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High C-reactive protein in Crohn's disease patients predicts nonresponse to infliximab treatment

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Abstract

Background: Infliximab (IFX) is effective in treating Crohn's disease (CD) and C-reactive protein (CRP) is a useful biomarker in assessing inflammatory activity.
Aim: Correlate CRP levels before beginning of IFX, at week 14 and CRP delta within the first year of IFX treatment.
Methods: Retrospective study of CD patients undergoing treatment with IFX. Primary nonresponse (PNR) was defined as no symptomatic improvement and CRP persistently elevated; sustained response (SR) as symptomatic improvement for at least 1 year without therapeutic adjustment; response after therapeutic adjustment (RTA) as analytic and clinical response but requiring IFX dose/frequency adjustment or association with another drug.
Results: Baseline CRP levels were higher in PNR compared with SR (26.2 mg/L vs 9.6 mg/L, p=0.015) and RTA (26.2 mg/L vs 7.6 mg/L, p=0.007). CRP levels greater than 15 mg/L at baseline predict PNR with 67% sensitivity and 65% specificity. Lower CRP levels at week 14 were more likely to predict SR relative to RTA (3.1 mg/L vs 7.6 mg/L p=0.019) and PNR (3.1 mg/L vs 9.1 mg/L; p=0.013). CRP levels greater than 4.6 mg/L at week 14 predict PNR with 67% sensitivity and 62% specificity. A higher CRP delta between beginning of treatment and week 14 is more likely to predict SR relative to RTA (5.2 mg/L vs 0.6 mg/L p=0.027).

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Conclusion: CRP levels at week 14 were associated with SR in patients treated with IFX, independently of baseline CRP serum levels. High inflammatory burden at beginning of IFX treatment was correlated with a worse response.

1. Introduction

Inflammatory bowel disease (IBD) is an idiopathic, chronic process of the bowel associated with decreased quality of life and increased morbidity.[1] It is believed to be the result of an imbalance between proinflammatory and anti-inflammatory mediators[2] and tumor necrosis factor (TNF)-α is now known to play a pivotal role in the onset and perpetuation of the inflammation. Infliximab (IFX) is a chimeric IgG 1 monoclonal antibody with high specificity and affinity to TNF-α.[3–8] Clinical benefit from IFX is reported in 60–70% of the patients in short and medium term,[9–13] however, secondary loss of response is intrinsic to the use of therapeutic antibodies and up to 30–40% of patients who initially respond to IFX, lose response within the first year.[11–13]

C-reactive protein (CRP), an acute phase reactant, is produced and released by hepatocytes in response to cytokine (interleukin-6, TNF-α and interleukin-1β) stimulation at the site of inflammation.[14] CRP plays an important role as a noninvasive inflammatory marker in patients with IBD, however, there is remarkable heterogeneity in the CRP response between Crohn's disease (CD) and ulcerative colitis (UC). Whereas CD is associated with a strong CRP response, UC has only a modest to absent CRP response.[14–19] Besides that, in CD, a significant number of patients present with low CRP levels despite clinically active disease. So far, no clear cut-off values have been determined as predictive of remission/nonresponse/relapse. Different studies suggest that lower baseline CRP levels can predict nonresponse, as it may correspond to absence of inflammation. Increased CRP levels in CD have been associated with relapse. Once a wide range of CRP values are observed, with significant overlap between different degrees of severity, the dynamics of CRP evolution and the comparison of the CRP value with previous values in a given patient, might be more important than a particular cut off value for CRP.[17,20–26]

Our aim is to correlate CRP levels before beginning of IFX, at week 14 and CRP delta between baseline and week 14 in patients that have primary nonresponse (PNR), sustained remission (SR) or response after therapeutic adjustment (RTA) within the first year of IFX treatment.

2. Material and methods

Retrospective study based on medical records from patients with CD undergoing treatment with IFX (followed at our institution) between January 2006 and February 2012. Diagnosis of CD was made by endoscopic, radiologic and histological criteria,[27] and indication for IFX treatment was judged by senior IBD gastroenterologists taking into consideration clinical, biological, and endoscopic findings.

Our study was performed with 148 CD patients and their serum CRP was evaluated. Serial blood samples were taken before each IFX infusion, and CRP was measured as part of standard follow-up by using an enzyme-linked immunosorbent assay (Olympus CRPLatex Calibrator Normal Set®). A CRP level below 3 mg/L was considered normal. In total, there were available 1776 serial CRP measurements, with a median of 12 per patient. Week 14 was the time point selected to evaluate if the induction therapy was successful once it corresponds to the end of the induction and the beginning of maintenance treatment. All clinical data and CRP values were collected from the patients' records and were related to clinical outcome, namely relapse of disease activity and the need for therapy adjustment. Harvey–Bradshaw index (HBI) was used to assess patients' symptoms, being assessed by the senior IBD gastroenterologist at each clinic visit; those who scored 4 or less were considered to be in clinical remission and those who scored more to have clinical activity. All patients were submitted to colonoscopy in the three months previous to beginning of IFX treatment, with all patients having endoscopic activity, with ulcers. Other causes that could mimic disease activity, including infections (clostridium difficile, cytomegalovirus, bacterial, mycobacterium tuberculosis) were ruled out. Standard imaging with abdominal ultrasound or computed tomography was performed, whenever there was a suspicion of abscesses, perforating disease with phlegmone or any other complication. None of our patients had any of those complications. A protocol is followed before IFX beginning and during therapy, with patients starting IFX only after discussion between senior IBD gastroenterologists responsible for the IBD outpatient clinic. In all our patients, IFX was started due to the severity of luminal disease and not due to perianal disease or for prevention of post-operative recurrence.

All patients received a 5 mg/kg IFX infusion at baseline and then received subsequent infusions of 5 mg/kg at weeks two, six and then every 8 weeks. In case of loss of clinical response, optimization of anti-TNF treatment was always considered as primary intention (dose escalation to 10 mg/Kg or shortening infusion interval to every 6 weeks were made if patients remained symptomatic) and was a decision of the patient's gastroenterologist. Neither IFX trough levels nor IFX antibodies were available. Therapy adjustments were considered clinically successful if symptoms disappeared (HBI score $\leq$ 4) and if IFX could be continued thereafter without further adjustments (increase dose, shorten interval or addition of immunomodulators). PNR was defined as absence of symptomatic improvement and CRP persistently high (despite therapeutic adjustments); SR as symptomatic improvement for at least 1 year without need for any dose or interval adjustment or any other changes in therapy; RTA as analytic and clinical response after IFX dose modification and/or association of another drug (steroids, immunomodulators);