Abstract: The production of CRP occurs almost exclusively in the liver by the hepatocytes as part of the acute phase response upon stimulation by IL-6, TNF-α and IL-1-β originating at the site of inflammation. Its short half-life makes CRP a valuable marker to detect and follow up disease activity in Crohn’s disease (CD). In contrast, ulcerative colitis has only a modest to absent CRP response despite active inflammation, and the reason for this is unknown. In CD, serum levels of CRP correlate well with disease activity and with other markers of inflammation as the CDAI, serum amyloid, IL-6 and faecal calprotectin. CRP is a valuable marker for predicting the outcome of certain diseases as coronary heart disease and haematological malignancies. An increased CRP (>45 mg/L) in patients with IBD predicts with a high certainty the need for colectomy and this by reflecting severe ongoing and uncontrollable inflammation in the gut. Finally, trials with anti-TNF and anti-adhesion molecules have shown that a high CRP predicts better response to these drugs. However, whether we need to include CRP as an inclusion criterion for future trials with biologicals is still a matter of debate.

Key Words: CRP, biomarker, IBD

C-reactive protein (CRP) is known to most clinicians as a marker of inflammation but has many other functions besides this. CRP acts as an opsonin and activates complement leading to phagocytosis of nuclear components and bacterial sequences. CRP therefore is an important molecule in the host’s innate immune system and in the protection against autoimmunity. In this paper, we discuss the role of CRP as a marker for inflammatory bowel disease (IBD).

HISTORY OF C-REACTIVE PROTEIN

C-Reactive protein (CRP) was first described in 1930 at the Rockefeller Institute by Tillet and Francis. These investigators observed that the serum of patients diagnosed with pneumonia precipitated when brought into contact with a soluble extract (the C-polysaccharide) of Streptococcus pneumoniae. Upon this observation, this substance was called “fraction-C,” a name that was later changed into CRP. Interestingly, the precipitation reaction disappeared when the pneumonia resolved but remained positive in patients with a fatal outcome. Later, it became clear that serum precipitation not only occurred with extracts from S. pneumoniae but also with other bacteria and fungi. No precipitation was however seen with viruses.

CRP AS AN ACUTE-PHASE PROTEIN

In the presence of an acute-phase stimulus, several proteins are up-regulated. A list of these acute-phase proteins is shown in Table 1. In humans, CRP is one of the most important acute-phase proteins. Stimuli that induce an acute-phase reaction can be of various origins: infectious (bacterial, fungal, mycobacterial, or severe viral), inflammatory, stress, tissue necrosis, trauma, childbirth, and neoplasia.

CRP shares 50%-60% homology with serum amyloid A-protein (SAA), which is the major acute phase protein present in mice. In humans, SAA plays only a minor role.

CRP is produced almost exclusively by hepatocytes. The main stimulus for production is IL-6. This response is enhanced in combination with IL1-β and TNF-α. There have been other sites of production described such as in peripheral lymphocytes, in neurons of patients with Alzheimer’s disease, and in the thickened intima of atherosclerotic plaques, although in much lower quantities. CRP has a half-life of 19 hours that is independent of any physiological or pathophysiological circumstances or of the concentration of CRP in the serum. Therefore, the synthesis rate of CRP by the liver is the only factor determining the plasma CRP concentration. Consequently, only liver failure or therapies affecting the acute phase stimulus may decrease CRP.

Under normal conditions, the baseline concentration of CRP in the plasma is around 0.8 mg/L and is in part genetically regulated.

The genes encoding CRP and SAA are located next to each other on the long arm of chromosome 1 (1q23-24) and are referred to as the pentraxine genes because of their protein structure. CRP and SAA each consist of 2 exons.
CRP is not only important in the host’s innate immune defense but also in the protection against autoimmune diseases by its ability to opsonize and phagocyte nuclear components. This is further underscored by several studies showing linkage to 1q23-24, the region harboring the CRP and SAA genes in SLE. Moreover, the murine equivalent of this region maps to mouse chromosome 1q and has also been identified in mice. The most important proof however lies in the observation that SAA−/− knockout mice spontaneously develop autoimmune syndromes and lupus-like glomerulonephritis. As mentioned before, CRP is one of the most important proteins up-regulated during an acute-phase stimulus in humans. Several conditions are associated with a CRP response: infectious stimuli (bacterial, fungal, or severe viral), inflammatory diseases, tissue necrosis, neoplasia, stress, and childbirth. There is a remarkable heterogeneity in CRP response among inflammatory diseases: certain diseases such as Crohn’s disease and rheumatoid arthritis are associated with a strong CRP response, whereas others such as systemic lupus erythematosus (SLE), dermatomyositis, Sjögren’s syndrome, or ulcerative colitis have only a modest to absent CRP response, despite active inflammation. This is an important fact to take into account when using CRP as a marker in clinical practice. The reason for this discrepancy remains speculative. The role of CRP as a marker in inflammatory bowel disease (Crohn’s disease and ulcerative colitis) will now be discussed.

**CRP as a Marker for Diagnosis and Differential Diagnosis of IBD**

A study from St Bartholomew’s Hospital, London investigated 91 children (mean age 11 years) referred for symptoms of abdominal pain, diarrhea, rectal bleeding, weight loss, or mouth ulceration that existed for 3 months or more. All children underwent a complete check-up with blood tests (hemoglobin, leukocyte count, platelet count, erythrocyte sedimentation rate (ESR), albumin, and CRP), ileocolonoscopy, and small bowel follow-through. Twenty-six children were finally diagnosed with CD, 13 with UC, 8 with polyps, two with TBC, three with indeterminate colitis, two with lymphoid nodular hyperplasia, and 37 had a normal investigation. The best biological parameter to diagnose IBD and to differentiate IBD

### TABLE 1. Acute Phase Proteins

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<td>Proteinase inhibitors</td>
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<td>Coagulation proteins</td>
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<td>Complement proteins</td>
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<td>Transport proteins</td>
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<td>Miscellaneous proteins</td>
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and did not contain polymorphic sequences. Recently, a dinucleotide repeat and a number of single nucleotide polymorphisms (SNPs) have been identified. Some of these polymorphisms have been associated with immune-mediated diseases, such as the association of CRP-G1846A located in the 3’UTR with systemic lupus erythematosus (SLE) and with the induction of antinuclear antibodies. Haplotype analysis has further correlated certain polymorphisms with a lower baseline CRP production.

In the presence of an acute-phase stimulus, CRP production is rapidly (within hours) up-regulated and may reach concentrations that are 500- to 1,000-fold higher than under basal circumstances. The short half-life of CRP also ensures that the concentrations quickly decrease once the acute-phase stimulus disappears, making CRP a very valuable marker to detect and follow-up inflammation, and this in contrast to other acute-phase proteins as for instance fibrinogen.
from normal individuals was CRP: all 26 (100%) Crohn’s disease (CD) patients and 8/13 (60%) ulcerative colitis (UC) patients had increased CRP levels in the plasma, as compared with none of the children with polyps or none of the children with a normal investigation. A study in adults by Shine et al at St Mark’s hospital London performed clinical examination, rectal biopsy, ESR, CRP, and α1 glycoprotein in 82 patients with chronic abdominal symptoms. Nineteen patients were diagnosed with CD, 22 with UC, and 41 with a functional bowel disorder. An increased CRP enabled to differentiate all IBD cases from functional bowel disorders: 19/19 CD patients and 11/22 UC patients had increased CRP as compared with 0/41 patients with functional symptoms. Similar findings were obtained by Poullis et al in 203 patients referred for symptoms suggestive of lower bowel disorder. All patients received complete check-up with blood test, cultures, and ileocolonoscopy. Twenty-one patients with known inactive UC served as controls. Thirteen patients (6.4%) were diagnosed with UC and 7 (3.4%) with CD. Using a cutoff of 5 mg/L, CRP had a sensitivity of 70% to detect IBD. When the cutoff was lowered to 2.3 mg/L, sensitivity reached 100%. CRP in patients with quiescent UC was not different from that of non-IBD patients, compared with 2.3 mg/L, sensitivity reached 100%. CRP in patients with quiescent UC was not different from that of non-IBD patients, suggesting that CRP is a marker especially to differentiate active IBD from functional bowel disorders.

CRP as a Marker of Disease Activity

No anti-inflammatory or immunosuppressive drug has proven to affect CRP production. Therefore, modifications of the CRP response during treatment occur only as a result of the effect of the drug on the underlying inflammation or disorder. A decrease in CRP in response to treatment even in patients with little change in symptoms is therefore an objective evidence of the beneficial effect of the drug on the intestinal inflammation. On the other hand, persistently raised CRP may imply failure of the drug to control the inflammation.

In CD, serum levels of CRP correlate well with disease activity: median CRP is higher in severe CD compared with moderate CD which is on its turn higher than mild CD. For UC, the same trend can be observed, although CRP is overall much lower than in CD. Population-based data from the Ibsen cohort in Norway showed increased CRP in most IBD patients at the time of diagnosis and again higher values in CD (median CRP 40 mg/L) than in UC (median CRP 20 mg/L). After 1 year of diagnosis and treatment, CRP levels dropped significantly to normal ranges (Moum B., Vatn M., personal communication). A recent study from the Mayo Clinic has correlated CRP with clinical, radiographic, and endoscopic activity in IBD patients. For CD, CRP was associated with endoscopic activity (OR 4.1; 95% CI 1.6–11) and severe inflammation on biopsies (OR 10; 95% CI 1.0–97). For UC, CRP was only associated with severe inflammation on histology (P = 0.029).

There is a good correlation between CRP and other markers of inflammation such as the Crohn’s disease activity index (CDAI), radioactive-labeled fecal granulocyte extraction, SAA, IL-6, and faecal calprotectin.

CRP as a Marker of Relapse

Relapses of Crohn’s disease occur in a random way. If a relapse could be reliably predicted, it might be possible to avoid them or to abort them with early treatment. In a prospective study by Boirivant et al in patients with Crohn’s disease, a raised CRP in the previous year was associated with an increased risk of relapse in the second year, as compared with patients with normal CRP. The GETAID group prospectively followed 71 CD patients with medically induced remission, and biological markers (full blood count, CRP, ESR, α1AT, orosomucoid) were measured every 6 weeks. Relapse was defined as a CDAI >150 with an increase of >100 points from baseline. In total, 38 patients relapsed after a median of 31 weeks. Two biological markers were predictive for relapse: CRP (>20 mg/L) and ESR (>15 mm). From these 2 markers, a binary biologic predictive score (BPS) was derived. A positive BPS (at least 1 of the 2 markers positive) was associated with an 8-fold increased risk for relapse compared with a negative BPS (defined as both markers lower than their limits). The negative predictive value was 97%, suggesting that a negative BPS rules out almost certainly relapse in the next 6 weeks.

Not all studies have come to similar conclusions. In the study by Wright et al, CRP, orosomucoid, α1-antitrypsin, and iron were all increased at the time of relapse as compared with 3 months before. However, only orosomucoid and α1-antitrypsin were raised 1 month prior to the attack and were therefore able to predict a relapse.

CRP as a Marker of Outcome and Risk for Surgery

CRP has shown to be a valuable marker in predicting the outcome of several diseases. In multiple myeloma, serum CRP together with β2 microglobulin is a highly significant prognostic factor that allows stratification of patients into 3 groups: low-risk group when CRP and β2 microglobulin <6 mg/L, intermediate-risk group when CRP or β2 microglobulin 6–16 mg/L, and high-risk group when CRP and β2 microglobulin ≥6 mg/L. In a prospective study in 162 newly diagnosed multiple myeloma patients, survival was 54, 27, and 6 months, respectively for the low-, intermediate-, and high-risk groups (P < 0.0001). CRP is also a significant predictor of cardiovascular disease and of bad outcome after myocardial infarction. A prospective, nested case-control study among 28,263 healthy postmenopausal women over a mean follow-up period of 3 years assessed the risk of cardiovascular events associated with baseline levels of markers of inflammation. The markers studied were high-sensitivity CRP (hs-CRP), SAA, IL-6, and soluble intercellular adhesion molecule type 1 (sICAM-1). hs-CRP was the only plasma marker (besides cholesterol) that independently predicted the risk of a cardiovascular event (RR...
CRP as a Marker of Treatment Response?

The introduction of anti-TNFα antibodies has proven very efficacious in patients with CD. A dramatic and very quick response is seen in one third of patients and a partial response in another one third. If the response to infliximab depends on the intensity of the acute TNF driven inflammation, then CRP could be a good marker to select patients with active inflammation. Louis et al studied 153 patients treated with infliximab and showed that response to infliximab was associated with an increased CRP at entry (76% responders vs 46% for patients with baseline CRP >5 mg/L compared with <5 mg/L, respectively, P = 0.004). The median CRP before treatment was higher in responders (16.8 mg/L) compared with nonresponders (9.6 mg/L) (P = 0.02). Similar results have been demonstrated for the more humanized anti-TNF molecules: for CDP-571, clinical response at week 2 was significantly superior to placebo only in those patients with baseline CRP >10 mg/L (49.5% for CDP-571 vs 15.5% in placebo). For the 292 patients included in the pegylated anti-TNF CDP-870 trial, the end point at week 12 was not reached when considering the total cohort, mainly due to the high placebo response (35.6% response for the CDP-870 treated arm vs 44.4% for the placebo-treated arm). However, post hoc exploratory analysis showed significant better response in patients with CRP >10 mg/L (53.1%) compared with placebo (17.9%) (P = 0.005). Response in the CDP-870-treated patients with CRP <10 mg/L was not different from placebo (46.7% and 37.5%, respectively). Subsequently, a cutoff of CRP >7 mg/L was defined as a predictor for response.

Similar to the anti-TNF strategies, also anti-adhesion molecule strategies have demonstrated the effect of baseline CRP on the clinical response. The recently completed ENACT-1 trial (N = 905), evaluating the effect of the anti-α4 integrin natalizumab, failed to reach its end point at week 10, again due to a large placebo response. Subanalysis of patients with raised CRP (no cutoff) showed significant benefit of natalizumab over placebo at both weeks 10 and 12. These findings raise the discussion whether we need CRP as an inclusion criterion for future trials with biologicals. Table 2 summarizes the pros and cons of such a strategy. On one hand, including only those patients with raised CRP will select patients with active gut inflammation who are more likely to respond, and this approach may optimize treatment. However, including only patients with raised CRP carries the risk that a drug and hence also the FDA label be restricted only to certain patients. When reviewing the data from Louis et al, some patients with low or normal CRP do show response (46%). So restricting the use of biologicals to patients with increased CRP would deny a good drug to certain patients. Finally, if including CRP, it is still not clear which cutoff point should be used to obtain maximal response?

TABLE 2. Pros and Cons of Including CRP in Clinical Trials with Biologicals

<table>
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<tr>
<th>Pros</th>
<th>Cons</th>
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<tr>
<td>1. Better selection of patients with active gut inflammation</td>
<td>1. Risk of restricting drug only to patients with high CRP</td>
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<tr>
<td>3. Which CRP cutoff value for maximal benefit?</td>
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CRP, C-reactive protein.

CRP is one of the most important proteins that is rapidly produced by hepatocytes during an acute-phase response upon stimulation by IL-6, TNF-α, and IL-1-β originating at the site of inflammation or pathology. CRP is therefore a good marker of measuring disease activity in CD and also explains why biologicals used for the treatment of CD work well in patients with increased CRP. The situation in UC is different, and it is not known why some diseases such as SLE and UC are associated with a lower CRP response despite active inflammation. CRP should be seen as an additive marker to our clinical observation (number of stools/day, general well-being) but could never completely replace it.
REFERENCES