Sa2044

Decrease in Serum Infliximab Level Precedes Loss of Clinical Response and Can Be Easily Detected by the Elevation 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 retrieval of IFX level by shortening the infusion interval resulted in recovery of clinical response in 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) score 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 8 week interval treatment (n = 31-57). 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, 75.9% of patients in whom IFX levels were 1 μg/mL at week 14 maintained response 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, transfferin, retinol binding protein, and interleukin-6. IFX levels were <1 μg/mL in 60-80% of patients with CRP >0.5 mg/dL, while IFX levels were 1 μg/mL in more than 80% of patients with CRP 0.5 mg/dL (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 elevation of CRP. Our findings suggest that CRP was an useful biomarker to predict clinical response or LOR to long term IFX therapy.

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Relationship Between Drug Serum Concentration and Clinical Activity in Patients With Crohn Disease Who Achieved Remission With Adalimumab - a Prospective Study

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Introduction: Serum levels of Adalimumab (ADA) and anti-ADA antibodies have been previously associated to loss of response. However, there is limited data regarding the influence of trough serum concentration and antibodies against ADA on clinical outcome in patients infliximab-naive who achieved remission with ADA. **Aim:** To evaluate the relationship between serum concentration of ADA and clinical activity in CD patients throughout a 2 year follow-up period. **Methods:** In this prospective study, 22 patients (13M/9F; mean age 41) with CD achieving remission and in maintenance treatment with ADA were included in a follow-up program. Patients have never been previously treated with infliximab. Blood samples were drawn at standardized time points just before injection of ADA. Trough serum concentration and antibodies against ADA were measured using an enzyme-linked immunosorbent assays (Matriks biotek). The lowest detectable level that can be distinguished from the zero standard was less than 10 ng/mL. During the visits, assessment of clinical activity was performed by means of the Harvey-Bradshaw Index score (HBI, remission <5, mild disease 5-7, moderate disease 8-16, severe disease > 16) and CRP blood level (normal if <5 mg/L). **Results:** Data on clinical and biological parameters measured are reported as mean (range) in the table below. Based on HBI score, 10/22 (45%) patients demonstrated sustained clinical remission until the end of follow-up. Out of the remaining 12 patients receiving maintenance therapy, 3 (14%) developed a mild disease, 6 (27%) a moderate disease and 3 (14%) a severe disease requiring therapeutic intervention. CRP levels paralleled with the HBI scores, since patients in remission had a mean CRP level lower than patients with mild, moderate and severe disease ($p<0.01$). Significantly higher ADA trough serum concentrations were measured throughout the follow-up period in patients in remission as compared with patients who developed a disease activity ($p<0.01$). Antibodies against ADA were present in 9% of the patients and did not affected ADA trough serum concentration. Four patients discontinued therapy due to loss of response and they had significantly lower ADA trough serum concentrations than patients who stayed on ADA (2.1 [0-3.9] vs. 6.7 [3.2-9.2]; $p<0.01$). **Conclusions:** Lower ADA trough serum concentrations are associated to loss of response and both clinical and biological relapse during a 2year follow-up period. ADA discontinuation was directly related to low ADA trough serum concentration. Presence of antibodies to ADA is a rare event and seems not to modify patients' outcome.
Patients with Crohn's Disease receiving maintenance therapy with Adalimumab classified by means of Harvey-Bradshaw Index

	Remission	Mild Disease	Moderate Disease	Severe Disease	
	n=10	n=3	n=6	n=3	
Parameters					*p Value (Anova)*
Harvey-Bradshaw Index, n	*4 (3-4)*	*6 (5-7)*	*9 (8-11)*	*17 (16-17)*	*<0,01*
ADA concentration, mcg/ml	*8,1 (6,7-9,2)*	*5,8 (5,2-6,1)*	*3,9 (3,2-4,7)*	*1 (0,1-2,6)*	*<0,01*
CRP, mg/L	*1 (0,-4)*	*3 (1.5,6)*	*10 (3,5-18,7)*	*18 (5,9-34,3)*	*<0,01*

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Infliximab-Mediated Modulation of Hepcidin Improves Iron Metabolism in Inflammatory Bowel Disease

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Background and aim Crohn's disease (CD) and ulcerative colitis (UC) are idiopathic inflammatory bowel diseases (IBD). Anaemia is a common feature of IBD, resulting from a combination of iron deficiency anaemia (IDA), secondary to chronic bleeding from gut mucosa together with nutrient malabsorption, and anaemia of chronic disease (ACD). ACD is characterized by macrophage iron retention induced by pro-inflammatory cytokines, such as TNF and IL-6. Hepcidin, an acute phase protein, is the master inducer of iron accumulation into the reticuloendothelial system, during ACD. Infliximab (IFX), a chimeric anti-TNF monoclonal antibody, is an effective therapeutic option in moderate to severe IBD, downregulating several pro-inflammatory mediators. Aim of the study is to evaluate if IFX therapy exerts direct effects on hepcidin production, leading to a restoration of normal iron homeostasis in IBD patients. **Methods** 42 sera were collected from 14 IBD patients (9 CD, 5 UC), before each IFX infusion, for the first 3 infusions of the therapeutic regimen. Pro-hepcidin, a dosable hepcidin precursor, was measured by means of a commercially available ELISA kit. Serum ferritin was determined by a solid-phase two-site chemiluminescent immunometric assay, instead transferrin and CRP levels were measured by a immunoturbidimetric and iron by a colorimetric assay. Statistical analysis was performed by means of paired Student's t test. **Results** Serum pro-hepcidin was significantly decreased between the 1st and the 3rd IFX infusion (140.9±20.5 vs. 95.9±9.5 ng/ml, $p<0.05$); consistently, CRP was reduced (2.06±2.26 vs. 0.49±0.52 mg/dl, $p<0.05$) and a trend towards ferritin decrease was detectable, although not significant (64.14±71.50 vs. 27.50±30.80 ng/ml, $p=0.06$); we also detected an increase in serum iron (36.71±11.98 vs. 48.14±19.51 g/dl, $p<0.05$) and total transferrin (202.57±43.11 vs. 252.29±39.90 mg/dl, $p<0.01$). Remarkably, a trend towards an increase of haemoglobin (11.51±0.29 vs. 12.04±0.32, $p=0.06$) was noted. **Conclusion** Anti-TNF therapy significantly improves iron metabolism and, subsequently, anaemia in IBD. This effect appears to be related to the modulation of the cytokine network, leading to a relevant decrease of hepcidin, a master regulator of ACD. As such, in IBD patients IFX seems to play a role in ameliorating ACD, during a 6 week treatment; however, in a long term treatment, IFX may also improve IDA, throughout the induction of mucosal healing.

Sa2047

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

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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 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 infliximab 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 three-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 patients (39.6%) had undergone colectomy (median time of 6.5 months (IQR: 2.3-13.4). For patients with evaluable serum samples (n=125), a detectable trough serum infliximab was present in 68 patients (54.4%), of whom 6 (8.8%) had detectable ATI. Amongst the 57 patients (45.6%) with undetectable serum IFX, 45 patients (78.9%) were ATI positive and 12 patients (21.1%) were ATI negative. A detectable trough infliximab > 2μg/ml, without or with ATI, was associated with a higher rate of clinical steroid free remission (69% vs. 16%; $P<0.001$), that was sustained over the follow-up period. For patients with a detectable trough serum infliximab and no ATI, only one developed lower titre ATI (< 10U/ml) with detectable drug and no loss of response. A trough serum infliximab < 2μg/ml with or without ATI formation was associated with an increased risk for colectomy (64% vs. 13%; $P<0.001$). **Conclusions:** For patients with steroid refractory ulcerative colitis treated with infliximab, a detectable trough serum infliximab > 2μg/ml is associated with sustained clinical remission and a lower risk for colectomy. A threshold serum infliximab ≤ 2μg/ml, irrespective of ATI status, is associated with a less favorable outcome.