Higher Adalimumab Drug Levels During Maintenance Therapy for Crohn's Disease Are Associated With Biologic Remission

Nikolas Plevris, MRCP,[*] Mathew Lyons, PhD,*[*] Philip W. Jenkinson, MRCS,*[*] Cher S. Chuah, MRCP,*[*] Lynne M. Merchant, MPharm,*[*] Rebecca J. Pattenden, MSc,[†] Eleanor F. Watson, MRCP,*[*] Gwo-Tzer Ho, PhD, FRCP,*[*] Colin L. Noble, MRCP, MD,*[*] Alan G. Shand, MD, FRCP,*[*] Shahida Din, MRCP, PhD,*[*] Ian D. Arnott, MD, FRCP,*[*] Gareth R. Jones, MRCP, PhD,*[*] and Charlie W. Lees, PhD, FRCP*[*]*

Background: Adalimumab is an established treatment for Crohn's disease. Limited data are available regarding the relationship between adalimumab drug levels and serum/fecal markers of gut inflammation. We therefore aimed to characterize the relationship between adalimumab levels and biologic remission during maintenance therapy.

Methods: A single-center prospective cross-sectional study was undertaken on Crohn's disease patients who had received adalimumab therapy for a minimum of 12 weeks after induction. Data on clinical activity (Harvey-Bradshaw Index), C-reactive protein (CRP), adalimumab drug and antibody levels, and fecal calprotectin were collected. Biologic remission was defined as a CRP <5 mg/L and fecal calprotectin <250 µg/g. Adalimumab drug and antibody levels were processed using the Immundiagnostik monitor enzyme-linked immunosorbent assay.

Results: One hundred fifty-two patients had drug and antibody samples matched with CRP and fecal calprotectin. Patients in biologic remission had significantly higher adalimumab levels compared with others (12.0 µg/mL vs 8.0 µg/mL, $P < 0.0001$). Receiver operating characteristic curve analysis demonstrated an optimal adalimumab level of >8.5 µg/mL (sensitivity, 82.2%; specificity, 55.7%; likelihood ratio, 1.9) for predicting biologic remission. Multivariable logistic regression revealed that adalimumab levels >8.5 µg/mL were independently associated with biologic remission (odds ratio, 5.27; 95% confidence interval, 2.43–11.44; $P < 0.0001$).

Conclusions: Higher adalimumab levels are associated with biologic remission. An optimal level of >8.5 µg/mL was identified.

Key Words: adalimumab, therapeutic drug monitoring, Crohn's disease, biologic remission

INTRODUCTION

Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease (IBD) that results in progressive damage to the gastrointestinal tract if left untreated.[1, 2] To reduce complications associated with persistent inflammation, objective therapeutic outcomes such as mucosal healing are increasingly accepted treatment targets for IBD.[3] Mucosal healing has been associated with sustained clinical remission, reduced hospitalization, and lower surgical rates.[4–8] However, regular endoscopic assessment to guide treatment is both invasive and costly.[9] Fecal calprotectin (FC) is therefore increasingly being adopted as a reliable surrogate marker for mucosal inflammation and healing.[10] The recently published CALM study demonstrated that in CD, early escalation of treatment aiming for normalization of the biomarkers, C-reactive protein (CRP; <5 mg/L) and FC (<250 µg/g), and symptoms (Crohn's Disease Activity Index < 150) resulted in superior rates of mucosal healing at 48 weeks when compared with a treatment strategy driven by clinical symptoms alone.[11] Furthermore, they showed that the majority of patients with a CRP <5 mg/L in addition to FC <250 µg/g were in endoscopic remission. Therefore, treating beyond symptoms to normalization of biomarkers is becoming increasingly accepted as a therapeutic goal.

Adalimumab (ADA) is a subcutaneously administered anti-TNF agent that is licensed for the treatment of CD.[12] Randomized, controlled clinical trials have demonstrated its ability to induce and maintain clinical remission and achieve mucosal healing in IBD.[12–16] Despite this, up to 45% of patients

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From the *The Edinburgh IBD Unit and [†]Department of Clinical Biochemistry, Western General Hospital, Edinburgh, UK

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Address correspondence to: Nikolas Plevris, MRCP, The Edinburgh IBD Unit, Western General Hospital, Edinburgh, EH4 2XU, UK (nikolas.plevris@nhslothian.scot.nhs.uk).

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will experience a secondary loss of response with time.[17] A number of exposure–response studies have shown that lower serum anti-TNF levels, in the absence or presence of anti-TNF antibodies, may contribute to the loss of response observed.[17] Therefore, the practice of therapeutic drug monitoring (TDM) to guide therapy is becoming increasingly adopted.[18] Limited published data are available on the relationship between ADA levels and objective outcomes, such as mucosal healing or normalization of biomarkers like FC. Initial small, retrospective cross-sectional studies have suggested that higher levels of ADA are associated with mucosal healing, with optimal cutoffs ranging from >7.1 to >12.0 µg/mL identified.[19–24] However, 1 retrospective study showed no significant association between ADA levels and Harvey-Bradshaw Index (HBI), CRP, or FC, suggesting that the relationship of ADA TDM with clinical and serum/fecal biomarkers in CD is not clear.[25]

The aim of this study, therefore, was to identify in a large cross-sectional cohort an association between ADA levels, during maintenance treatment for CD, and biologic remission, defined by a CRP <5 mg/L and FC <250 µg/g.

METHODS

Patients and Design

This was a single-center prospective cross-sectional observational study. Patients aged >16 years on ADA therapy were identified from our hospital pharmacy database, which holds information on all current ADA prescriptions. Inclusion criteria were a diagnosis of CD (based on standard clinical, radiological, endoscopic, and histological criteria) on weekly or fortnightly maintenance therapy (having completed a minimum of 12 weeks of treatment) after standard induction of 160 mg/80 mg. Patients with stomas were excluded. All patients were contacted in advance of their next routine IBD hospital appointment and advised to omit their ADA dose until after their appointment if due on the same day. At the clinic, HBI was calculated, serum for ADA levels/antibodies to adalimumab (ATA) and CRP was obtained, and a stool sample for FC was requested as part of routine clinical care. All samples were collected pro-actively irrespective of disease activity. Patient demographics and disease characteristics were obtained after review of electronic medical health records (TrakCare). The primary outcome was the association of ADA levels with biologic remission (CRP < 5 mg/L and FC < 250 µg/g). This definition was selected as it has been shown to correlate with mucosal healing.[10, 11] Secondary outcomes were associations of ADA levels with ATA, HBI, CRP, and FC. In patients who had more than 1 sample for TDM, only matched results at the first TDM sample were used so that clinicians were blinded to test results.

Adalimumab Drug and Antibody Assay

Adalimumab drug and antibody levels were processed at the Exeter Hospital Laboratories, United Kingdom, using the Immundiagnostik monitor enzyme-linked immunosorbent assay (ELISA), per the manufacturer's protocol. Drug levels and antibody levels were expressed in µg/mL and AU/mL, respectively. The assay detects drug levels ≥0.8 µg/mL and total ATA ≥10 AU/mL in the absence or presence of drug.

Fecal Calprotectin Assay

Fecal calprotectin collection kits with instructions were given to patients, and samples were returned to the hospital biochemistry laboratories either directly or via their general practitioner's practice (samples forwarded the same day). Patients were advised to obtain a sample from the first bowel movement of the day and return their samples within 24 hours of collection. Upon arrival at the laboratories, samples were stored at –20°C. Fecal calprotectin was measured using a standard ELISA technique (Calpro AS, Lysaker, Norway). Numerical values were generated between 20 and 2500 µg/g. All assays were performed in the Department of Clinical Biochemistry at the Western General Hospital, Edinburgh, United Kingdom. The same assay has been utilized since 2004, with now >4000 assays performed per year.

Statistical Analysis

SPSS, version 24 (IBM Inc., Chicago, IL, USA), and Prism, version 7.0 (Graphpad Software, San Diego, CA, USA), were used for statistical analyses and generation of graphs. Descriptive statistics are presented as medians with interquartile ranges (IQRs) for continuous variables and frequencies with percentages for categorical variables. Correlations were determined by Spearman's rank correlation test. For nonparametric continuous variables, the Mann-Whitney *U* test was used. Receiver operator characteristic (ROC) curves were generated to assess the sensitivity and specificity of ADA levels at determining biologic remission. An optimal ADA threshold was calculated using the Youden index. Adalimumab levels were also categorized in quartiles, and associations were compared across quartiles using the chi-square test (linear by linear association) for categorical variables and the Kruskal-Wallis test for continuous variables. A multivariable logistic regression analysis with backward elimination was used to identify factors that predicted the presence of ATA and factors that predicted biologic remission. Covariates for the 2 analyses are listed in Supplementary Table 1. Covariates were excluded when *P* values were greater than 0.1. A *P* value of <0.05 was considered significant for all statistical tests.

Ethics

This study was considered an audit of clinical practice as data were collected as part of routine clinical care. Caldicott Guardian (NHS Lothian) approval was granted for data analysis and dissemination.

RESULTS

Study Population

Two hundred fifty-nine patients were identified as receiving ADA maintenance therapy for CD. A total of 152 patients fulfilled the inclusion criteria and had TDM samples matched with HBI, CRP, and FC. Patient demographics and clinical characteristics at time of first TDM are shown in Table 1. The median age of the cohort (IQR) was 36 (28–50) years, with 74 (48.7%) patients receiving ADA as firstline biological therapy. The median time from diagnosis to initiation (IQR) of ADA was 8 (3–14) years, with a median duration of therapy of 2 (1–4) years. At the initiation of ADA therapy, 66 (43.4%) patients were receiving concomitant immunosuppression, with 32 (21.1%) patients remaining on concomitant therapy at the point of TDM testing.

Correlation of Serum ADA Levels With Clinical Outcomes

Overall, the median serum ADA level (IQR) was 10.0 (6.6–14.4) μg/mL. Patients on weekly therapy had significantly higher levels than those on fortnightly therapy (14.0 vs 10.0 μg/mL; $P = 0.0040$). No difference was observed in levels in patients receiving firstline ADA compared with those with previous biologic exposure (11.0 vs 9.3 μg/mL; $P = 0.1826$).

Seventy-three (48.0%) patients were in biologic remission. These patients had significantly higher ADA levels compared with those not in biologic remission (12.0 μg/mL vs 8.0 μg/mL; $P < 0.0001$) (Fig. 1), with increasing quartiles of ADA levels associated with significantly higher rates of biologic remission, with no plateau reached (Fig. 2). Similar associations were observed between ADA level quartiles and HBI, CRP, and FC (Fig. 3).

Receiver operating characteristic curve analysis revealed a positive correlation between ADA levels and biologic remission (area under the curve [AUC], 0.73; 95% confidence interval [CI], 0.65–0.81; $P < 0.0001$) (Fig. 4). An optimal ADA level of >8.5 μg/mL was identified for predicting biologic remission (sensitivity, 82.2%; specificity, 55.7%; likelihood ratio, 1.9) (Fig. 4). The predictive accuracy of ADA levels only increased modestly when patients with isolated small bowel disease were omitted (AUC, 0.78; 95% CI, 0.70–0.86; $P < 0.0001$), and the optimal ADA level remained at >8.5 μg/mL (sensitivity, 86.4%; specificity, 56.3%; likelihood ratio, 2.0) (Supplementary Fig. 1). When the FC cutoff was reduced to <100 μg/g, patients in biologic remission (n = 45/152, 29.6%) continued to have significantly higher ADA levels (12.0 vs 9.0 μg/mL; $P = 0.0008$). Receiver operating characteristic curve analysis also revealed a positive correlation with the new definition (AUC, 0.67; 95% CI, 0.58–0.76; $P = 0.0010$), with an optimal ADA level of >10.5 μg/mL (sensitivity, 66.7%; specificity, 59.8%; likelihood ratio, 1.6) identified (Supplementary Fig. 2).

TABLE 1: Patient Demographics and Disease Characteristics at Point of First TDM Sample

	n = 152
Male sex, No. (%)	80 (52.6)
Age, median (IQR), y	36 (28–50)
Disease duration, median (IQR), y	9 (5–17)
Montreal classification, No. (%)	
L1	45 (29.6)
L2	29 (19.1)
L3	78 (51.3)
+L4	22 (14.5)
B1	97 (63.8)
B2	32 (21.1)
B3	23 (15.1)
+perianal disease	37 (24.3)
Previous resectional surgery, No. (%)	60 (39.5)
Smoking, No. (%)	21 (13.8)
Firstline biologic, No. (%)	74 (48.7)
Time to ADA, median (IQR), y	8 (3–14)
Duration of ADA therapy, median (IQR), y	2 (1–4)
ADA dosing, No. (%)	
40 mg weekly	44 (28.9)
40 mg fortnightly	108 (71.1)
Concomitant immunosuppression at ADA initiation, No. (%)	66 (43.4)
Time on concomitant immunosuppression, median (IQR), y	2 (0.7–3)
Concomitant immunosuppression at time of TDM, No. (%)	32 (21.1)
Thiopurines	27 (17.8)
Methotrexate	5 (3.3)
HBI, median (IQR)	4 (1–5)
CRP, median (IQR), mg/L	3 (1–9)
Fecal calprotectin, median (IQR), μg/g	177 (53–568)
ADA levels, median (IQR), μg/mL	10.0 (6.6–14.4)
Incidence of ATA, No. (%)	26 (17.1)
ATA level in patients with detectable immunogenicity (≥10 AU/mL), median (IQR), AU/mL	44 (18–200)

Comparison of characteristics and demographics showed that the proportion of patients in clinical remission (HBI <5) was significantly higher in those with biologic remission vs not (Table 2). Furthermore, patients in biologic remission were older, had a longer duration on ADA therapy, and had a lower incidence of ATA, when compared with those not in biologic remission (Table 2). A multivariable logistic regression analysis identified ADA levels >8.5 μg/mL and longer duration of therapy as independent factors associated with biologic remission (Table 3).

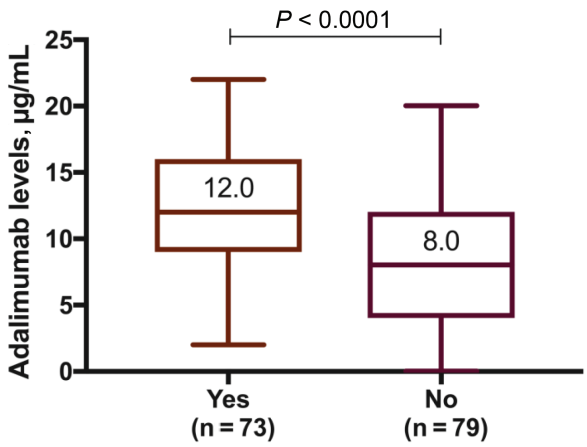

FIGURE 1. Adalimumab levels in patients in biologic remission (CRP < 5 mg/L and fecal calprotectin < 250 µg/g) compared with those not in biologic remission. Box plots show the median (central line), interquartile range (box lines), and maximum and minimum values (whiskers).

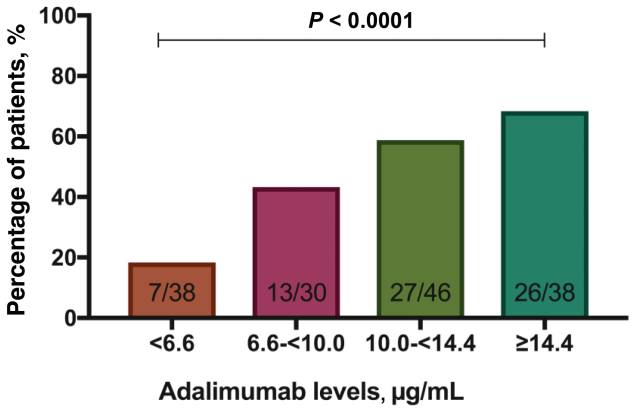

FIGURE 2. Association between adalimumab level quartiles and biologic remission (CRP < 5 mg/L and fecal calprotectin < 250 µg/g).

Serum ADA Levels and Antibodies to ADA

ATA (≥10 AU/mL) were present in 26/152 (17.1%) patients, of whom 8 had undetectable drug levels (<0.8 µg/mL). A significant negative correlation was observed between ADA levels and ATA (Spearman's $r = –0.5677$; $P < 0.0001$) (Fig. 5A). The median ADA levels (IQR) were 11.4 (8.0–15.0), 5.0 (4.0–6.7), and 1.0 (0.4–2.0) µg/mL in patients with ATA <10, 10–50, and >50 AU/mL, respectively ($P < 0.0001$) (Fig. 5B); 73.8% (93/126) of patients with ATA <10 AU/mL had ADA levels >8.5 µg/mL, which dropped to 15.4% (2/13) and 0% (0/13) at levels of 10–50 and >50 AU/mL, respectively. The incidence of ATA (≥10 AU/mL) at the time of TDM was not statistically different between patients on combination therapy (3/32, 9.4%) compared with mono-therapy ADA (23/120, 19.2%; $P = 0.1912$). However, multivariable logistic regression analysis revealed mono-therapy and absence of biologic remission as independent factors associated with the presence of ATA (≥10 AU/mL) (Table 4). Previous biologic exposure was not independently associated with ATA.

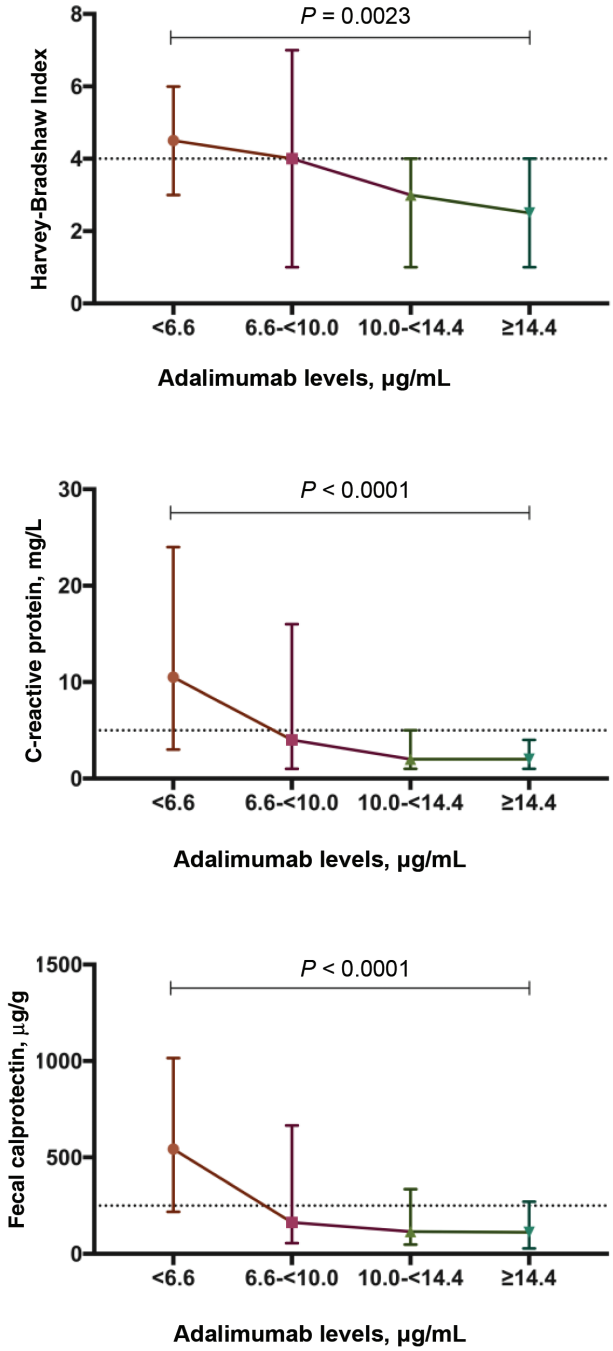

FIGURE 3. Associations between adalimumab level quartiles and Harvey-Bradshaw Index, CRP, and fecal calprotectin. Medians and interquartile ranges are shown; dotted line indicates cutoffs for clinical remission (Harvey-Bradshaw Index < 5) and normalization of CRP (CRP < 5 mg/L) and of fecal calprotectin (<250 µg/g).

DISCUSSION

To our knowledge, this is the largest cross-sectional study to date addressing the relationship between ADA levels and biologic remission during maintenance treatment in CD. In this study, we have shown that higher ADA levels are significantly

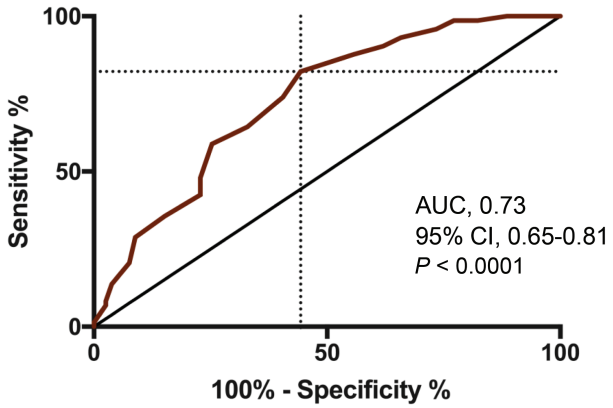

FIGURE 4. Receiver operator characteristic analysis for serum adalimumab levels and biologic remission (CRP < 5 mg/mL and fecal calprotectin < 250 µg/g). Optimal cutoff of adalimumab at >8.5 µg/mL is shown (sensitivity, 82.2%; specificity, 55.7%; likelihood ratio, 1.9).

associated with biologic remission (CRP < 5 mg/L and FC < 250 µg/g). An optimal ADA level of >8.5 µg/mL was identified and shown to be independently associated with biologic remission, with an odds ratio >5.

Previous studies have shown a significant relationship between ADA levels and clinical remission, with optimal cutoffs ranging from 4.9 to 5.9 µg/mL identified.[20, 26, 27] However, it is increasingly recognized that clinical symptom activity indices correlate poorly with the degree of underlying intestinal inflammation.[28] In the era of treating beyond symptoms, data are emerging that even higher serum drug levels are required to achieve objective end points like mucosal healing.[19–24] Most recently, Zittan et al. demonstrated in a cross-sectional cohort of 60 CD patients that individuals achieving mucosal healing had significantly higher ADA levels compared with those who did not achieve mucosal healing (14.7 vs 3.4 µg/mL; $P < 0.0001$).[23] Furthermore, they identified an optimal level of >8.1 µg/mL (sensitivity, 91.4%; specificity, 76.0%) for discriminating mucosal healing. However, the main limitations of these studies include their small sample sizes and retrospective methodology.[19–24] By adopting biologic remission (CRP < 5 mg/L and FC < 250 µg/g) as a surrogate for mucosal healing, we have been able to validate in a larger cohort the positive association of higher ADA levels. Although direct comparison cannot be made with others due to assay variability, the optimal ADA level of >8.5 µg/mL is in keeping with the published literature.

In the scenario of secondary loss of response, guidelines recommend utilizing TDM and switching out of class if drug levels are found to be within the therapeutic range.[29, 30] However, optimal target ranges remain to be elucidated. The recently published American Gastroenterological Association guidelines on TDM suggest an optimal trough ADA level of ≥7.5 µg/mL, whereas other algorithms recommend aiming for a window of 5.0–12.0 µg/mL.[29, 30] However, Juncadella et al. recently identified an ADA therapeutic window of 12–16 µg/mL for endoscopic remission.[24] Furthermore, within our cohort, quartile analysis revealed that the proportion of patients in biologic remission continued to increase even with ADA levels ≥14.4 µg/mL, with no obvious plateau (Fig. 2). Therefore, in patients with therapeutic ADA levels, defined by existing guidelines, further dose escalation may be warranted to try and recapture response to treatment.

Few studies have looked at associations between ADA levels and the biomarkers CRP and FC in CD. Ward et al. recently showed that in a cohort of CD patients on maintenance ADA, levels were similar between patients with active disease and those in remission, regardless of the outcome measure (HBI < 5 or CRP < 5 mg/L or FC < 60 µg/g).[25] However, their sample size was small (n = 95), and retrospective methodology was adopted with no clear indication of the interval between the assessment of outcome in relation to ADA level sampling. In contrast, our data demonstrate that increasing ADA levels correlate with lower HBI scores, CRP, and FC (Fig. 4).

Immunogenicity to anti-TNF agents is thought to account for a significant proportion of primary and secondary nonresponse to treatment likely mediated via increased drug clearance.[17, 18] A number of TDM guidelines recommend that patients with loss of response and low levels of ADA/ATA may benefit from dose escalation or the addition of an immunosuppressant, whereas in patients with low/absent ADA levels and high-titer ATA, switching to an alternative biologic is suggested.[29, 30] As expected, we found that ATA had a significant negative correlation with serum ADA levels (Fig. 5). However, we found that even in patients who had ATA between 10 and 50 AU/mL, only 15% had a drug level >8.5 µg/mL. Furthermore, no patients had drug levels >8.5 µg/mL in those with ATA >50 AU/mL, suggesting that any level of ATA >10 AU/mL has a significant negative effect on ADA levels. We also found that in patients with biologic remission, immunogenicity rates were significantly lower (8.2% vs 11.2%; $P = 0.0052$). This was further supported by our multivariable logistic regression, which showed that the presence of biologic remission was negatively associated with immunogenicity (OR, 0.14; 95% CI, 0.036–0.057; $P = 0.006$) (Table 4).

Overall immunogenicity rates within our cohort were low (17.1%) and in keeping with the published literature.[31, 32] The lower incidence of ATA compared with infliximab (IFX) has been attributed to the fact that ADA is a human monoclonal antibody and is theoretically less immunogenic.[31, 32] This has led to the belief that concomitant immunomodulation to prevent antibody production is less pertinent when using ADA compared with infliximab. However, our analysis revealed monotherapy as an independent factor associated with immunogenicity (OR, 10.73; 95% CI, 1.28–89.82; $P = 0.029$). Furthermore, recently presented data from the PANTS study have shown that, although to a lesser degree than for IFX, concomitant immunomodulator use significantly reduced the risk of immunogenicity for ADA (IFX: HR, 0.37; $P < 0.000$; vs ADA: HR, 0.34; $P < 0.0001$).[33]

TABLE 2: Demographic and Disease Characteristic Comparison Between Patients In vs Not In Biologic Remission (CRP < 5 mg/L and fecal calprotectin < 250 µg/g)

	Biologic Remission (n = 73)	Not in Biologic Remission (n = 79)	*P*
Age, median (IQR), y	40 (32–52)	32 (25–49)	0.0070
Male sex, No. (%)	34 (46.6)	46 (58.2)	0.1506
Smoking, No. (%)	6 (8.2)	15 (19.0)	0.0546
Montreal classification, No. (%)			
L1	24 (32.9)	21 (28.8)	0.3957
L2	14 (19.2)	15 (19.0)	0.9761
L3	35 (47.9)	43 (54.4)	0.4242
+L4	11 (15.1)	11 (13.9)	0.8412
B1	46 (63.0)	51 (64.6)	0.8432
B2	18 (24.7)	14 (17.7)	0.2947
B3	9 (12.3)	14 (17.7)	0.3540
+perianal	14 (19.2)	23 (29.1)	0.1538
EIM, No. (%)	15 (20.5)	15 (19.0)	0.8092
ADA duration, median (IQR), y	2 (1–5)	1 (1–3)	0.0015
ADA weekly, No. (%)	20 (27.4)	24 (30.4)	0.6854
Concomitant immunosuppressant, No. (%)	13 (17.8)	19 (24.1)	0.3456
Firstline therapy, No. (%)	41 (56.2)	32 (40.5)	0.0536
Clinical remission, No. (%)	62 (84.9)	43 (54.4)	<0.0001
ADA levels, median (IQR), µg/mL	12.0 (9.0–16.0)	8.0 (4.0–11.8)	<0.0001
Incidence of antibodies to ADA (≥10 AU/mL), No. (%)	6 (8.2)	20 (11.2)	0.0052

TABLE 3: Multivariable Logistic Regression Analysis Identifying Independent Factors Predicting Biologic Remission (CRP < 5 mg/mL and fecal calprotectin < 250 µg/g)

	Odds Ratio	*P*	95% Confidence Interval Lower Bound	Upper Bound
Duration of adalimumab	1.260	0.003	1.081	1.470
Adalimumab level >8.5 µg/mL	5.274	<0.001	2.431	11.441

TABLE 4: Multivariable Logistic Regression Analysis Identifying Independent Factors Predicting the Presence of Antibodies to Adalimumab

	Odds Ratio	*P*	95% Confidence Interval Lower Bound	Upper Bound
Monotherapy	10.728	0.029	1.281	89.823
Biologic remission (CRP < 5 mg/L and fecal calprotectin < 250 µg/g)	0.143	0.006	0.036	0.569

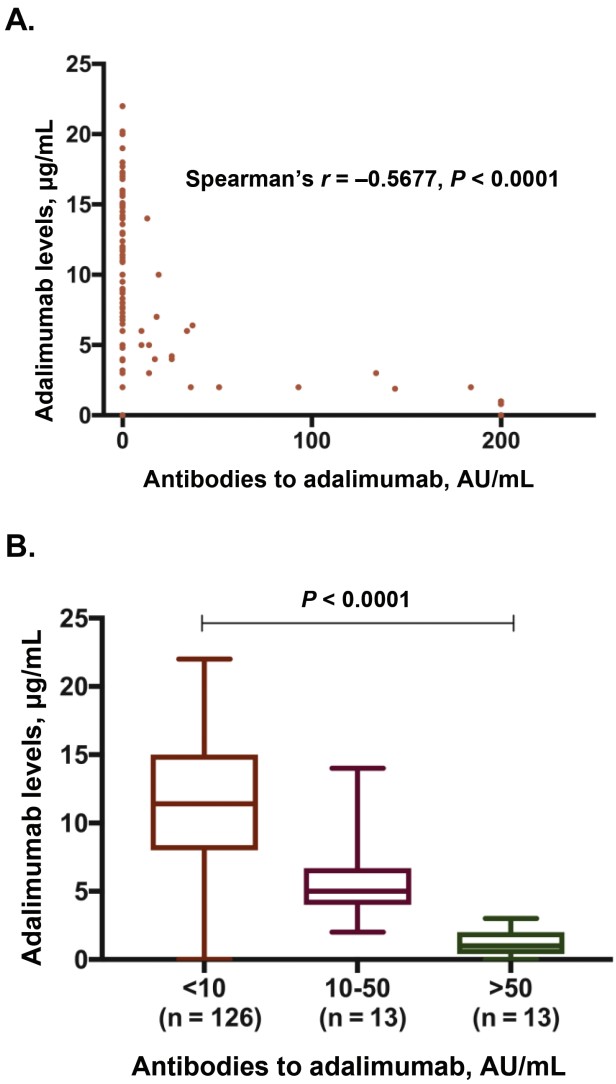

FIGURE 5. Negative association between antibodies to adalimumab and serum adalimumab levels. A, Antibodies to adalimumab are shown as continuous values. B, Antibodies to adalimumab are divided into 3 categories (<10 AU/mL, 10–50 AU/mL, >50 AU/mL). Box plot shows median (central line), interquartile range (box lines), and maximum and minimum values (whiskers).

The main limitation of this study is that ADA levels were taken at various time points between maintenance injections. The ability to obtain true trough samples for each patient was limited as the outpatient appointments were not always scheduled on the day ADA was due. However, pharmacokinetic studies have shown that ADA has a relatively stable drug concentration between doses.[34] Furthermore, in a recently published prospective study by Ungar et al., drug levels obtained at trough, days 1–4, days 5–9, and days 10–13 during a 2-week cycle were not significantly different, even when corrected for the presence of ATA.[35] Therefore, we adopted a pragmatic strategy that allowed TDM to be carried out at prescheduled appointments, reflecting real-life clinical practice. Consequently, we believe that such an approach is clinically practical and can be extrapolated to real-world practice, where ADA levels are likely to be obtained at various time points during treatment. Further limitations include the cross-sectional nature of our study. Analysis is based on a single time point during maintenance therapy, and drug levels were not measured sequentially throughout the treatment schedule. Therefore, it is unclear whether high ADA levels are required to achieve biologic remission or whether high ADA levels are because of reduced drug clearance and TNF burden in patients with biologic remission. As such, only associations can be made, and causality cannot be established. It was also not possible to obtain endoscopic data at the time of TDM. However, we used surrogate markers of mucosal inflammation that have been shown to correlate well with endoscopic appearances. D'Haens et al. have shown that in patients with CD, an FC cutoff ≤250 µg/g predicts endoscopic remission (Crohn's Disease Endoscopic Index of Severity [CDEIS] ≤ 3), with 94.1% sensitivity and 62.2% specificity (positive predictive value, 48.5%; negative predictive value, 96.6%).[10] Colombel et al. also demonstrated similar findings in the CALM study, where 78.6% of CD patients in biologic remission (CRP < 5 mg/L and FC < 250 µg/g) had a CDEIS <4 and no deep ulcers on endoscopy.[11] Changing our FC cutoff to <100 µg/g resulted in a higher optimal adalimumab level on ROC analysis of >10.5 µg/mL; however, the predictive accuracy and sensitivity/specificity were reduced (AUC, 0.67; sensitivity, 66.7%; specificity, 59.8%; likelihood ratio, 1.6) (Supplementary Fig. 2). Finally, intra-individual variability of FC may have also influenced our results.

CONCLUSIONS

In conclusion, we have identified that higher ADA levels are significantly associated with biologic remission (CRP < 5 mg/mL and FC < 250 µg/g). An optimal ADA level of >8.5 µg/L may be an appropriate target in the maintenance treatment of CD. Further prospective longitudinal studies are necessary to validate our findings and address the role of ADA TDM in achieving long-term therapeutic goals.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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