Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis


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ABSTRACT

Background and Aims: Antibodies to infliximab reduce serum infliximab with loss of clinical benefit, but undetectable trough serum concentrations of infliximab may occur without antibody formation. The relationship between trough serum infliximab and clinical outcomes was evaluated in acute ulcerative colitis.

Methods: In a cohort of 115 patients with ulcerative colitis treated with three-dose induction followed by scheduled maintenance infliximab, rates of clinical remission, colectomy, antibodies to infliximab and trough serum infliximab were determined.

Results: Rates of remission were 32% at week 10 and 37% at week 54. Colectomy occurred in 40% of patients, at a median of 5.3 (IQR 1.9–12.1) months. Detectable trough serum infliximab was present in 39% of patients and, among patients with undetectable infliximab, 41% were antibody positive and 20% were antibody negative. For antibody-positive and antibody-negative patients, rates of remission (18% vs 14%), endoscopic improvement (25% vs 35%) and colectomy (52% vs 59%) were not different. A detectable serum infliximab was associated with higher rates of remission (69% vs 15%; p<0.001) and endoscopic improvement (76% vs 28%; p<0.001). An undetectable serum infliximab predicted an increased risk for colectomy (55% vs 7%, OR 9.3; 95% CI 2.9 to 29.9; p<0.001). Concurrent immunosuppression was not associated with clinical outcomes.

Conclusions: For patients with ulcerative colitis treated with infliximab, a detectable trough serum infliximab predicts clinical remission, endoscopic improvement and a lower risk for colectomy. An undetectable trough serum infliximab, irrespective of antibody status, is associated with less favourable outcomes.

The therapeutic strategy for acute ulcerative colitis (UC) including 5-aminosalicylates, corticosteroids and immunosuppressive agents does not provide clinical benefit for all patients. Corticosteroid dependence is frequent and for patients with pancolitis up to 39% eventually require colectomy.1-3 Infliximab, a chimeric monoclonal immunoglobulin G1 (IgG1) antibody against tumour necrosis factor α (TNFα), is effective for induction and maintenance of remission in patients with Crohn’s disease.4-9 More recently, infliximab has been evaluated for moderate to severe UC, but the clinical results have been less uniform.6 The first randomised trial of steroid-dependent patients showed no difference in clinical outcome for infliximab compared with placebo.7 In contrast, the larger ACT 1 and 2 trials found that a higher proportion of patients with moderate to severe UC entered clinical remission by week 50 after infliximab compared with placebo.8

The explanation for variable rates of clinical benefit after infliximab treatment for UC is unclear. Older age at first infliximab infusion and perinuclear antineutrophil cytoplasmic antibody (pANCA)+/anti-Saccharomyces cerevisiae antibody (ASCA)+ serotype have been associated with a suboptimal early outcome.9 An alternative explanation for lack of response is incomplete suppression of TNFα activity because of insufficient serum levels of drug. Monoclonal antibodies are potentially immunogenic, and the development of antibodies to infliximab has received considerable attention as a key factor associated with undetectable serum infliximab and loss of clinical benefit.10 11 However, 16–39% of patients treated with scheduled infliximab have undetectable drug prior to the next infusion without antibody formation.12 Thus, variable rates of clinical remission also could occur independently of the development of antibodies, perhaps because of more rapid clearance of infliximab. Together, these observations suggest the trough serum concentration of infliximab prior to the next infusion may be the more important determinant of clinical outcome during treatment for acute UC, whether or not antibodies are present. In support of this concept are findings among patients with Crohn’s disease receiving scheduled maintenance infliximab, where a detectable trough serum concentration of infliximab was associated with higher rates of clinical remission, normal C-reactive protein (CRP) and endoscopic improvement.12

We studied the relationship between trough serum concentrations of infliximab and antibody formation on clinical outcomes, including the rates of clinical remission, endoscopic improvement and colectomy, in patients with moderately severe to severe, steroid-refractory acute UC treated with three-dose induction followed by scheduled maintenance infliximab.

METHODS

Patients

A consecutive cohort of 115 patients with moderately severe to severe UC who initiated infliximab treatment between March 2001 and April 2008 were studied. The diagnosis of UC was made using established clinical, endoscopic and histological criteria. The induction protocol was infliximab 5 mg/kg at 0, 2 and 6 weeks. Patients responding to induction infliximab received 5 mg/kg infliximab at scheduled intervals of 8 weeks.

The clinical remission rate for patients with antibody-negative status and detectable trough serum infliximab was 69% (95% CI 57% to 80%) compared with 15% (95% CI 8% to 26%) (p<0.001). Concurrent immunosuppression was not associated with clinical outcomes.

References:


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Adjustment of the infusion interval to 6 or 7 weeks and/or an increment of the dose to 10 mg/kg infliximab were undertaken at the discretion of the treating physician. Concomitant additional treatment for UC with mesalamine (4.0–4.8 g/day) and azathioprine (2.0–2.5 mg/kg/day) was administered as indicated. The study was approved by the institutional Research Ethics Board and all patients gave written informed consent.

Evaluations
Clinical evaluations included age, gender, disease location and duration, smoking status, concurrent use of mesalamine and azathioprine, and dose and duration of corticosteroids. Tuberculosis was excluded in all patients by a negative PPD (purified protein derivative) skin test and a normal chest x ray. Patients were assessed at baseline, prior to each induction infusion and at ≤4 month intervals prior to maintenance infusions. Complete blood count, chemistry tests (liver and renal profile), albumin, CRP, pANCA status and stool tests to exclude enteric pathogens and *Clostridium difficile* were performed.

Baseline UC disease activity was measured by the Mayo score. Severe disease was defined as a hospitalised patient, refractory to intravenous corticosteroid treatment for ≥7 days and a Mayo score of ≥10 points. Moderately severe disease was defined as the absence of a clinical response to at least 40 mg of prednisone orally for ≥10 days and a Mayo score of ≥6 points. Colonoscopy was performed within 2 months prior to the baseline infusion in all patients, and 109 patients consented to one or more follow-up examinations; 65 studies were performed after induction treatment, prior to week 14. An endoscopic activity score was calculated for each examination by the treating physician and by one additional investigator (CS), with a consensus score recorded. The endoscopic disease activity score ranges from 0 to 3, with 0 denoting normal mucosa, 1 granular mucosa with an abnormal vascular pattern, 2 friable mucosa with spontaneous bleeding and occasional microulceration and 3 gross friability and ulceration. A clinical response was defined as a decrease in a partial Mayo score (without endoscopic findings) of ≥3 points and at least 50% from the baseline score. Clinical remission was defined as a partial Mayo score of 0 and the absence of corticosteroid treatment for ≥4 weeks. Endoscopic improvement was defined as a reduction in the follow-up endoscopic score of at least one point compared with baseline. Endoscopic remission was defined as normal mucosa with disappearance of all mucosal lesions. Side effects were recorded, including the rate of early infusion reactions.

Concentrations of infliximab and antibodies against infliximab were evaluated in 108 patients from serum samples drawn immediately before an infusion in those who received maintenance treatment with a median interval from the baseline infusion of 10.7 (interquartile range (IQR) 6.3–18.4) months and in the event of early discontinuation related to colectomy or lack of benefit, within 8 weeks after cessation of infliximab (median interval from baseline infusion of 3.5 (IQR 2.5–3.5) months). Twenty-three consecutive patients had additional samples taken at 1, 2, 4, 6 and 14 weeks from the baseline infusion. Twenty-five patients who received maintenance treatment were randomly selected for a repeat analysis on a second preinfusion sample drawn a median of 20 weeks (range 2–56 weeks) after the first sample. Serum infliximab and antibodies against infliximab (Prometheus Laboratories, San Diego California, USA) were assessed blindly in duplicate, as described previously. Antibodies against infliximab were reported as negative when the concentration was <1.69 μg/ml and the serum infliximab was <1.40 μg/ml, and as positive when the concentration exceeded 1.69 μg/ml and the serum infliximab was <1.40 μg/ml. An inconclusive result was reported when the serum infliximab was ≥1.40 μg/ml, because infliximab interferes with the antibody against infliximab assay and antibody formation cannot be determined.

Statistical analysis
Comparison of differences within a group was performed by using the Student paired t test for normally distributed data and the Wilcoxon signed rank sum test for non-normally distributed data. Differences between groups were assessed by analysis of variance (ANOVA) or the Kruskal–Wallis ANOVA on ranks as appropriate. Categorical data were compared with the χ² test or Fisher exact test. Logistic regression was used to examine predictors of clinical remission and colectomy. The primary variable of interest was the presence of detectable trough serum infliximab. Other variables included gender, age, disease location, disease duration, baseline Mayo score ≥10, use of prednisone for ≥1 year prior to infliximab, use of concurrent azathioprine, pANCA status, baseline CRP >5 mg/l and the presence of antibodies to infliximab. Time to colectomy was analysed by the Kaplan–Meier method. p Values <0.05 were considered significant. Statistical analysis was performed by using SAS (version 9.1.2; SAS Institute, Cary, North Carolina, USA).

RESULTS
Patients
Baseline characteristics of the 115 patients are shown in table 1. The indication for infliximab was severe disease in 42 patients and moderately severe disease in 73 patients. The median baseline Mayo score for severe patients (11 points; range 10–12) was higher than for moderately severe patients (8 points; range 6–10) (p<0.001). The median dose of corticosteroids (prednisone equivalents) was 40 mg/day and 26 patients (25%) were receiving concurrent azathioprine.

Outcome of induction infliximab
Of the 115 patients who initiated infliximab induction treatment, 59% (68/115) had a clinical response and 52% (57/115) achieved a clinical remission at week 10. Patients with moderately severe disease compared with severe UC had a higher rate of clinical response (70% vs 41%; p = 0.004) and clinical remission (41% vs 17%; p = 0.015). Endoscopic remission occurred in 17% (11/65) of evaluated patients. The rate of endoscopic remission was higher for patients with moderate than for those with severe UC (26% vs 4%; p = 0.046). Among 22 patients who discontinued infliximab after ≤3 infusions, three (infusion reaction, n = 1; lack of benefit n = 2) received other medical treatments and 19 had a colectomy. Fourteen (13 severe and 1 moderate) of the 115 patients (12%) underwent colectomy by week 10.

Outcome of scheduled maintenance infliximab
Ninety-three of 115 patients (81%) treated with induction infliximab received one or more maintenance infusions (median 5 infusions; IQR 3–10) over a median period of 13.9 (IQR 6.4–22.3) months. At week 54, 48% of patients (55/115) achieved a clinical response and 57% (45/115) of patients were in steroid-free clinical remission. Patients with moderate compared with severe UC had a higher rate of clinical response (60% vs 29%; p = 0.003) and clinical remission (45% vs 19%; p = 0.009). The proportion of patients in clinical remission was similar with and without concurrent mesalamine (49% vs 48%; p = 0.94) and azathioprine (49% vs 46%; p = 0.97). Endoscopic improvement
patients with baseline Mayo scores of 6 or more were considered to have more severe disease activity. The proportion of patients with detectable infliximab tended to be lower with more severe disease activity but the difference for inconclusive patients treated with and without concurrent immunomodulators (6.5 vs 6.3 mg/L; p = 0.88). Forty-two patients (39%) were antibody inconclusive with and without concurrent immunomodulators (40% vs 41%; p = 0.78) were higher than the colectomy rates for antibody-positive and antibody-negative patients (52% vs 59%; p = 0.004; fig 2B). Conversely, the similar colectomy rates for antibody-positive and antibody-negative patients (52% vs 59%; p = 0.78) were higher than the colectomy rate of 7% for inconclusive patients (p<0.001; fig 2C).

**Antibody status and relationship to outcome**

An undetectable trough serum concentration of infliximab occurred in 55% (60/109) of patients and endoscopic remission was achieved in 16 (15%) patients. Infliximab was discontinued in 52% (60/115) of patients over the 13.9 month follow-up period. Forty-six of 115 patients (40%) required colectomy at a median of 5.3 (IQR 1.9–12.1) months from the baseline infusion, with 38 patients (33%) having undergone colectomy by week 54. The colectomy rate was higher for patients with severe compared with moderate UC (60% vs 29%; p = 0.002) and occurred at a shorter median time (2.8 vs 9.1 months; p = 0.001) (fig 1). The indications for discontinuation in the 14 non-colectomy patients receiving other medical treatment included infusion reaction (n = 5), lack of clinical benefit (n = 7), pregnancy (n = 1) and loss of follow-up (n = 1).

**Trough infliximab and relationship to clinical outcome**

Clinical outcomes evaluated by antibody status related directly to the presence (antibody inconclusive) or absence (antibody-positive and antibody-negative patients) of trough serum infliximab (fig 2). In accord with these findings, strong associations were identified between the trough serum infliximab concentration and clinical outcomes. Patients with a detectable serum infliximab concentration compared with those in whom the trough serum infliximab was undetectable had higher rates of clinical remission (69% vs 15%; p<0.001; fig 3A), endoscopic improvement (76% vs 28%; p<0.001; fig 3B) and endoscopic remission (27% vs 8%; p = 0.021), and a lower rate of colectomy (7% vs 55%; p<0.001; fig 3C).

**Table 1 Baseline patient characteristics**

| Gender, n (%) | 
| Females | 56 (49) |
| Males | 59 (51) |
| Age* (years) | 31 (16–72) |

**Disease features**

| Area of involvement, n (%) | 
| Left colon | 25 (22) |
| Pancolitis | 90 (78) |
| Duration* (years) | 7 (0.4–24) |
| Acute severe, n (%) | 42 (37) |

**Ulcerative colitis activity score**

| Ulcerative colitis activity score | 
| Acute severe* | 11 (10–12) |
| Moderately severe* | 8 (6–10) |

**Medications at initiation**

**Corticosteroids**

- Intravenous, n (%) | 58 (50)
- Prednisone, n (%) | 47 (41)
- Dose, mg; 20 mg/day, n (%) | 89 (77)
- Dependence >1 year, n (%) | 24 (21)
- Mesalamine, n (%) | 78 (68)
- Azathioprine, n (%) | 26 (23)
- CRP <5 mg/L, n (%) | 21 (18)

**pANCA positive, n (%) | 73 (63)**

**Values are median and range.**

**References**

1. Measured by the Mayo score: range is from 0 to 12, with higher scores indicating more severe disease.

2. Values are in prednisone equivalents at initiation of infliximab and are median and interquartile range.

3. CRP, C-reactive protein; pANCA, perinuclear antineutrophil cytoplasmic antibody.

4. Value of CRP <5 mg/L is within the normal range.

5. pANCA, perinuclear antineutrophil cytoplasmic antibody.
An undetectable trough serum infliximab also preceded antibody formation. Of the 23 patients who underwent sequential sampling from baseline, 56% (13/23) had a low serum infliximab (median 2.1 μg/ml; IQR 1.4–2.9) at 4 weeks and undetectable serum infliximab at 6 weeks. Among the 13 patients with undetectable serum infliximab, 77% (10/13) had developed antibodies to infliximab at 14 weeks and 54% (7/13) underwent colectomy at <24 weeks (median 11.5 weeks; IQR 6.6–17). Patients with a detectable trough serum infliximab level at week 6 (median 3.8 μg/ml; IQR 3.7–15.4) showed similar levels at week 14 (median 4.7 μg/ml; IQR 3.6–12.6).

Results of univariate analysis for factors that could potentially influence outcomes indicated that the baseline Mayo score, antibodies to infliximab and the trough serum concentration of infliximab were associated with clinical outcomes (table 2). Concurrent immunosuppression did not influence rates of clinical remission or colectomy. Multivariable logistic regression analysis showed a detectable trough serum concentration of infliximab to be a significant positive predictor for clinical remission (odds ratio (OR) 12.5; 95% CI 4.6 to 33.9; \( p < 0.001 \)) and endoscopic improvement (OR 7.3; 95% CI 2.9 to 18.4; \( p < 0.001 \)). Remission was also associated with a baseline Mayo score <10 (OR 3.1; 95% CI 1.1 to 9.1; \( p = 0.041 \)) and lack of prednisone dependence ≥1 year prior to infliximab (OR 5.1; 95% CI 1.3 to 20.2; \( p = 0.019 \)). Conversely, an undetectable
trough serum infliximab concentration was a significant positive predictor for colectomy (OR 9.3; 95% CI 2.9 to 29.9; p = 0.001). A baseline Mayo score ≥10 was also associated with an increased risk for colectomy (OR 3.3; 95% CI 1.2 to 9.1; p = 0.018).

**DISCUSSION**

Although infliximab is now a mainstay treatment for refractory Crohn’s disease, results from clinical trials of infliximab for acute UC have been variable. Thus, identifying factors that maximise the clinical benefit of infliximab for acute UC is an important therapeutic goal. The present study shows that clinical outcome for corticosteroid-refractory patients with UC treated with infliximab is strongly related to the trough serum concentration of infliximab. Clinical remission and endoscopic improvement were similar for antibody-positive and antibody-negative patients, two groups characterised by undetectable trough serum infliximab, and were significantly lower than for inconclusive patients, the group with detectable serum concentrations of drug. Moreover, an undetectable trough level of infliximab was a strong predictor for need for colectomy, whether or not antibodies were present. Together, these findings indicate an important relationship between the trough serum concentration of infliximab and clinical benefit for acute UC patients. Because undetectable infliximab levels occur independently of the presence of antibodies against infliximab, in clinical practice the trough serum infliximab concentration may provide a more useful guide for optimising clinical outcome. In this context, a positive antibody result would be considered a surrogate marker for the absence of drug.

After induction infliximab, our clinical remission rate of 32% at week 10 accords with the mean remission of 40% reported in a summary analysis of UC–infliximab trial studies, indicating that infliximab is moderately effective for induction treatment of corticosteroid-refractory moderately severe active UC. Clinical impact also requires long-term corticosteroid-free remission, and outcome data for maintenance infliximab treatment in UC are more limited. With scheduled 8 weekly infliximab, the ACT I trial reported comparable colectomy rates of 29% at 90 days and 42% at 1 year. A less favourable outcome was also observed in more severe patients, classified according to the Mayo activity index. These findings are consistent with reports evaluating corticosteroids and ciclosporin in acute UC, indicating disease severity impacts on the need for colectomy, regardless of the treatment employed.

The most striking finding was the difference in rates of remission and colectomy between patients with and without detectable trough serum concentrations of infliximab. A detectable trough serum infliximab was found to be the strongest predictor for remission, an association independent of disease activity. Noteworthy was the finding that two-thirds of patients achieving remission required a shortened infusion interval and/or dose escalation to 10 mg/kg infliximab. Although effective in only a minority of patients, both strategies increase trough serum infliximab and could account for the higher rate of remission than reported in the ACT 1 trial. The association between optimal clinical benefit and detectable trough infliximab levels is not without precedent. A similar relationship has been shown in psoriasis, rheumatoid arthritis and Crohn’s disease.

Conversely, the most significant predictor for colectomy was an undetectable serum infliximab, which carried a ninefold increased risk of surgery. This association was often an early event at <6 weeks during induction treatment. In the Jarnerot study trough serum infliximab levels were not reported, but given the similar rates of colectomy, the composite findings suggest single or three-dose induction of 5 mg/kg infliximab may not be the optimal strategy for avoiding colectomy in all patients with acute UC, notably those with a Mayo score ≥10. Whether an induction regimen incorporating a higher infliximab dose and shorter interval predicated on sustained trough serum concentrations of infliximab reduces the requirement for colectomy warrants study.

Notwithstanding scheduled treatment, 41% of our patients developed antibodies to infliximab, a value almost twofold higher than studies in Crohn’s disease and the ACT trials. The higher rate of antibody formation related, in part, to the prevailing concentration of infliximab, with an undetectable serum infliximab preceding antibody formation. This finding

### Table 2. Results of univariate analysis for predictors of clinical remission and colectomy

<table>
<thead>
<tr>
<th></th>
<th>Clinical remission</th>
<th>Colectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) p Value</td>
<td>OR (95% CI) p Value</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.74 (0.34 to 1.59) 0.57</td>
<td>0.81 (0.39 to 1.72) 0.73</td>
</tr>
<tr>
<td>Age</td>
<td>1.62 (0.75 to 3.52) 0.29</td>
<td>0.47 (0.22 to 1.02) 0.85</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>1.23 (0.49 to 3.16) 0.85</td>
<td>1.56 (0.61 to 3.97) 0.49</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.99 (0.41 to 2.42) 0.83</td>
<td>0.58 (0.25 to 1.37) 0.31</td>
</tr>
<tr>
<td>Baseline Mayo score</td>
<td>0.36 (0.15 to 0.83)</td>
<td>0.028 3.42 (1.56 to 7.51) 0.004</td>
</tr>
<tr>
<td>Prednisone ≥1 year preinfliximab</td>
<td>0.40 (0.14 to 1.17) 0.45</td>
<td>1.68 (0.69 to 4.15) 0.38</td>
</tr>
<tr>
<td>Concurrent immunosuppression</td>
<td>1.16 (0.47 to 2.88) 0.92</td>
<td>1.13 (0.46 to 2.75) 0.96</td>
</tr>
<tr>
<td>Baseline CRP &gt;5 mg/l</td>
<td>0.60 (0.21 to 1.69) 0.48</td>
<td>1.94 (0.65 to 5.81) 0.35</td>
</tr>
<tr>
<td>pANCA positive</td>
<td>0.89 (0.36 to 2.16) 0.79</td>
<td>0.58 (0.25 to 1.33) 0.28</td>
</tr>
<tr>
<td>Antibodies to infliximab</td>
<td>0.15 (0.06 to 0.40)</td>
<td>&lt;0.001 2.71 (1.22 to 6.01) 0.023</td>
</tr>
<tr>
<td>Detectable trough serum infliximab</td>
<td>12.0 (4.76 to 30.26)</td>
<td>&lt;0.001 0.13 (0.05 to 0.35)</td>
</tr>
</tbody>
</table>

Values in bold are statistically significant with a p value <0.05. CRP, C-reactive protein; pANCA, perinuclear antineutrophil cytoplasmic antibody.
Inflammatory bowel disease confirms observations in rheumatoid arthritis indicating that a low or absent trough serum infliximab is a precursor for the development of antibodies to infliximab. Our results also support findings in Crohn’s disease where a serum infliximab of <4 μg/ml measured 4 weeks after the first infusion has a positive predictive value of 81% for antibody formation later in the course of treatment.

The high proportion of patients with acute UC with absent trough levels of infliximab was unexpected and contrasts with our study in Crohn’s disease. The factors predisposing to this finding are uncertain, but a plausible explanation relates to more rapid clearance of infliximab. Although pharmacokinetic studies indicate that infliximab clearance is similar in rheumatoid arthritis, ankylosing spondylitis and Crohn’s disease, studies specific to UC have not been reported. In ankylosing spondylitis, clearance is not altered by disease activity, but in our study the proportion of patients with detectable infliximab tended to be lower for patients with more severe disease activity. It remains possible that disease-specific factors promote early formation of immune complexes in infliximab-treated patients with acute UC and impact on clinical outcome by reducing drug levels.

Although our analysis included steady-state single sampling, this approach provides valid pharmacokinetic parameter estimates. As reported previously for patients treated with maintenance infliximab, we found considerable interindividual variation in trough serum concentrations of infliximab, but, within patients, serum infliximab levels and antibody status remained relatively constant over time with infusions at regular scheduled intervals.

Clinical outcomes were independent of concurrent treatment with azathioprine. The ACT trials also pointed to a lack of additional benefit for patients receiving immunomodulators with infliximab. For immunomodulatory-naïve patients, uncontrolled observations indicated that the outcome at 12 months after a single induction dose of infliximab followed by maintenance azathioprine alone was similar to the outcome with maintenance infliximab in the ACT trials. Whether maintenance infliximab is a prerequisite for long-term remission is under prospective study in a trial of azathioprine-naïve, infliximab-responsive patients with UC to evaluate azathioprine alone, infliximab alone and the combination.

In conclusion, infliximab is beneficial and safe for patients with acute UC, particularly those with moderately severe steroid-refractory disease. The presence of detectable trough serum infliximab predicts clinical remission, whereas patients with undetectable infliximab are more likely to require colectomy. Factors in addition to antibody formation, probably pharmacokinetic, modulate serum concentrations of infliximab and impact on clinical benefit. Thus, the trough serum infliximab level appears to be a more useful predictor of clinical outcome than the presence of antibodies to infliximab, as it also takes into account the variable elimination of infliximab from the circulation. Mechanisms underlying the high proportion of UC patients with undetectable serum trough infliximab remain an area for further investigation, but the finding does suggest that evaluation of higher induction dosing at shorter infusion intervals, particularly for severe UC, may be warranted.

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