Positive relationship between infliximab and adalimumab trough levels at completion of induction therapy with clinical response rates, at a tertiary referral center

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Abstract
Background and Aim: Anti-tumor necrosis factor alpha (TNFα) therapies have improved outcomes for patients with inflammatory bowel disease. The aim of this study was to explore the relationship between infliximab (IFX) and adalimumab (ADL) trough and antibody levels with clinical response rates at the end of induction.

Methods: This was a prospective, single-center study. Patients were recruited from July 2015 to August 2016. Inclusion criteria were all inflammatory bowel disease patients older than 17 years who started treatment with IFX or ADL. Baseline clinical disease activity indexes were performed. Clinical response was defined as HBI ≤3 or partial Mayo score ≤4% or <30% reduction from baseline. Anti-TNFα trough and antibody levels were measured using standard ELISA techniques.

Results: Thirty-five patients were recruited, of whom 23 had Crohn’s disease and 12 had ulcerative colitis. Eighteen were treated with ADL and 17 with IFX. The mean age of the cohort was 40.3 years, 62.9% were females, 34.3% were on concomitant thiopurines, and 25.7% had prior anti-TNFα exposure. Overall response rate was 51.4%, 33.3% for ADL and 70.6% for IFX. Mean trough levels were 12.5 μg/mL for IFX and 4.4 μg/mL for ADL. There was a clear link between higher anti-TNFα trough levels and the end of induction with clinical response rates. For IFX, mean trough level was 16.4 μg/mL for responders versus 5.3 μg/mL for non-responders (P = 0.026). Area under the curve for association of IFX level at induction with clinical response was 0.864 (P = 0.0001). Similar link was present between higher ADL levels with clinical response, although not statistically significant.

Conclusion: Higher trough levels at the end of induction are associated with improved response. Ongoing work will define optimal targets at this key timeframe.

Introduction
Anti-tumor necrosis factor alpha (TNFα) therapies have significantly improved outcomes for patients with inflammatory bowel disease (IBD). They have long-standing proven efficacy in inducing and maintaining remission in IBD.1,2 However, for some patients response can be suboptimal, and primary loss of response (LOR) at the end of induction phase of anti-TNFα therapy can have significant implications for patients. At present, no consensus has been reached with regard to a definition of primary non-response to anti-TNFα therapy in IBD. It may be recognized as a failure to reach previously described decreases in clinical scores such as partial Mayo, HBI, or Crohn’s Disease Activity Index (CDAI) following completion of induction therapy.3

A number of different factors have been identified in contributing to primary LOR. These include disease characteristics such as phenotype, location, and severity. For example, there is evidence that fibrostenotic ileal Crohn’s disease (CD) is likely to not respond to anti-TNFα therapy and may be better managed surgically.4 Anti-TNFα itself may be involved through the impact of anti-TNFα drug pharmacokinetics, pharmacodynamics, and immunogenicity. There is evidence that immunogenicity, that is the formation of antibodies against anti-TNFα, can lead to primary LOR in a number of cases. Antibody formation against anti-TNFα can lead to reduced trough levels of anti-TNFα, which can lead to increased disease activity.5 In addition, there is evidence particularly for acute severe ulcerative colitis (UC) that the inflamed, ulcerated gut can act as a sink for anti-TNFα, with greater loss of anti-TNFα in stool and subsequent suboptimal response.6,7

Therapeutic drug monitoring (TDM) involves the measurement of an individual’s anti-TNFα trough and antibody levels.8–9 This can facilitate exploring an immune basis behind an individual’s primary LOR. It also offers the opportunity of...
adjusting a patient’s anti-TNFα dose at the end of induction therapy to help overcome primary LOR. This approach alongside the use of clinical endoscopic assessment as well as biomarkers, such as CRP and fecal calprotectin, can help improve response rates and outcomes for patients. The use of TDM has also been shown to be a more cost-effective strategy.10

Therapeutic anti-TNFα levels may also help to predict sustained response for IBD patients. A Czech study has shown that an infliximab (IFX) trough level of >3 μg/mL at the start of maintenance therapy was associated with sustained clinical response over a 2-year follow-up period.11 Similarly for adalimumab (ADL), Karmiris et al. have established in a study of CD patients on ADL that there is a defined trough level which they have shown to have a relationship with mucosal healing and therefore may be used to predict clinical response.12

TDM may help to overcome LOR in a number of ways. For example, individuals found to have low trough levels can have doses increased to increase the possibility of clinical response, or in patients with antibody formation and low trough levels, immunomodulators, like azathioprine, may be added to reduce antibody formation and improve trough levels. A recent study has shown that addition of azathioprine can help patients treated with ADL overcome LOR, by reducing antibody formation and improving drug trough levels.13

The aims of this study were therefore to explore the relationship between IFX and ADL trough and antibody levels with clinical and biochemical response rates at the end of induction therapy and 1-year follow up; to identify if TDM may be a useful predictor of primary non-response for both IFX and ADL; and finally to establish if dose-intensifying anti-TNFα based on clinical, endoscopic, and biochemical evaluations, and the use of TDM may help to regain clinical response at 1-year follow up.

Methods

Study was approved at the Tallaght Hospital/St James’s Hospital Joint Research Ethics Committee in July 2015, and informed consent was obtained from patients. This was a prospective, single-center study performed at Tallaght Hospital, Dublin. Patients were recruited from the gastroenterology department at our center from July 2015 to August 2016. Inclusion criteria were all IBD patients older than 17 years who had started treatment with either IFX or ADL during the study period. Baseline clinical disease activity indexes were performed (Harvey–Bradshaw index for CD and partial Mayo scores for UC). Clinical response was defined as a HBI of ≤3 or a partial Mayo score ≤4 or a reduction in clinical score of >30% from baseline.

CRP and serum albumin levels were recorded prior to their first maintenance infusion or subcutaneous injection. Standard induction regimens were used for IFX (5 mg/kg at weeks 0, 2, and 6) and ADL (160, 80, and 40 mg every other week). Patients were reviewed at the end of induction therapy. A decision was made to either continue with patient’s anti-TNFα therapy, consider dose escalation, or switch to alternative agents where appropriate. Overall clinical response was reviewed at the end of 1 year of anti-TNFα therapy. Clinical activity and biochemical markers were recalculated. Where possible, repeat endoscopy was performed.

Anti-TNFα trough and antibodies were measured at the end of induction therapy between weeks 10 and 12 as follows: Drug levels were assayed using a protocol adapted from Ungar et al.14 Briefly, ELISA plates (Thermo Scientific NUNC, Basingstoke, UK) were coated with 500 ng/mL recombinant human TNFα (Peprotech, London, UK) overnight at room temperature. Following blocking and washing steps, 100 μL of serum (diluted 1:100) was added to each well of the ELISA plates for 90 min. After washing, horse radish peroxidase (HRP)-conjugated goat anti-human IgG Fc fragment antibody (MP Biomedicals, Illkirch Cedex, France) was added at a concentration of 0.62 μg/mL for 60 min and subsequently reacted with tetramethylbenzidine substrate (Thermo Scientific NUNC). Following addition of the stop solution (2 N H2SO4), absorbance was read at 450 nm on an EL-800 plate reader (Biotek, Bad Friedrichshall, Germany). The drug concentration cut-off level was calculated using the average concentration obtained from unexposed controls plus 3 standard deviations.15

Anti-drug antibody levels were assayed using a protocol adapted from Ungar et al.14 ELISA plates (Thermo Scientific NUNC) were coated overnight with 500 ng/mL TNFα (Peprotech) as outlined above. Following blocking and washing, 100 μL of drug (0.1 mg/mL IFX or ADL) was added to the plates for 90 min followed by 100 μL of diluted serum (1:10 dilution) for 90 min. After washing, goat anti-human λ chain HRP-conjugated antibody (AbD Serotec, Oxford, UK) was added at a dilution of 2.5 × 104 for 60 min, which subsequently reacted with tetramethylbenzidine substrate and the reaction was stopped using 2 N H2SO4. Absorbance at 450 nm was determined on an EL-800 plate reader. Anti-drug antibody concentrations were determined by calibration to a standard curve generated using HRP-labeled goat anti-human IgG F(ab’2) two-fragment antibody (MP Biomedicals) at concentrations from 0 to 600 ng/mL. The anti-drug antibody concentration cut-off was calculated using the average concentration obtained from unexposed controls plus 3 standard deviations.16

Continuous variables were expressed as the median and standard deviation and categorical variables as number and percentage. Mann–Whitney test was used to compare continuous variables, and categorical variables were analyzed by Fisher’s exact test. A two-tailed P < 0.05 was considered statistically significant. A receiver-operated characteristic analysis was performed for evaluation of the accuracy of prediction of clinical response by IFX and ADL levels. Statistical analysis was performed using MedCalc Statistical Software version 17.4 (MedCalc Software, Ostend, Belgium).

Results

Baseline patient clinical characteristics are shown in Table 1. Of the 35 patients who were recruited, 23 had CD and 12 had UC. Eighteen patients were treated with ADL and 17 with IFX. The mean age of the cohort was 40.3 years, 22 (62.8%) were females, 12 patients (34.3%) were on concomitant immunomodulators, and 9 (25.7%) had prior anti-TNFα exposure. Of these, six (66.7%) were switched due to LOR and three (33.3%) due to side effects. These patients were switched to alternative agents on commencement of anti-TNFα therapy as part of this study. Overall clinical, endoscopic, and biochemical activities for the cohort at baseline included: HBI 8.9, partial Mayo 6.8, SES-CD...
There were no significant differences between patients treated with IFX and ADL in terms of age at onset of disease and disease location. However, there was a trend toward more patients treated with ADL, having underlying penetrating or perianal fistulating CD. In addition, patients treated with ADL clinically had more active disease at entry, mean HBI: 11.5, compared with 7.1 for IFX (P = 0.03, 95% confidence interval [CI]: 0.36–7.68). In addition, patients treated with IFX were more likely to have been previously treated with prior anti-TNFα, (7/17 patients, 41.7%) compared with ADL (2/18 patients, 11.1%) (P = 0.04, 95% CI: 0.01–0.59, odds ratio [OR]: 0.19). Overall response rate for our cohort was 51.4% (Table 2).

There was a statistically greater response rate in patients treated with IFX (70.6%) compared with those treated with ADL (33.3%) (P = 0.03, 95% CI: 0.04–0.70, OR: 0.16). In addition, for patients with UC treated with ADL, there was evidence of reduced clinical response (5/12 [41.7%] had primary non-response to ADL). Overall trough levels were 12.5 μg/mL for IFX (interquartile range [IQR]: 4.9–19.2) and 4.4 μg/mL (0.2–7.3) for ADL (P = 0.005, 95% CI: 2.67–13.58). The majority of patients (71.4%) had therapeutic trough levels >1 μg/mL.

There was a clear link between higher anti-TNFα trough levels at the end of induction and clinical response rates (Fig. 1). For IFX, mean trough level in responders was 16.4 μg/mL (IQR: 8.4–22.7) versus 5.3 μg/mL (0.5–8.8) for non-responders (P = 0.026, 95% CI: 1.50–20.7). Similarly, there was a link between higher ADL levels and clinical response, although not statistically significant. For ADL, mean trough level in responders was 6.6 μg/mL (IQR: 4.9–8.7) versus 3.0 μg/mL for non-responders (IQR: 0.1–2.7) (P = 0.135, 95% CI: 1.24–8.43).

The area under the curve for association of IFX level at the end of induction with clinical response was 0.864 (P = 0.0001). In addition, a trough level of 4.8 μg/mL predicted clinical response at the end of induction, with a sensitivity of 90.91% and a specificity of 67% (Fig. 2). Similarly, the area under the curve for association of ADL level at the end of induction with clinical response was 0.804 (P = 0.0001).
induction with clinical response was 0.766 ($P = 0.0377$) (Fig. 3). Furthermore, a trough level of 3.5 μg/mL helped to predict clinical response at the end of induction, with a sensitivity of 85.7% and a specificity of 81.8%.

There was clear correlation between anti-TNFα trough levels, with both clinical and biochemical responses. As mentioned for the group of responders who had higher anti-TNFα trough levels in comparison to non-responders, there was a significant improvement in clinical assessment tools. For responders, HBI improved from 9.7 to 3.4 in comparison to an actual increase in HBI for non-responders ($P = 0.004, 95\%\ CI: 6.31\text{ to }-2.19$). There were similar improvements in partial Mayo scores for the group who responded; again, this cohort had higher anti-TNFα trough levels.

With regard to biochemical markers, there was a significant improvement in mean CRP in the responders compared with non-responders. Mean CRP for the responder group was 20.5 mg/L pre-induction and 6.4 mg/L post-induction ($P = 0.0083, 95\%\ CI: 3.891\text{ to }-24.443$). There was no statistical change in CRP rates in non-responders (Fig. 4). Furthermore, week 14 CRP of <5 mg/L

### Table 2  Outcomes for anti-TNFα responders and non-responders

|                | Responders | Non-responders | Total | $P$-value | OR (95\% CI) |
|----------------|------------|----------------|-------|-----------|-------------|
| **Cohort**     | 18 (51.4\%)| 17 (48.6\%)    | 35    |           |             |
| **IFX (n)**    | 12 (70.6\%)| 5 (29.4\%)     | 17    | 0.015     | 0.16 (0.04\text{ to }-0.70) |
| **CD**         | 8 (66.7\%) | 2 (40\%)       | 10    | 0.005     |             |
| **UC**         | 4 (33.3\%) | 3 (60\%)       | 7     | 0.62      | 0.33 (0.03\text{ to }-2.87) |
| **ADL (n)**    | 6 (33.3\%) | 12 (66.7\%)    | 18    | 0.04      | 4.8 (1.14\text{ to }-20.1) |
| **CD**         | 5 (83.3\%) | 7 (58.3\%)     | 12    | 0.43      |             |
| **UC**         | 1 (16.7\%) | 5 (41.7\%)     | 6     | 0.017     | 3.57 (0.3\text{ to }-40.75) |

#### Clinical scores

- Mean HBI pre-induction: 9.7 vs. 7.4, $P = 0.25$
- Mean HBI post-induction: 3.4 vs. 7.6, $P = 0.004$
- Mean partial Mayo pre-induction: 6 vs. 6.57, $P = 0.79$
- Mean partial Mayo post-induction: 3 vs. 6.57, $P = 0.03$
- Mean CRP pre-induction (mg/L): 20.5 vs. 17.6, $P = 0.0083$
- Mean CRP post-induction (mg/L): 6.4 vs. 12.8, $P = 0.39$
- Mean albumin pre-induction (g/L): 39.5 vs. 41.8, $P = 0.58$
- Mean albumin post-induction (g/L): 38.4 vs. 41.6, $P = 0.90$

- CRP <5 mg/L post-induction (n): 15 vs. 8, $P = 0.02$
- Mean anti-TNFα trough level (μg/mL)
  - IFX: 16.4 vs. 5.3, $P = 0.026$
  - ADL: 6.9 vs. 3.0, $P = 0.138$
- Antibody level (n): 3 (16.6\%) vs. 3 (17.6\%), $P = 0.94$

ADL, adalimumab; CD, Crohn’s disease; CI, confidence interval; CRP, C-reactant protein; HBI, Harvey-Bradshaw Index; IFX, infliximab; OR, odds ratio; TNFα, tumor necrosis factor alpha; UC, ulcerative colitis.
has been shown to be associated with clinical response. For our cohort, 15 of 18 (83.3%) responders achieved this target versus 8 of 17 (47.1%) non-responders (P = 0.01, 95% CI: 0.08–0.70, OR: 0.17).

Antibody formation occurred in six patients (17.1%) overall. Antibody development was similar for IFX (16.6%) and ADL (17.6%), with three patients each with detectable antibodies after induction.

Depending on the overall clinical picture, biochemical markers, recent endoscopic assessment, as well as the information provided by TDM, patient’s management was reviewed at the end of induction therapy and tailored accordingly. The therapeutic strategy chosen for cohort was: 11 of 35 (31.4%) patients required no change in treatment, 16 of 35 (45.7%) patients required increased anti-TNFα dose or decreased infusion interval, 4 of 35 (11.4%) patients switched to another anti-TNFα drug, and 2 of 35 (5.7%) patients switched to non-anti-TNFαr (ustekinumab) (Table 3). It was seen that 11.4% of patients required surgical intervention after being assessed for secondary LOR to anti-TNFα therapy, and 17.1% had to stop anti-TNFα therapy due to side effects.

At 1 year, 25/35 (71.4%) of the cohort were well, 76.5% of IFX patients, and 66.7% of ADL patients. Analyzing the results, patients who were well at the end of the 1-year follow up had marked reduction in clinical, endoscopic and biochemical scores compared with non-responders. Mean HBI improved from 9.2 to 2.3 compared with an increase from 7.6 to 10 for non-responders (P = 0.0001, 95% CI: −9.7 to 5.7). Similarly, for endoscopic scores, SES-CD improved from 10.7 to 2.6 at 12 months for responders compared with an increase from 12.4 to 18.2 for non-responders (P = 0.0001, 95% CI: −20.5 to −10.6). Biochemical markers also illustrated the improved outcomes for responders with a reduction in mean CRP from 20.2 to 6.7 mg/L compared with an increase from 14.6 to 21.6 mg/L for non-responders (P = 0.03, 95% CI: −28.4 to −1.3). In addition, there was a difference in mean ADL trough levels at induction in responders (5.3 µg/mL) compared with non-responders (0.95 µg/mL) (P = 0.0048, 95% CI: 0.12–9.1).

### Discussion

Primary LOR to anti-TNFα therapy has significant implications for patient outcomes. Our study confirms the impact this has on patients with IBD. Our study showed a clinical response rate of 51.4%, with a significant difference in response between patients treated with ADL and IFX. A larger proportion of patients in the ADL non-responder group had UC compared with the responder group (41.7% vs 16.7%, P = 0.02).

Our study confirms the role of TDM in helping to predict clinical response. IFX patients who responded at the end of induction therapy had improved trough levels compared with non-responders. In addition, there was a trend toward an association between ADL trough levels and clinical response. These findings are supported from other similar studies, suggesting that aiming for therapeutic trough levels is associated with overall better response rates and clinical outcomes. For example, Kobayashi et al. have shown that week 2 trough level was significantly associated with 14-week clinical remission. Furthermore, it has been established that subtherapeutic anti-TNFα levels and/or anti-TNFα antibody formation helps to predict primary non-response anti-TNFα therapy. Post hoc analysis of the Karmiris et al.’s trial has shown that in a cohort of Crohn’s patients treated with ADL, week 4 trough levels of <5 µg/mL are

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**Table 3** Therapeutic strategy for each group

| Therapy | Infliximab | Adalimumab | Total |
|---------|------------|------------|-------|
| No change | 17 (45.6%) | 18 (51.4%) | 35 |
| Dose escalate | 10 (58.8%) | 4 (22.2%) | 14 (40%) |
| Regain response | 6 (35.3%) | 10 (55.6%) | 16 (45.7%) |
| Switch | 5 (83.3%) | 6 (60%) | 11 (68.8%) |
| Surgery | 1 (5.9%) | 2 (22.2%) | 3 (8.6%) |

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**Figure 3** Adalimumab levels as a predictor of clinical response at the end of induction (area under the curve = 0.766, P = 0.0377).

**Figure 4** Change in CRP for anti-tumor necrosis factor alpha responders and non-responders (CRP week 0; CRP week 14).
associated with an increased future risk of antibodies to ADL formation (hazard ratio: 25.12, 95% CI: 5.64–111.91, P = 0.0002). These patients were found to have higher CRP levels and greater risk of future gut inflammation.18

There is also evidence available to support the use of TDM to assess secondary LOR. A French study has shown that TDM of IFX helps strongly to predict the likelihood of mucosal healing after IFX intensification for both patients with UC and CD.19 In addition, clinically guided dose adjustment of anti-TNFα offers the opportunity of improving response rates and outcomes. Going forward, there is ongoing work at defining optimal trough levels and targets when using anti-TNFα therapy. For example, Ungar et al. have shown a significant association between serum levels of anti-TNFα and the level of mucosal healing in a retrospective study. They propose that serum levels of 6–10 μg/mL for IFX and 8–12 μg/mL for ADL are required to achieve mucosal healing in 80–90% of patients with IBD.20

Our study also supports the idea that biochemical markers, such as CRP, anti-TNFα trough and antibodies levels can help to guide and predict treatment response. For our cohort, mean trough levels were considerably higher in non-responders compared with responders for both CD and UC. In addition, a higher percentage of responders achieved a week 14 CRP of <5 mg/L.

TDM traditionally allows for doses to be adjusted or treatment to be tailored such as the introduction of immunomodulators, to reduce antibody formation and thereby improve anti-TNFα trough levels. It may also allow for more cost-effective use of anti-TNFα therapy helping to recognize situations where it is best to consider switching within anti-TNFα class or to consider alternative agents. The accepted advantage of TDM is that it helps to explore an immune basis behind primary LOR, taking into account underlying anti-TNFα pharmacokinetics. However, only 17% of our cohort had significant drug antibodies and antibody formation was not predictive of outcome. While the impact of antibody formation was less clear in our study, there was a definite association between trough levels and clinical and biochemical outcomes.

Our receiver-operated characteristic analysis suggests that target IFX and ADL trough levels of 4.8 and 3.5 μg/mL could help clinicians to predict response and offer a valid target for tailored therapy based on TDM after induction. Our study also adds further weight to the growing awareness that target/optimal trough levels rather than avoidance of low or suboptimal levels are likely to have a significant impact on clinical outcomes.

Our study confirms the role for dose intensification of anti-TNFα therapy in patients who have suboptimal response at the end of induction, with 68.9% of patients responding to this strategy. This is particularly true for ADL, where overall response improved from 33.3% at the end of induction to 66.6% at 1-year follow up. For ADL, dose intensifying can help to regain clinical response, avoiding the need to switch agents. A meta-analysis from 2011 has shown that the mean percentage of patients who required dose intensification among primary responders to ADL was 37% and the annual risk was 24.8% per patient-year.16 Thus, the combination of clinical, biochemical, and endoscopic evaluations and the increasing important role of TDM may help to address the difficulties of LOR to anti-TNFα, develop strategies to induce and maintain long-lasting clinical remission, and achieve mucosal healing.

Further larger randomized clinical trials are required to confirm the findings mentioned above.

Conclusion

In summary, this study suggests a role for TDM in the management of patients with IBD. We have demonstrated a clear link between clinical and biochemical response and anti-TNFα trough levels. There is now growing evidence that performing TDM during the induction period will identify patients at risk of LOR, and who would best benefit from dose intensification in a clinically guided fashion.

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References

1 Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn’s disease. Gastroenterology. 2005; 128: 862–9.
2 Feagan BG, Panaccione R, Sandborn WJ et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn’s disease: results from the CHARM study. Gastroenterology. 2008; 135: 1493–9.
3 Sprakes MB, Ford AC, Warren L, Greer D, Hamlan J. Efficacy, tolerability, and predictors of response to infliximab therapy for Crohn’s disease: a large single centre experience. J. Crohns Colitis. 2012; 6: 143–53.
4 Moran GW, Dubeau MF, Kaplan GG et al. Phenotypic features of Crohn’s disease associated with failure of medical treatment. Clin. Gastroenterol. Hepatol. 2014; 12: 434–42.e1.
5 Echarri A, Ferreiro R, Fraga-Iriso R et al. Sal264 drug trough levels and primary nonresponse to antiTNF therapy in moderate-severe Crohn disease. Results of the Optimiza study. Gastroenterology. 2014; 146: S247.
6 Yanur AJ, Jain A, Sussman DA et al. The association of tissue anti-TNF drug levels with serological and endoscopic disease activity in inflammatory bowel disease: the ATLAS study. Gut. 2016; 65: 249–55.
7 Brandse JF, van den Brink GR, Wildenberg ME et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology. 2015; 149: 350–5.e2.
8 Inaeda H, Takahashi K, Fujimoto T et al. Clinical utility of newly developed immunoassays for serum concentrations of adalimumab and anti-adalimumab antibodies in patients with Crohn’s disease. J. Gastroenterol. 2014; 49: 100–9.
9 Pappamichael K, Cheiletz AS. Therapeutic drug monitoring in IBD: the new standard-of-care for anti-TNF therapy. Am. J. Gastroenterol. 2017; 112: 673–6.
10 Steenholdt C, Brynskov J, Thomsen OØ et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn’s disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut. 2014; 63: 919–27.
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11 Bortlik M, Duricova D, Malickova K et al. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn’s disease. J. Crohns Colitis. 2013; 7: 736–43.
12 Karmiris K, Paintaud G, Noman M et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn’s disease. Gastroenterology. 2009; 137: 1628–40.
13 Ungar B, Kopylov U, Engel T et al. Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab. Aliment. Pharmacol. Ther. 2017; 45: 276–82.
14 Ungar B, Chowers Y, Yavzori M et al.; ABIRISK Consortium. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. Gut. 2014; 63: 1258–64.
15 Ben-Horin S, Yavzori M, Katz L et al. The immunogenic part of infliximab is the F(ab’)2, but measuring antibodies to the intact infliximab molecule is more clinically useful. Gut. 2011; 60: 41–8.
16 Billioud V, Sandborn WJ, Peyrin-Biroulet L. Loss of response and need for adalimumab dose intensification in Crohn’s disease: a systematic review. Am. J. Gastroenterol. 2011; 106: 674–84.
17 Kobayashi T, Suzuki Y, Motoya S et al. First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. J. Gastroenterol. 2016; 51: 241–51.
18 Baert F, Kondragunta V, Lockton S et al. Antibodies to adalimumab are associated with future inflammation in Crohn’s patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial. Gut. 2016; 65: 1126–31.
19 Paul S, Del Tedesco E, Marotte H et al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. Inflamm. Bowel Dis. 2013; 19: 2568–76.
20 Ungar B, Levy I, Yavne Y et al. Optimizing anti-TNFα therapy: serum levels of infliximab and adalimumab associate with mucosal healing in patients with inflammatory bowel diseases. Clin. Gastroenterol. Hepatol. 2016; 14: 550–7.e2.