Decrease in Serum Infliximab Level Precedes Loss of Clinical Response and Can Be Easily Detected by the Evaluation of C-Reactive Protein in Crohn’s Disease

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Background: Maintenance of remission is an important issue in Crohn’s disease (CD) treatment. We previously reported that the serum trough level of infliximab (IFX) correlated with the clinical response, and the removal of IFX level by shortening the infusion interval results in recovery of clinical response to an open-label prospective multicenter study. These findings strongly suggest that monitoring IFX level may be useful for maintaining remission. Here, we analyzed time points of decrease in IFX level and loss of response (LOR) using data from the study noted above. In addition, we analyzed useful biomarkers to detect decrease in IFX level, since IFX level is not suitable as a routine marker in daily practice.

Methods: IFX was administered at 5 mg/kg to CD patients at weeks 0, 2, and 6. Week 10 responders (n = 57) received IFX every 8 weeks thereafter. In those with LOR after week 14, the interval was switched to every 4 weeks. LOR was defined as a Crohn’s Disease Activity Index (CDAI) rise of 175 points, a CDAI score increase of 35%, or 70 points in comparison with the CDAI score that fulfilled the clinical response criteria for the first time. IFX level was measured by ELISA. Performance to detect IFX level 1 μg/mL was evaluated by receiver operating characteristic (ROC) curve analysis using data from patients who received the 8-week interval treatment (n = 31–37). Results: Among the 48 clinical responders at week 14, IFX levels of 15 were 1 μg/mL and only 2 patients (16.7%) met LOR criteria (3 who discontinued treatment were excluded). The number of patients with LOR gradually increased and 8 (66.7%) lost response by week 54. Meanwhile, 75% of patients in whom IFX levels were 1 μg/mL at week 14 maintained remission until week 54. ROC curve analysis revealed that C-reactive protein (CRP) showed better performance to detect IFX level <1 μg/mL than individual scores of CDAI (soft-liquid stools, abdominal pain, general well-being, hematocrit, percent below standard weight), albumin, prealbumin, transferrin, retinol binding protein, and interleukin-6. IFX levels were <1 μg/mL in 60-80% of patients with hematocrit, percent below standard weight, albumin, prealbumin, transferrin, retinol binding protein, and interleukin-6. However, CRP was a more sensitive marker to detect IFX level <1 μg/mL with a high positive predictive value (PPV) and negative predictive value (NPV). The area under the ROC curve (AUC) for CRP was 0.88 (95% CI: 0.83-0.92), while IFX levels were 1 μg/mL in more than 80% of patients with CRP <0.5 μg/mL (normal value). Conclusion: Decrease in IFX level was observed preceding LOR in CD patients receiving maintenance IFX. Decrease in IFX level could be monitored by the evaluation of CRP. Our findings suggest that CRP was an useful biomarker to predict clinical response LOR to long term IFX therapy.

Association of Serum Infliximab and Antibodies to Inflaximab to Long-Term Clinical Outcome in Acute Ulcerative Colitis


Background/Aims: Infliximab (IFX) induces clinical response and remission in ulcerative colitis (UC). Previous studies have shown that formation of antibodies to infliximab (ATI) is associated with a loss of clinical benefit and colectomy. However, solid phase ELISA ATI assay measurements are limited as they cannot detect ATI in the presence of circulating drug. We therefore evaluated the relationship between trough serum IFX and ATI to long-term clinical outcome in acute UC using a recently developed fluid phase assay that simultaneously detects ATI and drug. Methods: A cohort of 134 patients with steroid refractory acute UC treated with triple-dose IFX 5 mg/kg induction followed by scheduled maintenance therapy were included. Serum concentrations of IFX and ATI were measured by a fluid phase assay (Prometheus Laboratories, San Diego CA). Rates of steroid free clinical remission (Mayo score 0 and colectomy were assessed in relation to the presence or absence of detectable trough serum levels of IFX with or without ATI formation. Results: Of the 134 patients, 103 had pancolitis and 31 had disease to the splenic flexure. The median Mayo score was 9 (range: 6-12). After a median follow-up of 19.9 months (IQR: 7.6-47.4), the rate of steroid-free remission was 43.3% and 53% (39.6% vs. 64% vs. P=0.05) in patients with and without detectable steroid-free ATI. A detectable trough infliximab >2 μg/mL, without or with ATI, was associated with a higher rate of clinical steroid-free remission (69% vs. 69%, P<0.001), that was sustained over the follow-up period. For patients with a detectable trough serum infliximab and no ATI, only one developed lower grade ATI (13.0%) with detectable drug and no loss of response. A trough serum infliximab <2 μg/mL with or without ATI formation was associated with an increased risk for colectomy (6% vs. 13%, P<0.001). Conclusions: For patients with steroid refractory ulcerative colitis treated with infliximab, a detectable trough serum infliximab >2 μg/mL is associated with sustained remission and lower risk for colectomy. A threshold serum infliximab ≤2 μg/mL, irrespective of ATI status, is associated with a less favorable outcome.