The effect of infliximab dose escalation in inflammatory bowel disease patients with antibodies to infliximab

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Background Infliximab dose escalation (DE) can be used in inflammatory bowel disease patient; however, the long-term benefit remains unclear, especially in those with antibodies to infliximab (ATI). The aim was to assess the effect of DE in patients with ATI on drug level, clinical response and ATI status.
Methods All patients undergoing infliximab DE (a reduction in dose interval between infusions <8 weeks ± an increase in dose up to 10 mg/kg) at a referral centre between April 2016 and August 2019 were included.
Results Ninety-two patients were DE: 51 were men, 50 had CD and 63 were receiving immunosuppression. A total of 87 people received DE for a median of 44 weeks (range 4–176). Five stopped infliximab after 1 dose of DE: 2 for loss of response and 3 for infusion reaction. In patients with ATI ≤10 vs. >10 AU/mL, DE significantly increased drug levels: median infliximab levels of 1.4 and 0.9 at baseline, respectively, to 3.2 and 3.5 at week 24. After DE, 21/35 ATI-positive patients had a fall in ATI ≤10 AU/mL. At week 24 following DE 62/92 patients were in clinical remission. Duration of clinical remission was shorter in those with ATI >10 AU/mL (median 24 weeks, range 0–88) than in those with transient/ATI ≤10 AU/mL (median 36 weeks, range 0–126, $P = 0.06$).
Conclusions A strategy of DE for selected patients receiving infliximab is associated with an increase in drug levels and reduced ATI positivity. This is associated with clinical remission in approximately 70% of patients at 6 months. Eur J Gastroenterol Hepatol 34: 295–301

Introduction

Infliximab, an antibody against tumour necrosis factor-α, is effective at inducing and maintaining remission in both Crohn's disease and ulcerative colitis [1]. However, secondary loss of response may occur following the initial response. Reported rates of secondary loss of response vary depending on the definition but can be up to 50% at 12 months follow-up [1,2]. This may occur due to an aggressive disease phenotype, disease complications, such as strictures or fistulae, drug pharmacokinetics or a combination of these factors [3–5]. Low circulating drug levels may occur due to 'consumption' in the inflammatory process, loss through the colon, FcR gene polymorphisms [6,7] or immunologically mediated through the formation of antidrug antibodies, which competitively inhibit the drug's ability to bind to tumour necrosis factor-α (TNF-α) or increase the drug clearance [8,9].

Although there has been a rapid expansion in biological and small molecules available to treat inflammatory bowel disease (IBD) [10,11], it remains important to optimise existing regimes where possible.

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The availability of assays to measure drug levels and antidrug antibodies has enabled both proactive and reactive approaches to dosing regimens [12–14] and infliximab dose escalation (DE) can be used as a treatment strategy either to proactively optimise drug levels or reactively when loss of response occurs. DE can be achieved by shortening the dose interval, giving a higher dose or a combination of both of these [12,13]. Although infliximab DE is included in guidelines [10,15], formal long-term evaluation of a strategy of DE is limited, especially in the context of antibodies to infliximab (ATI) status.

The aim of this study was to assess the effect, in clinical practice, of DE in people with IBD on drug level, ATI status and clinical response.

Materials and methods

Patients and study design

All patients undergoing infliximab dose escalation between April 2016 and August 2019 were included. Proactive drug monitoring consisting of trough infliximab and ATI levels were measured at each infliximab infusion following the initial infusion, in all patients receiving infliximab, from May 2016 at a large tertiary referral centre. Infliximab was administered during induction as 5 mg/kg at 0, 2 and 6 weeks and continued every 8 weeks for maintenance therapy. Patients received 200 mg of intravenous hydrocortisone prior to each infliximab infusion. DE comprised of (1) interval shortening: reduction in dose interval

between maintenance infusions to less than 8 weeks, (2) dose doubling: increase of infliximab to 10 mg/kg, (3) combined dose escalation: combination of both interval shortening and dose doubling at each infusion or (4) variable dose escalation: the use of interval shortening or dose doubling at different infusions. Patients were included at individual time points if infliximab levels were available ±1 week. Patients were dose-escalated proactively whilst in clinical remission with subtherapeutic drug levels and reactively for loss of response.

Clinical assessment

Harvey–Bradshaw index (HBI) [16] for Crohn's disease and simple colitis activity index (SCAI) [17] for ulcerative colitis were documented at each infusion attendance. Additional patient contact including clinic review was also included in clinical assessment. Full blood count, urea and electrolytes, liver function tests, C-reactive protein (CRP) and erythrocyte sedimentation rate were measured at each infusion.

Remission was defined clinically and biochemically for CD as HBI ≤4 plus a CRP ≤5 mg/L and defined clinically in UC as SCAI ≤4. Loss of clinical remission was defined in CD as HBI >4 and or raised CRP and in UC as SCAI >4 or worsening of symptoms attributed to the IBD requiring an alteration in treatment. ATI-positive patients, following DE, were deemed to become sustained ATI negative (ATI ≤10 mg/L) if the ATI level remained negative for the duration of DE.

Therapeutic drug monitoring

Trough infliximab levels were assessed using IDKmonitor Infliximab drug level ELISA (Immundiagnostik AG, Bensheim, Germany) [18]. Trough infliximab levels which were defined as undetectable if <0.8 mg/L, subtherapeutic if 0.8–2.9 mg/L, therapeutic if 3–7 mg/L and supratherapeutic if >7 mg/L [19]. ATI was assessed using a drug-tolerant assay, IDKmonitor Infliximab total ADA (Immundiagnostik AG, Bensheim, Germany) [20]. This total antidrug antibody double bridging ELISA incorporates an immune complex dissociation step between ATI and Infliximab, allowing ATI to be assessed in the presence of the drug [20]. Individual ATI readings were calculated: patient sample optical density × 10/optical density of control (10 AU/mL). The cut-off control was established by diluting a sample, which was highly positive for ATI until no further linear dilution was possible. Using this cut-off, subsequent testing of sera from infliximab-naive patients confirmed 97.5% of patients to be negative for ATI. This was further confirmed by repeating this assessment in a local population as part of the laboratory accreditation. Positive ATI that resolved within two consecutive infusions were defined as transient. TDM values were included at follow-up intervals if patient had received an infliximab infusion and therefore had TDM performed a week before or after that time point.

Statistical analyses

Shapiro–Wilk was used to assess normality of distribution for infliximab and ATI levels. Wilcoxon signed-rank test with correction for multiple comparisons was used to assess paired infliximab and ATI levels pre-DE to levels post-DE as data was nonparametric. Receiver operated curve was used to assess the association between ATI levels pre-DE and subsequent ATI negativity post-DE. Kruskal–Wallis with pair-wise analysis and correction for multiple comparisons was used to compare the efficacy of the different methods of DE on infliximab levels and Kaplan–Meier with Tarone–Ware test for its effect on clinical remission.

Microsoft Excel, GraphPad Prism and IBM SPSS statistics software were used for statistical analyses. 95% confidence intervals with P value ≤0.05 were deemed statistically significant. Benjamini–Hochberg and Bonferroni correction was used to control for multiple comparisons false discovery rate.

Ethical considerations

Ethical approval was granted by Sheffield Research Ethics Committee and the Health Research Authority (IRAS project ID 213480, STH reference 19459). Treatment was part of routine clinical care.

Results

Patients

A total of 464 IBD patients were treated with infliximab between 2016 and 2019. Ninety-two people (20%) underwent infliximab dose escalation. 51/92 were men; 50 had CD; median age was 33 (16–81) and 63 were receiving concomitant immunosuppression (Table 1). Infliximab was the first biologic for 70/92 patients. Of the 22 patients with prior biologic exposure, 13 had previously been treated with infliximab, 6 with adalimumab, 1 with vedolizumab, 1 with adalimumab and vedolizumab and 1 with infliximab, adalimumab, vedolizumab and ustekinumab. Fifty-four had negative or transient ATI (median ATI levels 4 mg/L, range 1–9) and 38 had positive ATI (median ATI levels 31 mg/L, range 10–223). Fifty-nine patients were dose-escalated for LOR (17 with positive ATI and 42 with negative ATI) and 33 proactively to optimise therapeutic drug monitoring levels

Table 1. Demographic details and description of patients in inflammatory bowel disease cohort receiving infliximab dose escalation

Variables	ATI >10 AU/mL (n = 38)	ATI ≤10 AU/mL or transient (n = 54)	P value
Men, number (%)	21 (55)	30 (56)	NS
Median age (range)	34 (17–81)	31 (16–71)	NS
Crohn's disease, number (%)	20 (53)	30 (56)	NS
Previous infliximab, number (%)	6 (16)	8 (15)	NS
Reason for dose escalation, number (%)			
Loss of response	17 (45)	42 (78)	<0.01
Therapeutic drug monitoring	21 (55)	12 (22)	<0.01
Immunosuppression, number (%):	22 (58)	41 (76)	NS
Thiopurines	16 (42)	36 (67)	
Methotrexate	6 (16)	5 (9)	
Type of dose escalation, number (%)	9 (24)	11 (20)	NS
Interval shortening			
Dose doubling	16 (42)	16 (30)	
Combined dose escalation	6 (16)	11 (20)	
Variable dose escalation	7 (18)	16 (30)	

ATI, antibodies to infliximab.

(Table 1). Eighty-seven people received DE for a median of 44 weeks (range 4–176). 5 stopped infliximab after a single further dose: 2 for LOR and 3 due to infusion reaction.

The effect of dose escalation on trough infliximab levels

Infliximab levels after DE were compared to paired pre-DE values in 87 patients who had more than 1 DE dose. DE significantly increased trough drug levels at subsequent follow-up to week 48 across the cohort. At baseline, median infliximab levels were 1.4 mg/L and 0.9 mg/L, respectively, for patients with negative/transient ATI and positive ATI and these increased to 3.2 mg/L and 3.5 mg/L respectively at week 24, $P < 0.001$; <0.001 (corrected for multiple comparisons) (Fig. 1).

The effect of infliximab dose escalation on antibodies to infliximab levels

ATI levels after DE were available for 35/38 (92.1%) patients with positive ATI. 21/35 (60%) ATI-positive patients had a fall in ATI to below the positive threshold (ATI ≤10 AU/mL) at any point following DE. However, this was only sustained in 13 (22.9%) patients (median follow-up 58 weeks, range 21–104). There was no significant difference in ATI levels before dose escalation between those who subsequently became ATI negative (n = 13 median ATI 23 AU/mL, range 12–103) compared to those who remained ATI positive (n = 22 median ATI 37 AU/mL, range 10–223). Figure 2 shows that median ATI levels in those with ATI >10 AU/mL decreased after DE (corrected for multiple comparisons). ATI levels pre-DE in those with positive ATI poorly predicted subsequent ATI negativity after infliximab DE with an area under the curve of 0.56 (P = 0.6, 95% CI, 0.36–0.76).

The effect of infliximab dose escalation on clinical outcomes

33/92 (36%; 21 ATI positive and 12 ATI negative) patients were in clinical remission prior to DE. Following DE – at week 24 – 62/92 (67%) patients were in clinical remission (Fig. 3). Of these 42/59 (71%) were recaptured following loss of response (11 ATI positive and 31 ATI negative or transient) and 20/33 (60%) were maintained in remission (11 ATI positive and 9 ATI negative or transient). Duration of clinical remission was numerically shorter in ATI-positive patients (median 24 weeks, range 0–88) than in those with transient or negative ATI (median 36 weeks, range 0–126, P = 0.06, Fig. 4).

There was no difference in acute infusion reactions between those with positive ATI (3/38) and those with transient or negative ATI (2/54, P = 0.4).

Comparison of the different methods of dose escalation

The different methods of DE were assessed for their effect on infliximab trough levels and clinical response. There was a significant difference in infliximab trough levels at week

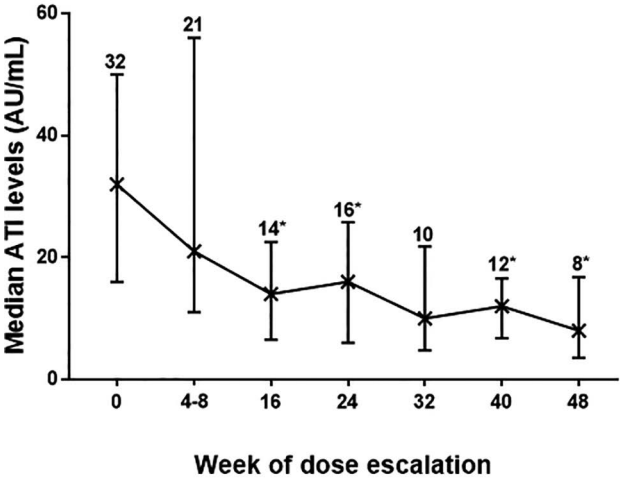

Fig. 2. Median antibodies to infliximab levels (error bars indicate the 25–75th percentiles) following dose escalation in patients with positive antibodies (>10 AU/mL). *Antibodies to infliximab levels at weeks 16, 24, 40 and 48 of infliximab dose escalation were significantly decreased compared to baseline with correction for multiple comparisons (P < 0.05). ATI, antibodies to infliximab.

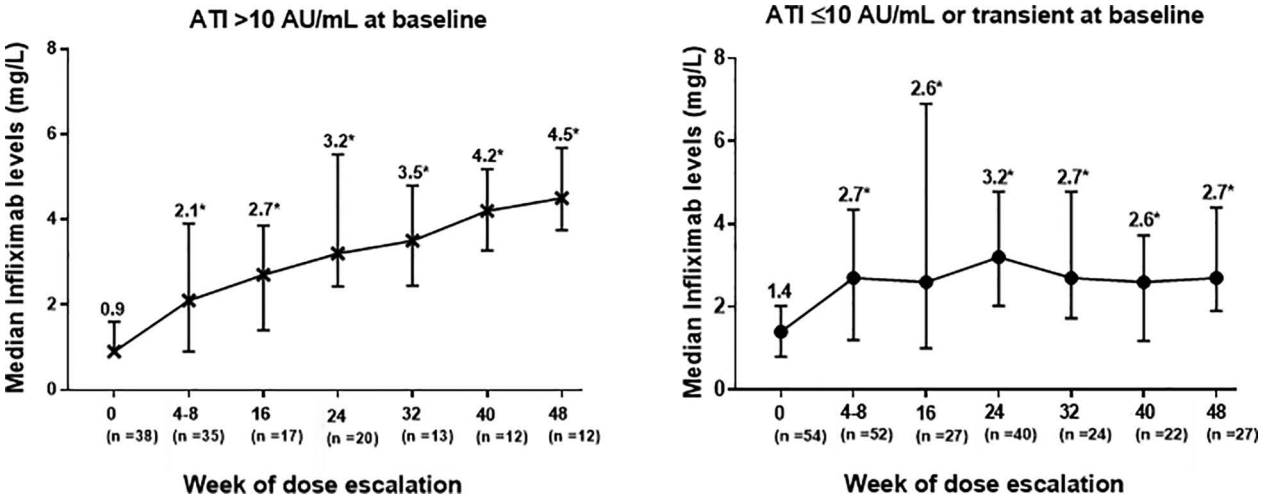

Fig. 1. Median trough drug levels (error bars indicate the 25–75th percentiles of the trough drug levels) following infliximab dose escalation in patients (a) with ATI >10 AU/mL at baseline and (b) with ATI ≤10 AU/mL at baseline. *Infliximab levels at this time point were significantly increased compared to baseline with correction for multiple comparisons (P < 0.05). ATI, antibodies to infliximab.

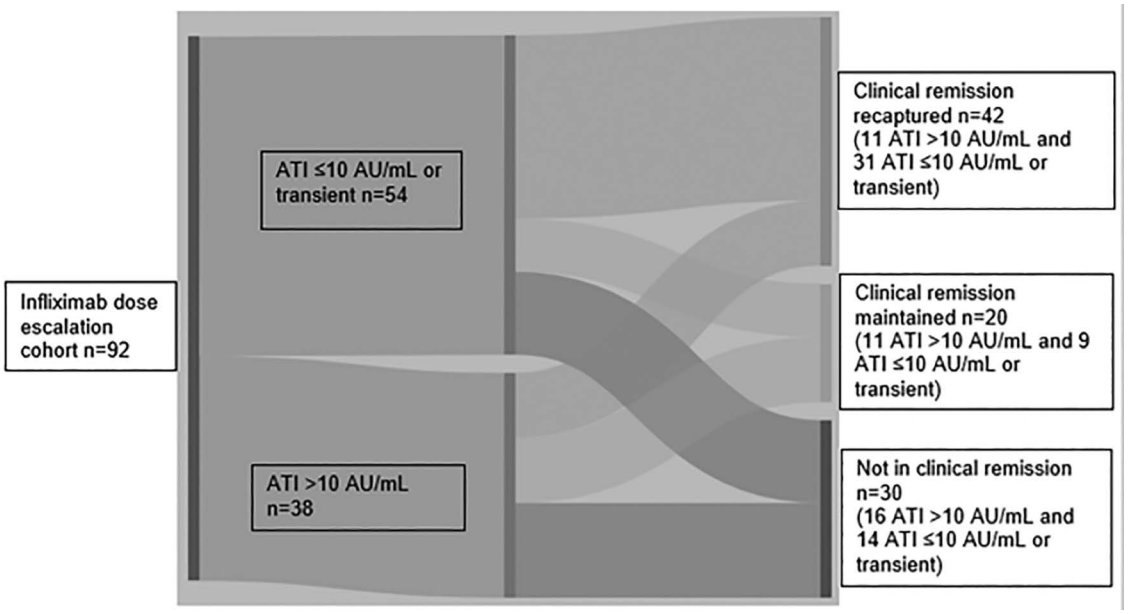

Fig. 3. Sankey diagram to illustrate clinical outcomes of patients receiving infliximab dose escalation at week 24 on the basis of initial ATI and clinical status. At week 24, 62/92 (67.4%) patients were in clinical remission; 42/59 (71.2%) recaptured following loss of response and 20/33 (60.1%) were maintained in remission. ATI, antibodies to infliximab.

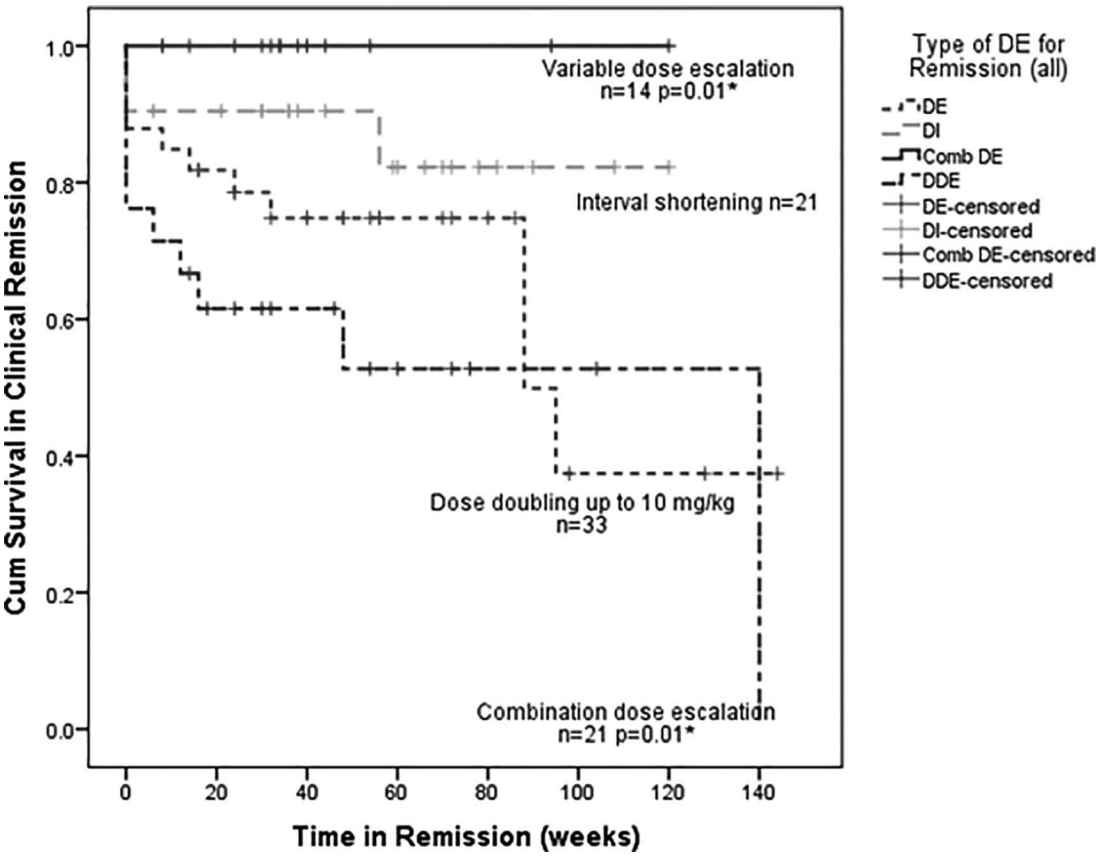

Fig. 4. Time in clinical remission following different methods of infliximab dose escalation. *Significant difference in duration of clinical remission between combined dose escalation and variable dose-escalation despite correction for multiple comparisons (P = 0.01).

24 between those who received dose doubling to 10 mg/kg (median drug level of 2.5 mg/L, range 0.8–7.5) and combined dose escalation (median drug level of 5 mg/L, range 2.7–16.7). This same difference was mirrored in the ATI-negative cohort but not in the ATI-positive cohort (Table 2). There was a significant difference in duration of clinical remission between those receiving variable dose escalation and combined dose escalation with a decrease in time to loss of remission in the latter method (Fig. 4). This significant difference between these two methods was not present on subgroup analysis of ATI-positive and negative cohorts.

Table 2. Comparison of infliximab trough level following different methods of dose escalation in patients with inflammatory bowel disease

Type of infliximab dose escalation	Median infliximab trough levels		
	Entire cohort (*n* = 92)	ATI >10 AU/mL (*n* = 38)	ATI ≤10 AU/mL or transient ATI (*n* = 54)
Week 0			
Interval shortening	1.3	1.3	1.3
Dose doubling	0.9	0.8	1.2
Variable DE	1.7	0.8	1.8
Combined DE	0.8	0.8	0.8
P value	0.05	0.33	0.16
Week 4–8			
Interval shortening	3.7	2.6	3.8
Dose doubling	2.1	3.1	2
Variable DE	2.7	1.7	2.7
Combined DE	2.3	2.0	3.5
P value	0.28	0.77	0.17
Week 16			
Interval shortening	5.3	2.3	7.2
Dose doubling	2.1	2.7	1.9
Variable DE	4.5	2.7	6.1
Combined DE	4.6	No values	4.6
P value	0.11	0.92	0.05
Week 24			
Interval shortening	3.2	3.1	3.2
Dose doubling	2.5[a]	2.5	2.4[a]
Variable DE	2.8	5.3	2.7
Combined DE	5[a]	4.6	5[a]
P value	0.02[a]	0.70	0.02[a]
Week 32			
Interval shortening	2.3	2.4	2.2
Dose doubling	2.7	3.6	2.2
Variable DE	3.6	3.5	3.6
Combined DE	6.8	8.8	4.7
P value	0.26	0.40	0.22
Week 40			
Interval shortening	3.6	3.7	3.4
Dose doubling	3.1	4.7	2.3
Variable DE	2.5	3.9	2.5
Combined DE	1.2	No values	1.2
P value	0.65	0.94	0.64
Week 48			
Interval shortening	3.2	4.3	3.1
Dose doubling	2.5	4.5	2.6
Variable DE	2.3	4.6	2.2
Combined DE	5.2	9.4	4.3
P value	0.61	0.45	0.70

P values are generated from comparing the infliximab levels gained at each time point from using the different methods of dose escalation: (1) interval shortening: reduction in dose interval between maintenance infusions to less than 8 weeks, (2) dose doubling: increase of infliximab to 10 mg/kg, (3) combined dose escalation: both interval shortening and dose doubling at each infusion and (4) variable dose escalation: the use of interval shortening or dose doubling at different infusions

[a]Significant difference in infliximab trough level is noted at week 24 between dose doubling and combined dose escalation ($P = 0.01$) on pair-wise analysis and correction for multiple comparisons.

DE, dose escalation.

Discussion

Secondary loss of response to biological therapies remains a significant problem in the treatment of IBD. The role of DE for secondary loss of response to infliximab is not clear in people with ATI [13,14,21,22]. In particular, there remains a lack of long-term data with therapeutic drug monitoring following DE. This report describes the experience of infliximab DE in a large tertiary centre. Both proactive and reactive dose escalation was assessed, as both methods are used in clinical practice. DE was effective in significantly increasing trough drug levels to therapeutic levels in those with positive and negative ATI, reduced ATI in those above the threshold of 10 mg/L and maintained or recaptured remission in nearly 70% at 6 months post-DE.

In our cohort, following DE, all patients had TDM, CRP and clinical severity scores assessed at every infliximab infusion. Patients received premedication with intravenous hydrocortisone prior to each infliximab infusion, which may have reduced immunogenicity rates. A total antidrug antibody assay was used as the aim was to identify all patients with ATI. At baseline, prior to DE, all patients had individual ATI levels assessed and 38/92 were above our assay's threshold for ATI positivity (>10 AU/mL). In our cohort, infliximab DE was associated with an increase in drug levels up to week 48 compared to baseline in both those with positive and negative ATI. Previous studies have suggested that DE may not be effective in those with 'high' ATI: above 481 or 9 mcg/mL [13,21). However, the use of different antidrug assays in the literature creates difficulty in determining a clinically relevant threshold of ATI, which is generalisable. In our cohort, despite significant levels of ATI in the ATI-positive group (median 32 mg/L, range 10–223) infliximab DE did lead to a significant increase in trough drug levels. It would have been of interest to review whether 'grouping' patients into ATI levels affected their response to dose escalation. However, the number of patients in the ATI-positive group limited this. Interestingly, infliximab levels post-DE were higher for the ATI-positive group. There was no significant difference in the different methods of DE used between the ATI-positive and negative groups. However, significantly more ATI-negative patients received DE for loss of response. The increased inflammation and circulating TNF-α may have led to increased drug consumption, explaining the lower drug level in this group. More people were reactively dose-escalated in the ATI-negative group as the combination of LOR and high ATI levels may have led to alternative management decisions such as switching to a different biologic as per clinical guidelines [10].

Both proactive and reactive dose escalation was assessed, as both methods are used in clinical practice. However, different drug pharmacokinetics may be present in these two groups affecting their response to DE. A limitation of our study is that the effect of DE was not assessed separately on the basis of whether proactive or reactive DE was used. Combination therapy with thiopurines and methotrexate was used in 58% of patients with positive ATI and 76% of patients with negative ATI. Analysing the effect combination therapy with dose escalation in the ATI-positive and negative groups was not performed due to small numbers in the subgroups.

Infliximab DE was associated with a high rate of clinical remission, nearly 70% of patients at 6 months. The duration of clinical remission did appear to be shorter in those undergoing dose escalation with ATI >10 AU/mL, compared to those with ATI ≤10 AU/mL. Although patients were closely monitored and had a clinical review and CRP at every infusion, a limitation is that remission was not defined endoscopically or with routine faecal calprotectin assessment.

Our study shows that total ATI levels can reduce following DE. There was no significant difference in baseline ATI levels between those who became ATI negative and those who remained positive after DE. ATI levels in the

former group ranged greatly from 12–103 AU/mL. The lack of association between baseline ATI level in predicting ATI negativity following DE may be due to the small numbers but also suggests other factors may be more important. HLA genotype is associated with the development and persistence of antidrug antibodies to TNF agents [25]. It is therefore also possible that these individuals will also respond less favourably to DE. There is also evidence that different types of ATI may be generated [4,26] and it may be that the different antibodies respond differently to DE.

The best way to dose escalate in clinical practice remains unclear. In this study, combined dose escalation (using both interval shortening and dose doubling) was associated with a significantly higher infliximab levels, but only at week 24, compared to dose doubling (increase of infliximab from 5 to 10 mg/kg). In addition, combined dose escalation was associated with a reduced duration of clinical remission compared to the other methods -though this may reflect selection bias as a more aggressive method of DE is likely to be used for those with loss of response or adverse prognostic features.

Conclusion

This study has demonstrated that infliximab dose escalation increases through drug levels, reduces antidrug antibodies, and results in remission being maintained or recaptured in the majority of patients at week 24. It, therefore, has an important role in how infliximab dose-escalation is used in those with antidrug antibodies. More detailed studies to evaluate the optimum method of dose escalation, a threshold at which antibodies may not be suppressed and the cost-effectiveness of the approach, using drug-tolerant assays are now needed.

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G.T. designed the study, performed the data collection, data analysis and wrote the first draft of the manuscript. A.L. designed the study, performed data analysis, reviewed, contributed and approved the final version of the manuscript. L.T., L.M., K.R., A.W., G.W., R.S., M.H., A.B. and T.C. reviewed, contributed and approved the final version of the manuscript.

Conflicts of interest

A.J.L. would like to declare speaker fees, advisory board membership or consultancy for Takeda, Janssen, MSD, Vifor, Shield Therapeutics, Abbvie, Pfizer, Janssen, Medtronic.

T.S.C. would like to declare speaker fees for Takeda and Pfizer. For the remaining authors, there are no conflicts of interest.

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