Original Article

Anti-TNF Therapeutic Drug Monitoring in Postoperative Crohn’s Disease


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Abstract

Background: Anti-TNF prevents postoperative Crohn’s disease recurrence in most patients but not all. This study aimed to define the relationship between adalimumab pharmacokinetics, maintenance of remission and recurrence.

Methods: As part of a study of postoperative Crohn’s disease management, some patients undergoing resection received prophylactic postoperative adalimumab. In these patients, serum and fecal adalimumab concentration and serum anti-adalimumab antibodies [AAAs] were measured at 6, 12 and 18 months postoperatively. Levels of Crohn’s disease activity index [CDAI], C-reactive protein [CRP] and fecal calprotectin [FC] were assessed at 6 and 18 months postoperatively. Body mass index and smoking status were recorded. A colonoscopy was performed at 6 and/or 18 months.

Results: Fifty-two patients [32 on monotherapy and 20 on combination therapy with thiopurine] were studied. Adalimumab concentration did not differ significantly between patients in...
endoscopic remission vs recurrence [Rutgeerts ≥ i2] [9.98 µg/mL vs 8.43 µg/mL, \( p = 0.387 \)]. Patients on adalimumab monotherapy had a significantly lower adalimumab concentration [7.89 µg/mL] than patients on combination therapy [11.725 µg/mL] \( [p = 0.001] \), and were significantly more likely to have measurable AAA [31% vs 17%, \( p = 0.001 \)]. Adalimumab concentrations were lower in patients with detectable AAA compared with those without [3.59 µg/mL vs 12.0 µg/mL, \( p < 0.001 \)]. Adalimumab was not detected in fecal samples. Adalimumab serum concentrations were lower in obese patients compared with in non-obese patients \( [p = 0.046] \).

**Conclusion:** Adalimumab concentration in patients treated with adalimumab to prevent symptomatic endoscopic recurrence postoperatively is, for most patients, well within the therapeutic window, and is not significantly lower in patients who develop recurrence compared with in those who remain in remission. Mechanisms of anti-TNF failure to prevent postoperative recurrence remain to be determined in these patients.

**Key Words:** Inflammatory Bowel Disease; adalimumab; anti-TNF; therapeutic drug monitoring

1. Introduction

Adalimumab [Humira; AbbVie Laboratories, AbbVie Park, IL] is a subcutaneously administered, recombinant, fully humanized, immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to human TNF. Controlled trials have demonstrated safety and efficacy of adalimumab in the treatment of moderate to severe Crohn’s disease for induction and maintenance of remission.\(^1\)\(^-\)\(^4\) Although anti-TNF therapy is the most effective at preventing disease recurrence after intestinal resection,\(^5\) it is not always effective. The factors that cause some patients to have disease recurrence after surgery despite such therapy are unknown. Primary and secondary loss of response to anti-TNF drugs when treating established luminal disease is common,\(^6\) but whether this applies in the postoperative setting, in which the disease burden is very low, is unknown.

A low serum concentration of adalimumab and the development of anti-adalimumab antibodies [AAAs] have been implicated in the development of adalimumab failure and poor clinical outcomes in Crohn’s disease.\(^7\)\(^-\)\(^8\) When treating luminal disease, serum concentrations of adalimumab are higher in those achieving clinical remission and mucosal healing and have been found to be inversely associated with C-reactive protein,\(^9\)\(^-\)\(^10\) although prospective data are lacking. In the Trough Level Adapted Infliximab Treatment [TAXIT]\(^11\) trial, dose optimization of anti-TNF therapy to achieve “target” or optimal drug concentration increased the proportion of patients in clinical remission. In the maintenance phase of the study, anti-TNF therapeutic drug monitoring led to a reduction in the number of disease flares and reduction in C-reactive protein [CRP].

Primary non-response or secondary loss of response are relatively easy to recognize in the setting of luminal disease. However, the nature of the disease–drug relationship in the postoperative setting, in which the starting point is absence of macroscopic disease, is unknown. Small studies to date examining this relationship have presented contradictory messages about the utility of therapeutic anti-TNF monitoring postoperatively.\(^12\)\(^-\)\(^13\) The most recent and largest study, a retrospective review of 73 anti-TNF patients treated postoperatively, found that lower IFX concentrations and presence of anti-infliximab [IFX] antibodies were associated with the likelihood of endoscopic recurrence postoperatively, but no such association was demonstrated for adalimumab.\(^14\)

In a study of 6 patients on prophylactic adalimumab monotherapy, drug concentrations and AAAs in relation to endoscopic and clinical outcomes were assessed after intestinal resection in Crohn’s disease. Bodini et al.\(^12\) found that median adalimumab trough concentrations in patients with clinical or endoscopic recurrence were lower than in those who maintained remission, implying that measurement of adalimumab concentration and AAAs after surgery could be useful in reducing postoperative recurrence.\(^12\) In another study of 5 patients on low-dose IFX, none experienced postoperative endoscopic recurrence one year following surgery, despite subtherapeutic IFX concentrations.\(^13\)

This study aimed to explore the relationship between adalimumab drug pharmacokinetics and disease course in the postoperative setting, when disease burden is usually low. We aimed to determine specifically whether postoperative Crohn’s disease recurrence relates to low serum adalimumab concentration, with or without the development of antibodies to adalimumab.

The role of adalimumab pharmacokinetics in the recurrence of Crohn’s disease after resection was prospectively studied by relating serum adalimumab and AAA concentrations to endoscopic disease recurrence, clinical recurrence as measured by the Crohn’s disease activity index [CDAI], the serum marker of inflammation CRP, the marker of early microscopic inflammation faecal calprotectin [FC], smoking and BMI. This study also aimed to explore a possible role of faecal drug loss.

2. Methods

2.1. The clinical postoperative recurrence [“POCER”] study

The Post-Operative Crohn’s Endoscopic Recurrence [“POCER”] study was a prospective randomized controlled trial that assessed the value of postoperative endoscopic assessment and treatment intensification for early mucosal recurrence. Patients were stratified according to risk of recurrence. Smokers, patients with perforating disease; or patients with ≥1 previous resection were classified as “high-risk”; all others were “low-risk”. All patients underwent resection of all macroscopic disease and then received 3 months of metronidazole. High-risk patients also received daily azathioprine [2 mg/kg/day] or 6-mercaptopurine [1.5 mg/kg/day]. High-risk patients intolerant of thiopurine received adalimumab induction [160 mg/80 mg] and then 40 mg 2-weekly. Low-risk patients received no further medication.

Patients were randomized to colonoscopy at 6 months [active care] or no colonoscopy [standard care]. For endoscopic recurrence [Rutgeerts score ≥ i2] at 6 months, patients stepped-up to thiopurine, fortnightly adalimumab with thiopurine, or weekly adalimumab. The primary end-point was endoscopic recurrence at
18 months. Endoscopic remission was defined as Rutgeert’s score i0 or i1 [i0 = no lesions, i1 = mild superficial anastomotic lesions], and recurrence defined as i2, i3 or i4 [moderate to severe lesions].

One hundred and seventy-four patients were included at 17 hospitals in Australia and New Zealand. One hundred and one of 122 patients randomized to the active arm [ileo-colonoscopy at 6 months with drug adjustment based on endoscopic findings] were high-risk, compared with 44 of 56 in the standard care arm [Figure 1].

CDAI, CRP and FC were measured pre-operatively [baseline] and at 6, 12 and 18 months postoperatively. Patient BMI and smoking status were recorded at study entry.

All patients provided written informed consent before inclusion in the study. Ethical approval for the study was obtained from the Human Research Ethics Committees of the participating hospitals [Clinical Trial Registration: NCT00989560].

2.2. Endoscopic disease assessment
At ileo-colonoscopy, mucosal recurrence at the anastomosis and neo-terminal ileum was assessed according to the Rutgeerts score15 by the endoscopist, who was aware of the patient’s treatment. For the 6- and 18-month colonoscopies, endoscopic remission was defined as Rutgeert’s score i0 [no lesions] or i1 [≤5 aphthous lesions] and recurrence as i2 [>5 aphthous lesions or larger lesions confined to anastomosis], i3 [diffuse ileitis], or i4 [diffuse inflammation with large ulcers and/or narrowing].

Photographs of the anastomosis and neo-terminal ileum were scored again by 2 investigators [PDC and MAK] blinded to the endoscopist’s score and the patient’s identity and treatment.

A final consensus score was determined by the 2 blinded assessors.

2.3. Adalimumab and anti-adalimumab antibody concentration measurements
Serum samples were taken at 6, 12 and 18 months postoperatively from patients receiving adalimumab for at least 6 months, according to when adalimumab was commenced postoperatively. Serum samples were taken irrespective of the timing of the last administered dose of adalimumab.

Samples were stored at –20°C until the conclusion of the clinical study, at which time all samples were analysed simultaneously. Adalimumab and AAA concentration measurements were performed by Prometheus Laboratories [San Diego, CA, USA], using a liquid-phase mobility shift assay. The threshold level for both adalimumab and AAA were defined as 1.65 SDs from the mean, obtained previously, of 100 samples from adalimumab-exposed participants [0.58 µg/mL for adalimumab and 1.7 U/mL for AAA].

2.4. Faecal adalimumab drug concentration
Stool samples were collected pre-operatively and at 6, 12 and 18 months after surgery. Samples were stored at –80°C until the conclusion of the clinical study, at which time all samples were analysed simultaneously.

Faecal adalimumab concentrations were measured in patients exposed to adalimumab postoperatively using a proprietary, sensitive, fluorescence-based immunoassay performed by Prometheus Laboratories. Detailed methodology is included in a supplementary document.

Figure 1. Patient flow diagram for this study.
2.5. Faecal calprotectin measurement

Stool samples were collected pre-operatively and at 6, 12 and 18 months after surgery. Samples were stored at −80°C until the conclusion of the clinical study, at which time all samples were analysed simultaneously.

FC was measured by a quantitative enzyme immunoassay [FCAL \textsuperscript{TM}, Bühlmann, Schonenbuch, Switzerland] as per the manufacturer's instructions, without knowledge of patient data. Concentrations were expressed as μg/g of stool.

The upper limit of the normal range of FC in patients without gut inflammation is well defined as 50 μg/g.\textsuperscript{16} Faecal calprotectin > 100 μg/g is accurate for the diagnosis of postoperative endoscopic recurrence for patients with Crohn's disease.\textsuperscript{17,18}

2.6. Statistical analysis

Data were analysed using STATA12 [StataCorp, College Station, TX]. Associations between categorical data were assessed using either Chi-square or Fisher's exact test. Non-parametric comparison of continuous variables was performed using Wilcoxon rank sum. Associations between endoscopic disease and adalimumab titre, AAA, CDAI, CRP and FC were assessed by logistic regression analysis for binary outcomes and by the determination of Spearman's rank correlation coefficient [\(\rho\)] for non-parametric correlations. Gamma regression was used to determine the predictors of the drug concentration at both 6 and 18 months. Smoking was analysed as a binary variable by comparing current with past and never smokers, and the reverse.

3. Results

3.1. Patient study disposition and patient demographics

Table 1 shows the patient demographics. Of the 174 patients who received treatment as part of the POCER study, 72 patients received adalimumab at some point during the trial. Of these, 52 patients [mean age 38 years, 26 male] had matched endoscopic data available and were included in this sub-study with a total of 125 serum samples collected for analysis. Thirty-two [61.5%] patients were on adalimumab monotherapy and 20 [38.5%] patients were on adalimumab plus thiopurine combination therapy. Seven patients had previously been exposed to adalimumab at some point prior to surgery. Of the 52 patients, 20 [38.5%] were smokers at the time of surgery.

3.2. Adalimumab serum drug concentration, endoscopic recurrence, clinical recurrence, smoking status, CRP and FC

Patient randomization details [active versus standard care] are shown in Figure 1. Of the 52 patients, 43 were in the active care arm and nine in the standard care arm. All patients in the active care arm had a colonoscopy at 6 months, and 40 of 43 had a colonoscopy at 18 months; 3 of the 43 had dropped out of the study between 6 and 18 months. In the standard care arm, all 9 patients had a colonoscopy at 18 months.

Forty-three patients had an endoscopy at 6 months and 49 at 18 months. One hundred and twenty-five serum samples could be

<table>
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<th>Table 1. Patient demographics.</th>
<th>Overall</th>
<th>Standard care</th>
<th>Active care</th>
<th>(p)</th>
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<td>0</td>
<td>20 [46.5]</td>
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*Three patients dropped out prior to 18-month colonoscopy
matched to an endoscopy at either 6 or 18 months. Endoscopic recurrence [Rutgeerts score ≥ i2] was seen in 24 patients [58%] at 6 months and 18 patients [37%] at 18 months. Combining 6- and 18-month endoscopic outcomes, adalimumab concentration did not differ significantly between those in endoscopic remission compared with recurrence [9.98 µg/mL (interquartile range [IQR] 4.69–14.95) vs 8.43 µg/mL (IQR 4.47–10.98), p = 0.387] Figure 2. When examined at 6 and 18 months separately, there was no significant difference in drug concentration between those with endoscopic remission [n = 18] vs recurrence [n = 3] at 6 months (10.50 µg/mL [IQR 5.58–14.22] vs 8.43 µg/mL [IQR 0–12.93], p = 0.482) or 18 months [10.5 µg/mL [n = 31; IQR 4.69–16.13] vs 8.62 µg/mL [n = 18; IQR 4.45–10.98], p = 0.642), respectively.

There were no significant differences when adalimumab drug concentrations were compared between each of the Rutgeerts scores, namely i0 to i4 [p = 0.495]. The median adalimumab drug concentration was 9.52 µg/mL [IQR 5.58–14.14] for Rutgeerts score i0 [n = 37], 9.375 µg/mL [IQR 2.1–16.25] for i1 [n = 24], 8.87 µg/mL [6.85–12.65] for i2 [n = 14], 0 µg/mL for i3 [n = 1] and 6.68 µg/mL [IQR 4.85–16.38] for i4 [n = 4] (Quartile 1 vs Quartile 3; p = 0.228). Adalimumab concentration values from this study were divided evenly across four quartiles. The median plasma adalimumab concentrations were 10.33 µg/mL (IQR 4.47–10.98), 7.89 µg/mL (IQR 4.45–10.98), 6.45 µg/mL (IQR 4.49–9.10) for i4 [n = 6]. When 6- and 18-month time points were examined separately, median drug concentrations across Rutgeerts score were not significantly different.

The adalimumab concentration was not significantly different, at 6 or 18 months, according to prior-to-study adalimumab exposure. The median drug concentration for adalimumab-naïve patients compared with previously exposed patients were 6.45 µg/mL [IQR 0–11.99] vs 4.13 µg/mL [IQR 0–9.98], p = 0.646 [6 months] and 9.83 µg/mL [IQR 4.85–15.92] vs 6.85 µg/mL [IQR 3.44–9.30], p = 0.128 [18 months], respectively.

The relationship between adalimumab concentration and endoscopic, clinical and biochemical outcomes was analysed further by dividing adalimumab concentration values into quartiles, with the number of samples distributed evenly across the quartiles: Quartile 1 [19 samples], Quartile 2 [23 samples], Quartile 3 [16 samples], Quartile 4 [18 samples]. Figure 3 shows the matched endoscopic outcome data, where available, across the 4 quartiles. The higher adalimumab plasma concentration quartiles were not associated with higher rates of endoscopic remission [p = 0.228] or clinical remission [CDAI < 150] [p = 0.171], normal CRP < 5 [p = 0.687] or FC < 100 [p = 0.460]. Endoscopic and clinical remission rates were 74% and 29%, respectively, for patients in the lowest adalimumab quartile, 56% and 53% in Quartile 2, 81% and 42% in Quartile 3 and 83% and 53% in Quartile 4, respectively.

The adalimumab concentration was significantly higher at 18 months in those patients who were commenced on adalimumab at 6 months in response to disease recurrence, when compared with those commenced on adalimumab immediately following surgery (10.33 µg/mL [IQR 8.03–15.71] vs 7.43 [2.11–12.65], p = 0.044). This likely reflects the fact that patients commenced on adalimumab immediately postoperatively [baseline] were on adalimumab monotherapy, whereas most patients commenced on adalimumab at 6 months were also on a thiopurine. The adalimumab concentration was significantly lower in patients on monotherapy (7.89 µg/mL [IQR 3.81–13.02]) compared with patients on combination therapy (11.725 µg/mL [IQR 8.45–16.38], p = 0.001) when samples from all available time points were considered [Figure 4]. Twenty patients [39%] in this study were current smokers, compared with 32 who were non-smokers. Median adalimumab concentrations for these patients, across all time points, were...
not significantly different between smokers (8.86 µg/mL [IQR 4.20–13.01]) and non-smokers (9.45 µg/mL [IQR 4.92–14.85], \( p = 0.665 \)).

3.3. Serum adalimumab drug concentration and body mass index

Of the 52 patients, 46 [88%] had a body mass index [BMI] calculated. BMI was classified as underweight \(<18.5\), healthy weight \([18.5–24.9]\), overweight \([25–30]\) or obese \(\geq30\) as per the World Health Organization guidelines.\(^{19}\) The median adalimumab concentration was highest in underweight patients \((14.54 \, \mu \text{g/mL} \, [\text{IQR} 12.65–16.43])\) and decreased as BMI increased [Figure 5]. These differences were significant when all 4 groups were compared \( [ p = 0.046 ] \).

3.4. Faecal adalimumab drug concentration

Of the 52 patients, 47 had faecal samples available for adalimumab concentration analysis. A total of 91 samples were collected at 6, 12 or 18 months postoperatively. All samples tested showed results below the lower limit of quantification.

3.5. Serum adalimumab concentration and endoscopic findings, CDAI, CRP and faecal calprotectin

There was a weak inverse correlation between serum adalimumab concentration and FC \( [ r = -0.246, \, p = 0.034 ] \) and CDAI \( [ -0.381, \, p < 0.001 ] \), but not with CRP \( [ r = -0.191, \, p = 0.096 ] \) or Rutgeerts score \( [ r = -0.080, \, p = 0.491 ] \).

3.6. Anti-adalimumab antibodies

AAAs were present in 15 of the 52 [29%] patients and 35 of 125 [28%] samples. AAAs were found more frequently in patients with Adalimumab experience prior to study entry [43%] compared with those who were adalimumab naïve [26%], although numbers of adalimumab-experienced patients were small [7 patients]. The presence of AAAs was not associated with a higher risk of endoscopic recurrence when compared with those without when 6- and 18-months endoscopic outcomes were combined [20% vs 26%, \( p = 0.597 \)]. Statistical analysis of the 6- and 18-month postoperative outcomes was not performed independently because of the small number of patients with antibodies present.

AAAs were more prevalent in those on monotherapy versus combination therapy [31% vs 17%, \( p = 0.001 \)]. Median adalimumab concentrations were lower in patients with detectable AAAs compared with those without \((3.59 \, \mu \text{g/mL} \, [\text{IQR} 1.50–5.58] \, vs \, 12.0 \, \mu \text{g/mL} \, [\text{IQR} 8.26–16.10], \, p = 0.001 \) Supplementary Figure S1]). If AAAs were detected, they persisted in all subsequent samples in all patients. In 11 of the 15 patients, AAAs developed within the first 6 months of commencing adalimumab.

3.7. Multivariate analysis

No association between endoscopic recurrence and adalimumab drug level was observed at 6 or 18 months when adjusted for the presence of AAAs, CRP or BMI. At 18 months, only the presence of AAAs and increasing BMI were significantly associated with a reduction in adalimumab drug concentration when adjusted for endoscopic recurrence and CRP. Those with detectable AAAs had a 92% lower serum adalimumab concentration \( [\text{CI} \, 42–143\%], \, p < 0.001 \). A 1-point increase in BMI led to a 5% reduction in serum adalimumab concentration \( [\text{CI} \, 0.5–9.4\%], \, p = 0.028 \). Detectable AAAs at 6 months influenced adalimumab drug concentration at 18 months, with these patients having a 98% lower drug concentration at 18 months \( [\text{CI} \, 41–155\%], \, p = 0.001 \). No other factors at 6 months predicted drug concentration at 18 months.

4. Discussion

There is growing evidence that therapeutic drug monitoring of anti-TNF drugs and antibodies against anti-TNF drugs may guide therapeutic decision-making for Crohn’s disease patients.\(^{10}\) Higher concentrations of anti-TNF drugs are associated with better outcomes, including clinical remission and mucosal healing, in patients with active luminal disease.\(^{20}\) Adalimumab serum drug concentrations associated with clinical remission in luminal Crohn’s disease range from 3 to 5.85 µg/mL,\(^{10,11}\) with a sensitivity and specificity of 68% and 71%, respectively. A concentration cut-off of 8.1 µg/mL has been found in a retrospective study to best discriminate between mucosal healing and lack of healing, with a sensitivity and specificity of 91% and 76%, respectively.\(^{9}\) In many of these studies, endoscopic disease burden is unknown and is likely to be a factor affecting drug concentration. This study assessed therapeutic drug monitoring in patients who had undergone surgical resection of all active intestinal
Crohn’s disease, providing a unique setting for the understanding of the effect of anti-TNF drug concentration on the development of disease. This study found that adalimumab drug concentrations did not correlate with endoscopic recurrence after Crohn’s disease resection. A significant but weak correlation was seen between adalimumab drug concentration and FC, suggesting that higher anti-TNF concentrations are associated with less microscopic inflammation, a probable precursor to later macroscopic inflammation.

Three studies have previously examined anti-TNF drug titres in Crohn’s disease patients postoperatively, with inconsistent results. In one study, 6 patients were treated with prophylactic adalimumab monotherapy after intestinal resection for Crohn’s disease. Adalimumab trough concentration and AAAs were analysed with respect to endoscopic and clinical outcomes. Median adalimumab concentrations in patients with postoperative clinical or endoscopic recurrence were lower when compared with those who maintained remission. All patients remained in clinical and endoscopic remission for an average of 18 months following surgery, despite subtherapeutic IFX drug concentrations [mean ± SE 2.0 ± 0.3 µg/mL]. In the second study, 5 patients were treated with low-dose IFX [3mg/kg] postoperatively to prevent endoscopic recurrence. The need for dose optimization as well as trough IFX concentration and the presence of antibodies to IFX were significantly associated with postoperative endoscopic recurrence. The optimal IFX concentration for prediction of endoscopic recurrence was low, at 1.8µg/g, suggesting that low-dose treatment may be sufficient for sustaining endoscopic remission. Interestingly, in this study no such association was observed for adalimumab-treated patients where drug concentration or AAA development was not associated with endoscopic recurrence.

The recurrence of disease in the short to medium term, in the presence of satisfactory serum drug concentrations, may reflect non-drug responsiveness [“primary non-response”]. Alternatively, inflammatory mechanisms that predominate over TNF-mediated mechanisms may be important in those patients with early disease recurrence. The same is true of recurrence in the patients who smoke. In the longer term, it might be expected that secondary loss of response to prophylactic drug therapy may lead some patients to experience disease recurrence, in a situation analogous to the treatment of established luminal Crohn’s disease.

The serum adalimumab concentration has been shown to be relatively constant when given at maintenance doses of 40 mg subcutaneously once per fortnight. This is due to a combination of low-dose subcutaneous administration of the drug and the long half-life of 10–20 days, with time to peak concentration of 6.5 days. Although some studies examining the relationship between adalimumab drug concentration and clinical outcomes have only included trough concentrations, the pharmacokinetic profile of adalimumab suggests that serum measurement of drug concentration is accurate at any time during maintenance therapy, regardless of the timing of drug dosing.

Although associated with an increased risk of loss of response to anti-TNF treatment, smoking has not been associated with a lower anti-TNF drug concentration. Smoking in the POCER study was associated with a significantly increased risk of endoscopic recurrence. In this study, there was no significant difference in drug concentration between smokers and non-smokers, suggesting that the mechanism by which smoking increases the risk of Crohn’s disease recurring after surgery is not related to adalimumab pharmacokinetics.

The influence of BMI on adalimumab efficacy and drug concentration has been debated in the literature. BMI has been shown to be important in predicting adalimumab efficacy. Patients with a higher BMI have been shown to be at increased risk of loss of response to adalimumab and are more likely to need dose escalation when compared with those with a lower BMI. Studies in Crohn’s disease patients have not shown a significant impact of BMI on drug pharmacokinetics to explain these clinical findings. However, recent data have shown a significantly lower serum adalimumab concentration in patients with a BMI of >30, compared with those with a BMI of <30. Increased visceral adipose tissue has been associated with increased inflammation and poorer outcome in patients with inflammatory bowel disease and is a predictor of postoperative endoscopic recurrence in Crohn’s disease.

In this study, antibodies to adalimumab were seen in one-quarter of patients and most commonly developed within the first 6 months of adalimumab treatment. The development of AAAs was not associated with higher rates of endoscopic recurrence compared with those without. Once detected, antibodies were persistent, not transient, and were associated with lower drug concentrations compared with when antibodies were not found. The presence of AAAs at 6 months predicted a dramatically lower drug concentration at 18 months. In most antibody-positive patients, however, the drug concentration remained within the therapeutic range. Antibody identification is therefore of uncertain significance. The development of AAAs may be related to reconstituted immunomodulator therapy and is unclear. The lower detection rate of AAAs in this study [28% of patients] may reflect the high incidence of combination therapy [38.5%] compared with in previous published studies, or the low number of patients with exposure to adalimumab prior to study entry.

A novel aspect of this study was the assessment for the presence of faecal adalimumab. We aimed to establish whether faecal loss of adalimumab occurs in the postoperative setting, and the possible effect on serum drug concentration and clinical or endoscopic outcomes. Faecal adalimumab was not detected in any sample in this study. Most likely this relates to the small disease burden with localized recurrent inflammation. Faecal IFX loss has been described in acute severe ulcerative colitis, in association with a low serum drug concentration and lack of clinical response. In the current study, disease was mild and localized to a small section of the intestine.

Limitations of this study include the relatively small sample size and the fact that serum samples were taken irrespective of the timing of the last administered dose of adalimumab.

In conclusion, lower drug concentrations soon after intestinal resection in patients on adalimumab therapy may not relate to endoscopic Crohn’s disease recurrence. Mechanisms other than inadequate anti-TNF drug concentration are therefore likely to be important. The same is true of the increased recurrence related to smoking. The mechanistic cause of disease recurrence after surgery requires further research.

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Conflict of Interest

EKW, ALH, AG, LP, SLJ, THF, HD, DS, IK and GR-S have no conflicts of interest to declare. PDC has received travel grant support from AbbVie and Schering-Plough. MAK has acted as an advisor to AbbVie and Janssen, has received research support from AbbVie, and has acted as a speaker at symposiums sponsored by AbbVie and Janssen. FS and FP are paid employees of Prometheus Laboratories. DL has served on advisory boards and received research grants from AbbVie. ICL has been on an advisory board for AbbVie and Janssen, a speaker for AbbVie and Janssen, and has held research and travel grants from AbbVie and Janssen. JMA has been an advisory board member for both Janssen and AbbVie, spoken for both AbbVie and Janssen, received research funds from both AbbVie and Janssen, and received travel grants from both AbbVie and Janssen. PAB has been on advisory boards for Janssen and AbbVie, has received research funding from AbbVie, and travel sponsorship from both AbbVie and Janssen. PRG has received consulting fees from AbbVie, Janssen, and Schering-Plough; research support from AbbVie; and payments for lectures from AbbVie and Janssen. BG has been on an advisory board for AbbVie and Janssen, a speaker for AbbVie and Janssen, and held research, educational and travel grants from AbbVie and Janssen. FAM has been on an advisory board to Janssen, has received travel grants from AbbVie, and has received clinical research support from Janssen, AbbVie and MSD. WS has been on an advisory board for AbbVie. SJF has received travel assistance from AbbVie. SJF has received travel support and speaker fees from both AbbVie and Janssen. WRC has been on an advisory board for Janssen and a speaker for AbbVie and Janssen.

Author Contributions

EKW, PDC and MAK—study concept and design; acquisition of data; analysis; data interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding. ALH—acquisition of data; analysis and interpretation of data; drafting of the manuscript. FS and FP—laboratory analysis; acquisition of data. AG and DL—analysis and interpretation of data; drafting of the manuscript; statistical analysis. LP, ICL, JMA, PAB, SLJ, THF, PRG, HD, FAM, DS, IK, GR-S, WS, SJF, SJF, WRC—acquisition of data and critical review of manuscript.

Supplementary Data

Supplementary data for this article can be found at ECCO-JCC Online.

References


