

ORIGINAL ARTICLE

Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial

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ABSTRACT

Introduction Data on immunogenicity to adalimumab (ADL) therapy in patients with IBD is limited. We performed additional analyses on the Karmiris cohort using the homogeneous mobility shift assay (HMSA) focusing on the inter-relationship of serum ADL concentration, antibodies-to-adalimumab (ATA), inflammatory markers and sustained response.

Methods 536 prospectively collected serum samples were available for analysis of ADL concentration and ATA using HMSA. We studied the role of week 4 serum ADL concentration and immunomodulator (IMM) use on ATA formation with a Cox proportional hazards model. Mixed model repeated measures analysis was performed to assess the independent effects of serum ADL concentration and ATA on C-reactive protein (CRP) and response.

Results ATA was detected in 20% of patients after a median of 34 (12.4–60.5) weeks. ATA-positive samples correlated with lower serum ADL concentration ($p<0.001$). Cox regression modelling showed that week 4 ADL concentration of $<5 \mu\text{g/mL}$ significantly increased the future risk of ATA formation ($\text{HR}=25.1$; 95% CI 5.6 to 111.9; $p=0.0002$) and that IMM co-treatment prevented ATA formation ($\text{HR}=0.23$; 95% CI 0.06 to 0.86; $p=0.0293$). Regression modelling showed a negative correlation between CRP and ADL concentration ($p=0.0001$) and a positive one with ATA ($p=0.0186$). The model revealed that both lower serum ADL concentration and ATA were independently associated with future CRP ($p=0.0213$ and $p=0.0013$ respectively). ATA positivity was associated with discontinuation of ADL because of loss or response ($\text{OR}=3.04$; 95% CI 1.039 to 9.093; $p=0.034$).

Conclusions ATA were detected in 20% of patients. Risk of ATA formation increased with lower early serum ADL concentration and in patients not on IMM. ATA and ADL were strongly associated with higher future CRP level and discontinuation of ADL.

INTRODUCTION

During infliximab (IFX) and ADL therapy for IBD, anti-drug antibody formation can lead to loss of response (LOR) to the drug.^{1 2} As with IFX, dose optimisation of adalimumab (ADL) is frequently

Significance of this study

What is already known on this subject?

- Infliximab (IFX) therapy can lead to anti-drug antibody formation, possibly inducing loss of response (LOR) over time.
- Antibodies-to-adalimumab (ATA) formation during adalimumab (ADL) maintenance therapy is considered rare and has not been shown to be clinically significant in IBD.
- Serum ADL concentration correlates with long-term clinical effect, including mucosal healing.

What are the new findings?

- Using a high-sensitive technique, we have demonstrated the presence of ATA in 20% of Crohn's disease patients during ADL maintenance therapy.
- A low serum ADL concentration after the induction regimen increases the risk of ATA formation.
- The use of concomitant immunomodulators (IMMs) is negatively correlated with ATA formation.
- ATA formation is associated with inflammation progress in the future and discontinuation of therapy.

How might it impact on clinical practice in the foreseeable future?

- These data suggest that combination therapy with IMMs and early drug and ATA level monitoring could help ADL treatment optimisation and improvement in patient outcome.

needed to maintain a durable response. There is limited data on reasons for LOR to ADL therapy in IBD.^{3 4} The registration trials for ADL in Crohn's disease, CHARM, CLASSIC II and GAIN, do not report on serum ADL concentration or on the clinical effects of immunogenicity to ADL.^{5–7} Karmiris *et al*¹ reported in a single-centre open-label study on 168 Crohn's disease patients treated with ADL maintenance therapy during a median follow-up of

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2 years. Of the 156 patients receiving maintenance therapy, 102 patients (65%) needed dose escalation and 60 (38.5%) discontinued therapy due to LOR. Lower serum ADL concentration was measured throughout the study in patients who discontinued therapy. Antibodies-to-adalimumab (ATA) were measured in 9.2% of patients and affected serum ADL concentration.

Here, we performed additional analyses on this cohort using the homogeneous mobility shift assay (HMSA),⁸ focusing on the inter-relationship of serum ADL concentration, ATA and different markers of inflammation including C-reactive protein (CRP) and sustained clinical benefit. We hypothesised that low drug levels lead to ATA formation, accelerated ADL clearance, progression of inflammation and finally no response or LOR.

METHODS

Study design

Retrospective single-centre cohort study of a consecutive series of IBD patients followed at the University Hospitals Leuven, Belgium.

Study population and treatment modalities

All patients included in this study were Crohn's disease patients who were initially treated with IFX. Eight patients (6%) had no primary response. All other patients (94%) had an initial response and subsequently became intolerant to IFX (ie, having experienced an acute and/or delayed hypersensitivity reaction) or lost response (ie, worsening of clinical status as judged by the treating physician) despite dose adjustments. The present study included 148/168 (88%) patients of the Karmiris cohort, of whom serial serum samples were available for analysis of ADL concentration, ATA and different markers of inflammation (see below). For more details, we referred to the initial publication.¹ ADL was administered as an open-label induction scheme of 160/80 mg at weeks 0 and 2 and 40 mg every other week thereafter. Dosing interval was decreased to once weekly in patients who presented with symptoms of a flare-up of active luminal disease, accompanied by an increase in CRP concentration or endoscopic lesions. In patients predominantly treated for perianal fistulising Crohn's disease or for extraintestinal manifestations, these clinical conditions were used as indications for escalating from every other week to weekly therapy. The treating physicians were not aware of serum ADL concentration and ATA measurements at the time of treatment decisions.

Data collection

Clinical information on treatment modalities was collected from the electronic charts of the patients. In addition to demographic data, the following were collected: disease duration, prior IFX use, concomitant use of immunomodulators (IMMs), induction scheme, need for dose escalation and reason for ADL discontinuation.

Study objective

This was an exploratory study. We re-analysed the patients' serum samples from the Karmiris cohort¹ with the HMSA tests focusing on immunogenicity to ADL therapy. The objectives were to study the rate and timing of ATA formation and the correlation between serum ADL concentration and ATA. In addition, we studied the clinical relevance of ATA and ADL by looking for their correlation with different markers of inflammation (see below) and with sustained clinical benefit (defined as the continuation of ADL therapy during the 2-year follow-up) versus discontinuation of ADL therapy due to LOR.

Serum samples

Serum samples from predefined time points were available through systematic bio-banking, which started in 1997 as part of the VLECC (Flemish Study for Genetics Research on IBD) research programme (Medical Ethical approval numbers: B322201213950/S53684). All patients in our centre routinely underwent 10 mL serum sample collection when seen at the outpatient clinic. Patients were instructed to receive ADL injection after the visit, and therefore, the samples could be considered 'trough concentration'. We tried to have serum samples available at start, 4 weeks, 12 weeks after the start of ADL and thereafter every 3 months. The samples were divided in 500 µl aliquots and stored at -20°C. We re-analysed 536 prospectively collected serum samples from 148/168 patients of the Karmiris cohort.

Laboratory methods

In addition to routine blood tests, all serum samples were analysed for serum ADL concentration and ATA using the HMSA (Prometheus Laboratories, San Diego, California, USA).⁸ Serum ADL concentration was expressed as µg/mL. The limit of detection (LOD) for ADL was 0.33 µg/mL. Hence, all values below 0.33 µg/mL were considered undetectable. The lower limit of quantification (LLOQ) was 1.6 µg/mL and the upper limit of quantification (ULOQ) was 50 µg/mL. ATA were expressed in units per millilitre (U/mL) arbitrarily. For the ATA assay, the LOD was 0.026 U/mL, the LLOQ was 1.7 U/mL and the ULOQ was 55 U/mL. Samples were classified as ATA negative (ATA < LLOQ), ATA detectable (0.78 functional LOD ≤ ATA < LLOQ) or ATA quantifiable (LLOQ ≤ ATA). ATA and ADL concentration detectability for the purpose of the study were defined as at least one sample per patient (non-week zero samples) with a value ≥ LLOQ. ATA formation was defined as 'transient' when a patient tested positive for ATA on at least one time point during follow-up and negative at the last available time point.

Serum samples were also tested for the following markers of inflammation: CRP, serum amyloid A proteins (SAA), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). These markers of inflammation were run using high sensitivity ELISA (Prometheus, San Diego, California, USA).

LOD, LLOQ and upper limit of normal values based on the upper 95% CI derived from the serum of 120 normal volunteers are shown below.

	CRP ng/mL	SAA ng/mL	ICAM ng/mL	VCAM ng/mL
LOD	0.10	0.09	0.01	0.07
LLOQ	0.70	0.50	0.09	0.70
Upper limit of normal	3.84	5.05	0.27	0.29

Statistical analysis

To study the effect of early drug levels and IMM on ATA formation, a time-to-ATA Cox proportional hazards survival analysis was performed on a subset of n=74 patients for which week 4 post-induction ADL levels were available. The time-to-first-ATA > LLOQ (in months) was calculated for each patient. Data were censored at the last time point for a given patient in patients with absence of ATA in all measurements. ADL was transformed into a binary variable with a serum level cut-off of 5 µg/mL.⁹⁻¹¹ Concomitant steroid use, gender and disease

duration were included in the model as potential confounding variables. An identical model was used, but with ADL as a continuous variable (unit differences: 1 µg/mL were used), to investigate whether applying the 5 µg/mL cut-off introduced spurious results. For all models, variables were log transformed as necessary. The proportional hazards assumptions were met for all variables and for each model as a whole.

To explore the relative effects of drug and anti-drug antibody on inflammation, regression analysis was performed using CRP as a response variable, ATA and ADL as predictor variables, controlling for gender, age and disease duration. Since these data represented repeated measures of multiple serum samples per patient, linear mixed modelling with repeated measurements techniques were used, in which the data were known to be clustered by patient. Variables were log transformed as necessary, and no cut-offs were applied to continuous variables. Two linear models were made: the first regressed the predictors against CRP values in the same sample. The second looked at CRP values in the patient's future relative to the predictor variables. This second model was additionally controlled for the time difference between prediction and response serum collection dates. Adding induction scheme or concomitant IMM to each model did not quantitatively alter the models to predict inflammation. Both models were repeated with alternative inflammatory markers as response variables; namely, SAA, ICAM and VCAM. The results of the regressions for these markers were not different than for CRP.

In order to study patient outcome in terms of inflammatory markers, Mann-Whitney U tests were performed to compare median CRP, SAA, ICAM and VCAM in the last sample for patients that was ATA positive at any time with median CRP, SAA, ICAM and VCAM in the last sample of patients that was always ATA negative.

To study the influence of ATA on LOR, we compared per-patient ATA positivity to a subset of $n=108$ patients who: (a) did not stop ADL therapy or (b) stopped therapy due to LOR. Reasons for ADL therapy cessation other than LOR (adverse events; primary non-response) were omitted from this analysis. The Fisher's exact test was used to test the association between clinical response and ATA formation and between clinical response and week 4 ADL concentration dichotomised by less than or greater than 5 µg/mL.

RESULTS

Baseline demographics of the patient population at ADL therapy initiation are detailed in [box 1](#). The median (IQR)

Box 1 Baseline characteristics at adalimumab (ADL) therapy initiation (n=148)

Female/male (%): 104/44 (70.3/29.7)
 Median (IQR) age at diagnosis (years): 24 (19–30)
 Median (IQR) age at initiation of ADL therapy (years): 36.2 (27.2–44.2)
 Median (IQR) disease duration (years): 10.3 (5.3–15.4)
 Median (IQR) baseline C-reactive protein (CRP) level (mg/L; n=148): 4.54 (1.17–12.13)
 Concomitant medication (%):
 Corticosteroids 30.5%
 Azathioprine/6-mercaptopurine 25%
 Methotrexate 13.3%
 Indication for ADL treatment in relation to infliximab (IFX) failure (%):
 No response to IFX 6.25%
 Infusion reactions or hypersensitivity reactions to IFX 34.4%
 Loss of response to IFX 57.8%
 Smoking status at ADL start (%):
 Never smoked 38.3%
 Ex-smokers 19.5%
 Current smokers 42.2%

follow-up on ADL treatment was 22.7 (12.7–34.2) months. Ninety patients (60.8%) were dose escalated to 40 mg weekly at least once after a median of 15 weeks (range 1–101 weeks).

ATA positivity, time-to-ATA development, relation of ATA with ADL serum concentration

ATA were detected in 20.2% of patients ($n=30/148$) after a median of 34 (IQR: 12.4–60.5) weeks. Of those, 23% (7/30) exhibited 'transient' antibodies. Serum ADL concentration was detected in 96.6% (143/148) of patients. Samples with ADL concentration in the lower two quartiles were more often ATA positive compared to samples in the 3rd and 4th quartile ($p<0.0001$) ([figure 1](#)). The median serum ADL concentration was significantly higher in ATA-negative compared to ATA-positive samples (both detectable and >LLOQ) 10.82 µg/mL (IQR: 7.69–21.50) and 2.86 (1.23–6.25) respectively ($p<0.001$). Starting week 4 after induction, the median serum ADL concentration separated over time according to (future) ATA status ([figure 2](#)).

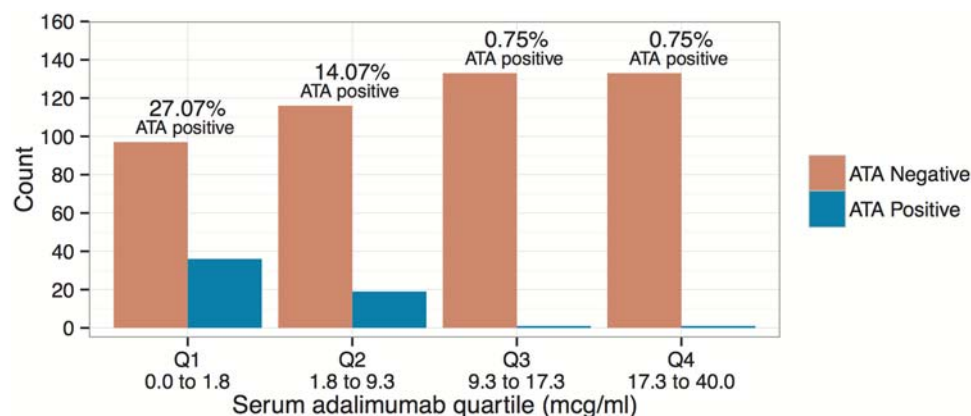


Figure 1 Number of antibodies-to-adalimumab (ATA) positive and negative serum samples according to serum adalimumab (ADL) concentration divided per quartile (µg/mL).

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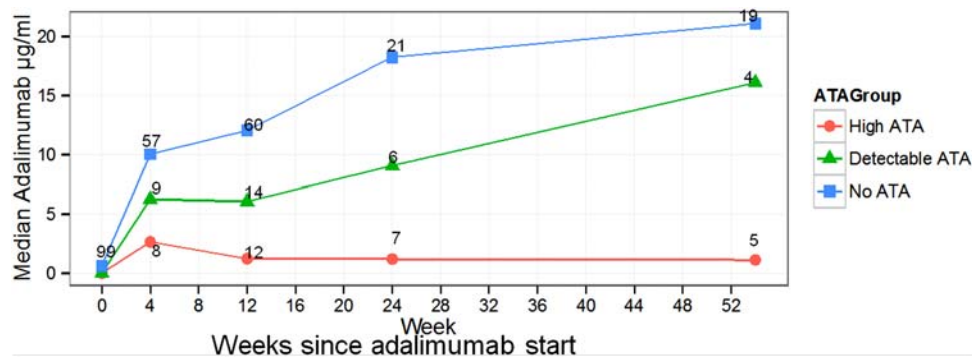


Figure 2 Median adalimumab (ADL) serum concentration over time according to antibodies-to-adalimumab (ATA) group. High ATA was ATA >1.7 U/mL (=lower limit of quantification (LLOQ)). Detectable ATA was ATA >0.78 and <1.7 (LLOQ). No ATA is a zero ATA value.

Post-induction serum ADL concentration as a risk factor for developing ATA

We used two different Cox proportional hazards models to examine the relationship between low serum concentration and IMM use on ATA formation both controlled for age and disease duration. Using serum ADL concentration as a continuous variable with unit differences (1 µg/mL), we found that a higher post-induction concentration decreased the risk of ATA formation (HR: 0.105; 95% CI 0.04 to 0.28; $p < 0.001$). With the HMSA test, anti-drug antibodies could be detected in the presence of detectable drug concentration.⁸ Therefore, using week 4 serum ADL concentration as binary variable (less than or greater than 5 µg/mL), Cox regression modelling was able to show that week 4 ADL <5 µg/mL significantly increased the future risk of ATA formation compared to >5 µg/mL (HR: 25.12; 95% CI 5.64 to 111.91; $p = 0.0002$) (figure 3) and that concomitant use of IMM at ADL therapy initiation prevented ATA formation (HR: 0.23; 95% CI 0.06 to 0.86; $p = 0.029$). We found no

association between the use of steroids at ADL therapy initiation and future ATA formation.

Correlation of serum ADL concentration and ATA with inflammatory markers

Regression modelling showed a negative correlation between the last available CRP and the first serum ADL concentration (regression coefficient: -1.251; $p < 0.0001$) and a positive association with ATA (1.066; $p = 0.019$). Also, when the model was used to predict CRP in a future blood sample (median 7.8 (IQR: 4.0–15.8) weeks between samples), ADL concentration was negatively associated with future CRP ($p = 0.0213$), and ATA was positively associated with future CRP ($p = 0.0012$). All inflammatory markers (CRP, ICAM-1, VCAM-1 and SAA) were significantly higher in ATA-positive compared to ATA-negative patients (see online supplementary figure 1).

Serum ADL concentration, ATA and (dis)continuation of therapy

Early serum ADL concentration >5 µg/mL predicted continuation of treatment (OR: 4.5; 95% CI 1.46 to 14.7; $p = 0.006$). Conversely, ATA positivity was significantly associated with discontinuation of ADL therapy due to LOR (OR: 3.04; 95% CI 1.049 to 9.09; $p = 0.034$).

DISCUSSION

In this large consecutive cohort of Crohn's disease patients treated with ADL maintenance therapy, ATA were detected in 20% of patients, compared to 9% as previously reported.¹ This higher proportion of ATA-positive patients could be explained by the use of a drug-tolerant assay that was able to detect ATA even in the presence of ADL. Low serum ADL concentration together with ADL monotherapy was found to increase the future risk of ATA formation. This was an important finding as lower serum ADL concentration was observed throughout the follow-up in patients positive for ATA. Furthermore, ATA were found to be a predictor of the value of future CRP and subsequent discontinuation of ADL therapy due to LOR. ATA could increase clearance of ADL and decrease the efficacy of ADL by forming neutralising immune complexes. Even though this relationship was bi-directional, our findings suggested that ADL administration caused the development of ATA, which acted to reduce serum concentration. Interestingly, low early drug concentration after induction had an impact on the risk of ATA formation. These findings underscore the predictive value of measuring serum ADL concentration early, which may guide treatment optimisation before symptoms occur.

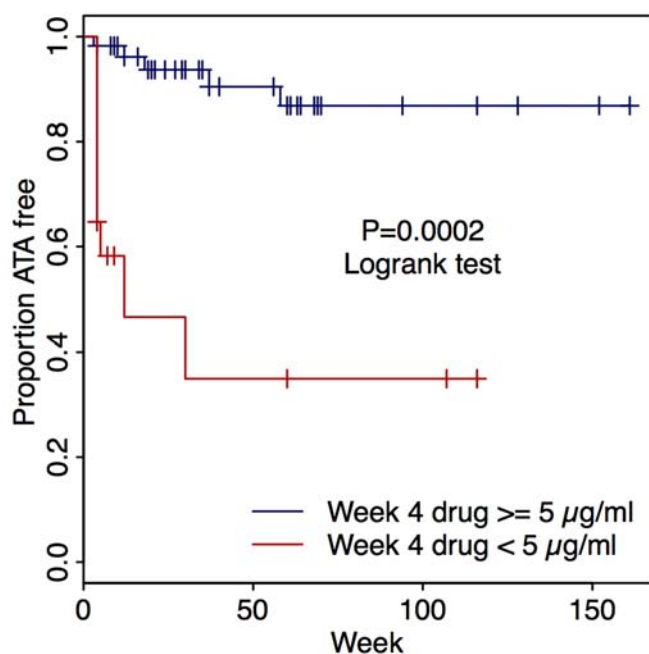


Figure 3 Time to antibodies-to-adalimumab (ATA) detection analysis according to adalimumab (ADL) concentration below or above 5 µg/mL, 4 weeks after start (analysis based on n=74 patients with week 4 samples available).

In this study, we also showed a correlation between ATA and different objective markers of inflammation, as ATA-positive patients had markedly higher inflammatory marker values in their last available serum sample than patients with no observed ATA. Also, we observed that ATA formation was predictive of significant negative clinical consequences. First, ATA-positive patients had higher odds of eventual LOR to ADL therapy. Second, ATA and serum ADL concentration predicted inflammatory markers in a regression model. ADL concentration and ATA were associated with CRP within the same sample and had the capability of predicting future CRP levels. In addition, it had been shown that immunogenicity was a dynamic phenomenon.^{12 13}

This and other studies add evidence to the conceptual framework of immunogenicity to monoclonal antibody therapy. In IBD, most data are related to the use of IFX, a chimeric monoclonal antibody to TNF- α . However, it has been shown that high early post-induction serum concentration of fully human monoclonal antibodies such as ADL and golimumab also correlate with long-term sustained clinical benefits.^{1 14 15} As with IFX, and in line with what has been shown with ADL in other autoimmune diseases, we have demonstrated that concomitant use of IMM at start of ADL therapy reduces ATA. It is still unclear whether ATA formation is decreased because of a synergistic effect of both anti-inflammatory drugs on the immune system or because the IMM alters the pharmacokinetics of the anti-TNF- α drug leading to higher drug exposure and less sensitisation.

The relationship between ATA status and serum ADL concentration over time in this cohort, as demonstrated in [figure 2](#), is remarkably similar to what has been shown in rheumatoid arthritis.^{16 17}

All patients in this study had been exposed to IFX in the past and were either primary non-responders, became intolerant to or lost response to IFX. It could be hypothesised that patients developing antibodies to IFX had a higher chance to develop ATA. Therefore, the proportion of patients developing ATA reported here might be higher due to the prior use of IFX compared to anti-TNF- α naïve patients. However, in this cohort, we did not find a higher proportion of ATA formation in the patients who discontinued IFX for infusion reaction. On the other hand, the vast majority of patients in this cohort had at least a temporary primary response to IFX, and hence represented a selected population of patients prone to respond to ADL.^{18 19}

Our study had limitations. Although serum was collected prospectively, clinical data were collected retrospectively from the charts of the patients. In addition, patients were treated in a non-randomised fashion, including different induction regimens, use of concomitant IMM or not, and non-standardised dose optimisation, including dose escalation to weekly and dose de-escalation to every other week again. Therefore, this study has, by its design, to be considered as an exploratory study. However, this is the first study that reflects a real-life situation, including several potential risk factors. Unlike in the Karmiris study, in this study, the HMSA is used. HMSA can detect both functionally active and inactive high- and low-affinity anti-drug antibodies and hence does not make a distinction between neutralising and non-neutralising antibodies.²⁰ Also, we here report only correlations and associations. With our study design, we cannot prove the temporal relationship between ADL and ATA. It is possible that other confounders interact with both ADL and ATA.

This study further illustrates that the use of standard maintenance therapy, the humanisation and subcutaneous administration does not solve the problem of immunogenicity to monoclonal antibodies.²¹

Conceptually, we propose the following sequence of events. After drug administration, several known and unknown factors specific to monoclonal antibodies, including induction dose, baseline inflammation, serum albumin, concomitant IMM and body mass index (some of which influence the clearance of the drug), lead to a broad range in serum concentration.²² Lower serum concentration and lack of combination therapy are the risk factors for ATA formation. ATA can lead to drug neutralisation and to accelerated drug clearance through antigen-antibody complex formation.²³ This constitutes a positive feedback loop as lower drug concentration is in turn a risk factor for ATA formation. Eventually, lower or absent drug concentration leads to inflammation due to lack of TNF neutralisation, disease flare-up and poor patient outcomes.

Here, we have demonstrated that early low serum ADL concentration and not using combination therapy with IMM are risk factors for the formation of ATA. Next, we have observed that serum ADL concentration is low in ATA-positive patients, and this effect increases over time. As a consequence, higher inflammatory markers are indicating lack of disease control.

This and other studies provide evidence for the use of pharmacokinetic monitoring of monoclonal antibody therapy in IBD.²⁴ We speculate that the use of combination therapy and early dose optimisation, guided by serum ADL concentration, might reduce the rate of immunogenicity. Moreover, we have showed that a combination of objective markers of inflammation, serum ADL concentration and ATA might help to make objective treatment decisions and maximise treatment outcomes of ADL maintenance therapy. Although this remains to be shown prospectively, personalised dosing may optimise patient care as opposed to the current uniform dosing strategies. Meanwhile, we recommend to measure serum ADL concentrations early after induction (eg, after 4 weeks). Higher serum concentration (ie, $>5 \mu\text{g/mL}$) are predictive for good and lasting response. Whereas patients with lower early serum ADL concentration ($<5 \mu\text{g/mL}$) are at risk of ATA formation and LOR and should be monitored more closely with a low threshold to dose optimise.

Contributors Guarantor of the article: FB. FB: analysis and interpretation of data, drafting of the manuscript, final version of the manuscript; VK: additional statistical analysis as requested by the reviewers, critical revision of the manuscript; SL: acquisition and analysis of data, statistical analysis, figures; NVC: interpretation of the drug levels and ATA data and critical revision of the manuscript; SH: acquisition and analysis of data, critical revision of the manuscript; SS: acquisition and analysis of data, critical revision of the manuscript; KK: data collection, conducting the initial study and critical revision of the manuscript; MF: critical revision of the manuscript; AG: co-promoter, interpretation of the serum concentrations and ATA data and critical revision of the manuscript; SV: mentor-promoter of the project, several critical revisions, obtained funding.

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