yes/no for infliximab only; D) Use of concomitant immunomodulators, yes/no for adalimumab only; E) Previous use of adalimumab for those in the adalimumab treatment group only; F) Previous use of infliximab for those in the infliximab treatment group only;
G) Analysis of concomitant immunomodulator use in those who had no immunomodulator (none), <50% of the time,≥50% <100% of the time, and 100% of the time, all patients; H) Analysis of concomitant immunomodulator use in those who had no immunomodulator (none), <50% of the time,≥50% <100% of the time, and 100% of the time, infliximab only; I) Analysis of concomitant immunomodulator use in those who had no immunomodulator (none), <50% of the time,≥50% <100% of the ti me, and 100% of the time, adalimumab only.

Supplementary Figure-1: Survival curves - monotherapy
(A) Infliximab monotherapy versus adalimumab monotherapy and (B) infliximab plus immunomodulator versus adalimumab monotherapy

TABLES

Table 1: Demographic and clinical characteristics of study population

Characteristic		Total (N=327)	Adalimumab (N=144)	Infliximab (N=183)	*p*-value
CDAI at first infusion	Median (IQR)	350.5 (81.8)	343.0 (73.0)	357.0 (87.5)	0.046
Age at first infusion	mean (SD)	35.0 (12.7)	37.4 (12.2)	33.2 (12.9)	***0.002***
Treatment duration	Weeks, median (IQR)	61.8 (100)	61.1 (95.4)	63.2 (102.4)	0.311
CRP	median (IQR)	8.2 (19)	8.9 (22.8)	6.6 (16.8)	0.385
Weight	mean (SD)	72.0 (19.3)	73.6 (16.2)	70.8 (21.2)	0.229
Gender	Female	178 (54%)	84 (58%)	94 (51%)	
	Male	149 (46%)	60 (42%)	89 (49%)	0.209
Smoking	Never	187 (57%)	76 (53%)	111 (61%)	
	Current	73 (22%)	31 (22%)	42 (23%)	
	Ex	64 (20%)	36 (25%)	28 (15%)	0.090
	missing	3 (1%)	1 (<1%)	2 (<1%)	

Disease duration	≤2	68 (21%)	21 (15%)	47 (26%)	
(years)	> 2≤5	59 (18%)	24 (17%)	35 (19%)	
	>5	198 (61%)	99 (69%)	99 (54%)	*0.019*
	missing	2 (<1%)	0	2 (<1%)	
Location	Ileal	76 (23%)	42 (29%)	34 (19%)	
	Colonic	91 (28%)	32 (22%)	59 (32%)	
	Ileocolonic	154 (47%)	68 (47%)	86 (47%)	*0.034*
	missing	6 (2%)	2 (<1%)	4 (2%)	
Behaviour	Non stricturing, non penetrating	154 (47%)	66 (46%)	88 (48%)	
	Stricturing	80 (24%)	39 (27%)	41 (22%)	
	Penetrating	89 (27%)	38 (26%)	51 (28%)	0.649
	missing	4 (1%)	1 (<1%)	3 (2%)	
Perianal disease	No	172 (53%)	83 (58%)	89 (49%)	
	Yes	154 (47%)	61 (42%)	93 (51%)	0.117
	missing	1 (<1%)	0 (0%)	1 (<1%)	
Surgery previous	none	184 (56%)	74 (51%)	110 (60%)	
(resection)	at least 1	143 (44%)	70 (49%)	73 (40%)	0.115
	missing	0	0	0 (0%)	
Previous adalimumab	No	281 (86%)	107 (74%)	174 (95%)	
	Yes	44 (13%)	36 (25%)	8 (4%)	*5.48E-08*
	missing	2 (1%)	1 (<1%)	1 (<1%)	
Previous infliximab	No	245 (75%)	102 (71%)	143 (78%)	
	Yes	78 (24%)	40 (28%)	38 (21%)	0.135
	missing	4 (1%)	2 (<1%)	2 (<1%)	
Immunomodulator	None	63 (19%)	33 (23%)	28 (15%)	
	Azathioprine	148 (45%)	54 (38%)	91 (50%)	
	Mercaptopurine	62 (19%)	32 (22%)	35 (19%)	
	Methotrexate	52 (16%)	23 (16%)	29 (16%)	
	Other	2 (1%)	2 (1%)	(0%)	0.100
	missing	0	0	0	

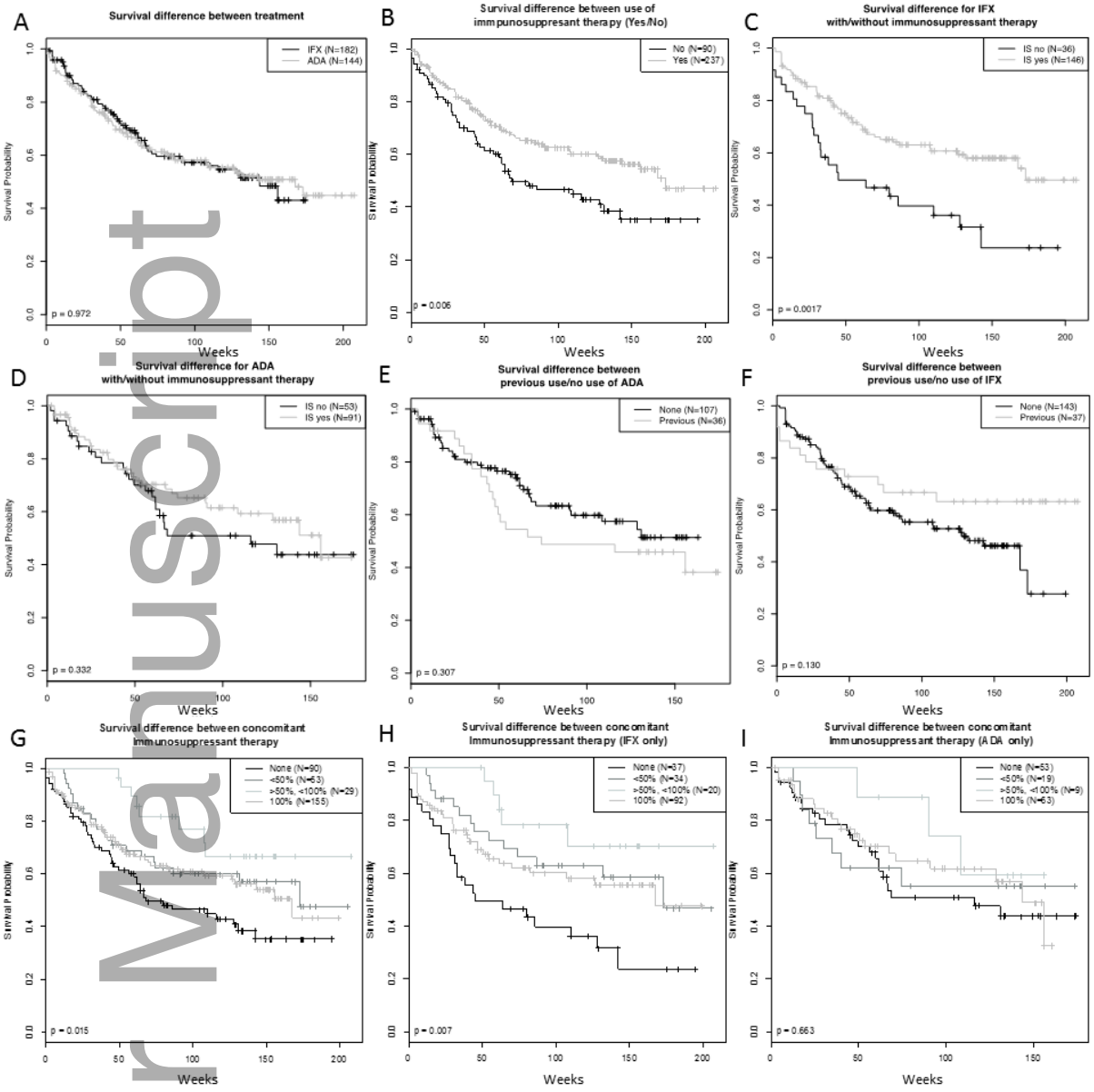
Table 2: Adverse event frequencies within the different treatment groups

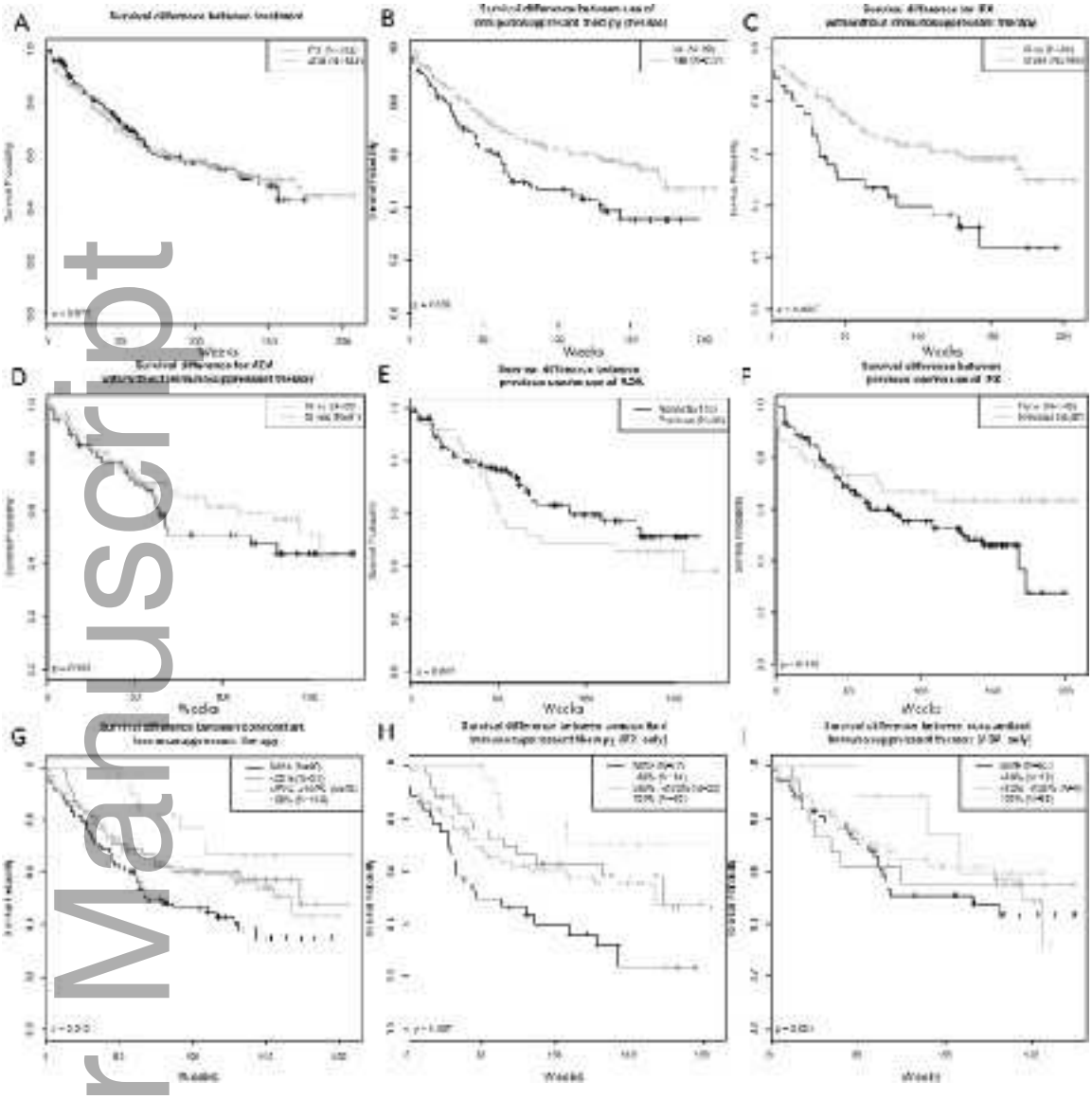
	Adalimumab			**Infliximab**		
Treatment	**All**	**Without IM**	**With IM**	**All**	**Without IM**	**With IM**
N Semesters	544	202	342	730	133	597
All AE	289	116	173	371	80	291
IBD flare	191 (66%)	78 (67%)	113 (65%)	246 (66%)	59 (74%)	187 (64%)
Other	42 (15%)	12 (10%)	30 (17%)	31 (8%)	4 (5%)	27 (9%)

Anti-TNF	15 (5%)	7 (6%)	8 (5%)	36 (10%)	9 (11%)	27 (9%)
Infection	41 (14%)	19 (16%)	22 (13%)	58 (16%)	8 (10%)	50 (17%)
IBD flare	191	78	113	246	59	187
Change in steroid	109 (57%)	49 (63%)	60 (53%)	147 (60%)	33 (56%)	114 (61%)
Hospital admission	38 (20%)	18 (23%)	20 (18%)	43 (17%)	11 (19%)	32 (17%)
Perianal event	37 (19%)	8 (10%)	29 (26%)	49 (20%)	13 (22%)	36 (19%)
Surgery	7 (4%)	3 (4%)	4 (4%)	7 (3%)	2 (3%)	5 (3%)

FIGURES

Figure 1: Survival curves (defined as time in weeks to primary non-response or secondary loss of response following commencement of either anti-TNFα agent) - between treatments and with or without concomitant immunomodulator





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