BIOMARKERS CALPROTECTIN AND C-REACTIVE PROTEIN CUT-OFF VALUES PREDICT 48-WEEK RESPONSE TO INFLIXIMAB INDUCTION THERAPY

Per M Hellström and Hetzel Olenia Diaz Tartera, Gastroenterology & Hepatology, Dept of Medical Sciences, Uppsala University, Sweden

Background:
The neutrophil granulocyte-derived protein calprotectin in the feces (FC) is an inflammatory marker in Crohn's disease (CD) and ulcerative colitis (UC). We assessed the importance of the numerical decrease of FC with infliximab induction therapy with C-reactive protein (CRP) and clinical activity evaluated by Harvey-Bradshaw index (HBi) and partial Mayo score (pMS).

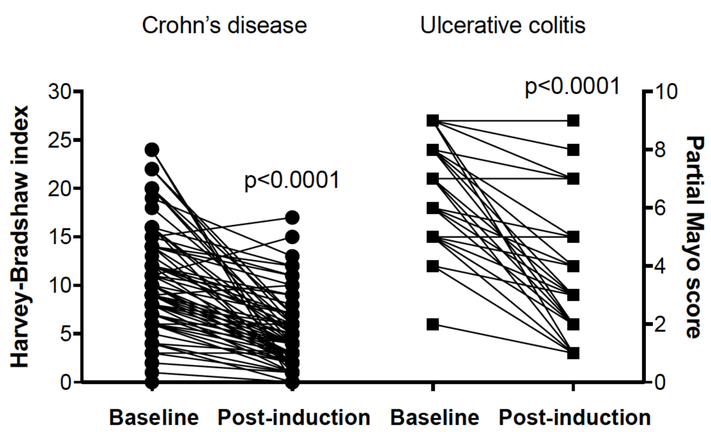
Aim: To assess the importance of the biochemical biomarkers FC and CRP at 12 weeks using bedside clinical activity evaluated by Harvey-Bradshaw index and partial Mayo scor in order to predict the outcome of infliximab induction therapy within the next 36 months for sustained treatment response as reduced by an incident in terms of 1) *surgery*, 2) *increased infliximab dosage* or 3) *shortened infliximab interval.*

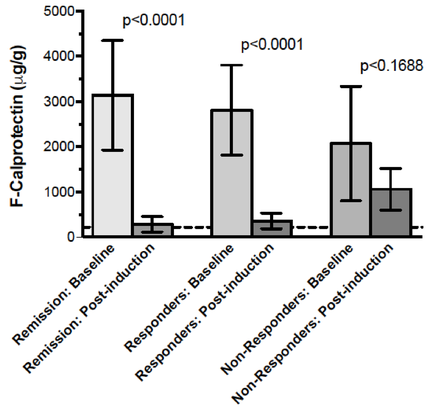
Methods: Of a total of 180 patients with IBD treated with infliximab, 72 with CD and 37 with UC considered as responders to treatment were studied over 48 weeks. Indices FC and CRP were evaluated on two occasions: at baseline before infliximab introduction and after 12 weeks. Responders were then followed another 36 weeks further to assess the FC values with incident outcome. Values are presented as median and interquartile range (IQR). Spearman nonparametric correlation test served for correlation analyses.
Sensitivity, specificity and likelihood ratio were analyzed using ROC (receiver operating characteristic) curve. Survival curves were analyzed with Kaplan-Meier analysis and log-rank test. $P<0.05$ was significant.

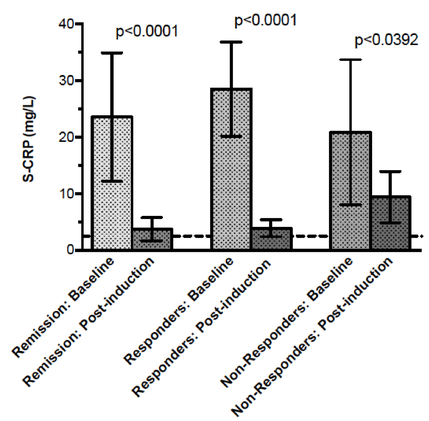
Results: After induction, 109 patients (61%) responded to therapy, 36 of which (59%) attained clinical remission ($p<0.0001$). Following induction therapy, indices of FC and CRP in responders declined from baseline levels (all $p<0.0001$), more markedly in those achieving clinical remission.

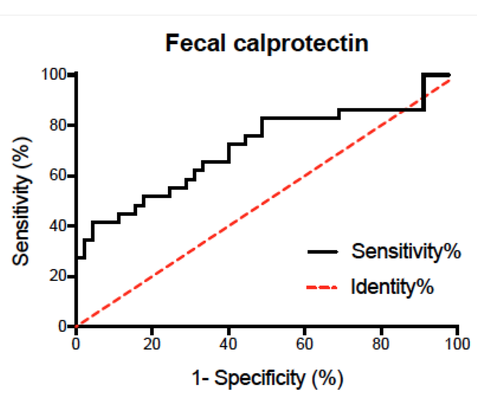
Clinical responders were followed 48 weeks for incidents (dosage increase, shortening of infusion interval, surgery) based on FC levels. The ROC optimal cut-off point was FC 221 µg/g (sens 90%, spec 71%, likelihood ratio 3.15) and AUC 0.88. Using FC 221 µg/g as cut-off, FC exceeding 221 µg/g after induction therapy was studied in conjunction with an incident within 48 weeks. In those with FC <221 µg/g, two out of 75 patients (3%) had an incident within 48 weeks of induction therapy, among those with FC >221 µg/g that number was 25 out of 34 (73%) within the same period. Clinical activity correlated with FC (Spearman r=0.62, p<0.001) as well as with CRP (Spearman r=0.60, p<0.001). CRP showed ROC not clearly discriminant from identity. Optimal cutoff was set at 2.0 mg/L (sens 54%, spec 60%, likelihood ratio 1.4) but significant only in UC.

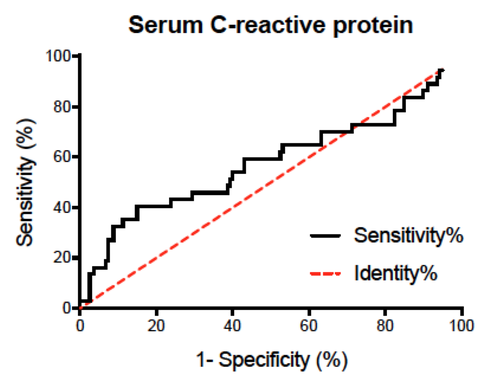
Parameter	Baseline	12 weeks (non-responders)	12 weeks (responders)	12 weeks (remission)
HBi	11 (6.5-16.5)	>6	-3	≤3
pMS	7.0 (5.5-8.5)	>5	-3	≤2
F-Calprotectin (µg/g)	2160 (1495-5507)	1425 (304-2171)	210 (70-358)**	207 (75-354)**
S-CRP (mg/L)	13 (6.5-35.5)	5.5 (3.5-27.5)	2.7 (1.0-4.0)**	2.0 (1.0-3.5)**

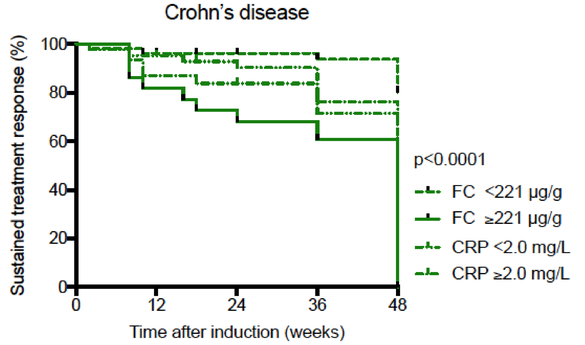


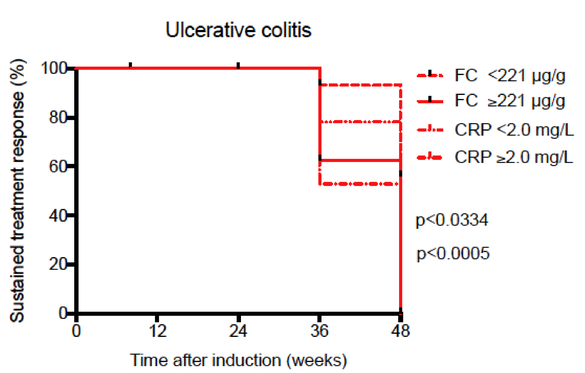












Conclusions:
Clinical indices (HBi, pMS) correlate well with FC and CRP levels during infliximab induction therapy. The indices, FC and CRP levels decreased significantly from baseline levels among patients responding to infliximab treatment. However, a FC level >220 µg/g after induction therapy is associated with a disease incident within the following 48 weeks in two-thirds of the cohort.