C-reactive protein as a valuable marker of the clinical activity of Crohn's disease

Białko C-reaktywne jako marker aktywności klinicznej w chorobie Leśniowskiego-Crohna

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Key words: C-reactive protein, Crohn's disease, clinical activity.

Słowa kluczowe: białko C-reaktywne, choroba Leśniowskiego-Crohna, aktywność kliniczna.

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Abstract

Introduction: The measurement of Crohn's disease activity is very useful in clinical practice as well as in clinical trials. However, traditionally used clinical scores lack precision. C-reactive protein has been known to be a sensitive marker for inflammation and tissue injury.

Aim: The aim of the study was to correlate the CRP level with the disease activity and to assess its value in predicting Crohn's disease severity.

Material and methods: 89 consecutive patients (43 men and 46 women) with active or inactive Crohn's disease were included in the study without any preselective criteria. CRP was measured and CD activity was calculated by means of Crohn's Disease Activity Index (CDAI).

Results: The median CDAI score was 224 (interquartile range 192-243) and the median CRP was 20 mg/l (interquartile range 5-38 mg/l, upper limit of normal 5 mg/dl). 49.4% of our patients had CRP >20 mg/l. CRP was significantly correlated with CDAI (p=0.000001). The diagnostic value for CRP predicting CDAI >220 was high.

Conclusions: CRP appears to be useful to evaluate CD activity.

Streszczenie

Wstęp: Określenie aktywności w chorobie Leśniowskiego-Crohna odgrywa dużą rolę w codziennej praktyce, jak i próbach klinicznych. Jednakże rutynowo wykorzystywane w tym celu skale są mało precyzyjne. Białko C-reaktywne (CRP) uważa się za czuły marker stanu zapalnego oraz uszkodzenia tkanki.

Cel pracy: Określenie korelacji poziomu CRP z aktywnością choroby oraz jego znaczenia w przewidywaniu ciężkości przebiegu choroby.

Materiał i metody: Badaniem objęto 89 pacjentów (43 mężczyzn i 46 kobiet) z aktywną bądź nieaktywną postacią choroby. U każdego określano poziom CRP oraz aktywność choroby przy użyciu skali CDAI.

Wyniki: Wartość mediany dla CDAI wynosiła 224 (odstęp międzykwartylowy 192–243), a wartość mediany dla CRP 20 mg/l (odstęp międzykwartylowy 5–38 mg/l, górna granica normy 5 mg/l). U 49,4% pacjentów CRP było >20 mg/l. CRP wykazywało istotną statystycznie korelację ze skalą CDAI (p=0,000001). Znaczenie predykcyjne CRP było wysokie przy CDAI >220.

Wnioski: CRP jest dobrym wskaźnikiem aktywności klinicznej w chorobie Leśniowskiego-Crohna.

Introduction

The assessment of clinical activity in Crohn's disease (CD) is one of the most challenging problems in gastroenterology [1]. During recent decades many methods of measuring activity have been created, but none of them has been widely applied by gastroenterologists in everyday practice. Clinicians prefer to use global medical evaluation rather than numeric activity indices, which are often complex and time-consuming. Activity of the inflammatory process in Crohn's disease should be assessed especially in clinical trials in order to evaluate patients' response to treatment. Activity indices have to be simple, reproducible, and relatively inexpensive. The most used and validated clinical scores are: the Crohn's disease activity index (CDAI) [2], the Perianal Disease Activity Index [3], the Harvey Bradshaw index [4], the van Hees or Dutch index [5], endoscopic indices such as the Crohn's Disease Endoscopic Index of Severity [6] or quality of life scores [7]. Each of them has some

shortcomings. However, up to the present time CDAI is the most frequently used index for clinical trials and must be considered the gold standard for evaluation of disease activity [8]. CDAI scores of 150-219 are considered as mildly active disease and scores of 220-450 as moderately active disease. The limit between active and very severe disease was defined as a cut-off value of 450 points [9].

Limitations of the numeric CD activity scores prompted clinicians to frequent use of biochemical and subclinical markers of activity in everyday practice. C-reactive protein seems to be a reliable biochemical marker of Crohn's disease activity. C-reactive protein (CRP) was first detected in 1930 by Tillet and Frances, who identified a substance in the serum of patients infected with pneumococcal pneumonia [10]. This was early evidence of the body's chemical response to inflammatory states. CRP was subsequently considered to be an "acute phase protein" an early indicator of infectious or inflammatory conditions. CRP production is stimulated by cytokines, particularly IL-6, IL-1, and tumour necrosis factor [11].

C-reactive protein levels are usually increased in patients with active Crohn's disease [11]. However, the prognostic role of C-reactive protein levels is not well established.

Aim

The aim of our study was to assess the predictive value of CRP levels in the course of CD, their role in predicting a lack of activity or a low activity of the disease and to determine the optimal CRP level threshold for patients with moderate or high CD activity.

Material and methods

Eighty-nine patients (43 men and 46 women) with CD, confirmed by clinical, radiological, endoscopic and histological criteria, were enrolled in the study. All CD patients without any preselective criteria were recruited from the Gastroenterology Department of the Medical University in Lublin. The mean age was 37.1 years (range 16-76). The mean duration of disease was 3.1 years (range 0.25-22). Fifty patients (56.2%) had CD limited to the small bowel, thirty-two (35.9%) had ileocolonic disease, and 7 (7.9%) had colonic involvement. 23 patients had resection performed in the course of disease.

Disease activity was determined in all patients using the CD activity index (CDAI). CD was considered nonactive or weakly active if the CDAI was <220 (38 patients) and moderately or highly active if the CDAI was ≥220 (51 patients).

CRP was measured in all patients using a turbidimetric immunoassay. The CDAI and CRP were determined at the same time. The correlation between CRP and CDAI was studied. We used the receiver operating characteristic (ROC) curve to determine the optimal threshold separating moderate or highly active CD from inactive or low active CD. To estimate the predictive value of CRP, the sensitivity (SE), the specificity (SP), the positive predictive value (PPV) and the negative predictive value (NPV) were defined. In our study, SE was the probability that CRP was ≤5 mg/l if CDAI was <220, SP was the probability that CRP was >5 mg/l if CDAI was ≥220. The PPV represented the probability that the CDAI was <220 if CRP was ≤5 mg/l, and the NPV was the probability that CDAI was ≥220 if CRP was >5 mg/l.

Statistical analysis

The Mann-Whitney non-parametric test, Statistica 6.0 PL and Excel (version 2000) software were used for statistical analysis. The Spearman coefficient of correlation (r) was used to assess the correlation between CRP and CDAI. The ROC curve was used to estimate the optimal threshold for CRP predicting CDAI >220. Specificities, sensitivities, positive predictive values and negative predicting values were calculated. For every test, p value of <0.05 was considered as significant.

Results

The CRP median was 20 mg/l (IQR 5-38 mg/l). The median CDAI score was 224 (IQR 192-243). CRP was closely correlated with the CDAI (Fig. 1; r=0.783; p=0.000001). CRP level was not different according to the site of disease. CRP was higher in patients with CDAI ≥220 (30 mg/l, IQR 25-63 mg/l) than in patients with CDAI <220 (5 mg/l, IQR 4-12 mg/l, p=0.000001).

The diagnostic value of low level of CRP to predict a lack of activity or a low activity of Crohn's disease was high. The sensitivity – the probability that CRP ≤5 mg/l if CDAI was <220 – was 0.560 (95% CI, 0.421-0.744). The specificity – the probability that CRP >5 mg/l if CDAI ≥220 – was 1 (95% CI, 0.929-1.000). No patient with a CRP ≤5 mg/l had CDAI ≥220. The positive predictive value – the probability that CDAI was <220 if CRP was ≤5 mg/l – was equal to 1 (95% CI, 0.893-1.000) and the negative predictive value was 0.760 (95% CI, 0.662-0.840).

The predictive value of CRP for CDAI >220 was studied by means of the ROC curve (Fig. 2). The area under the ROC curve was large (0.902; 95% CI, 0.826-0.979; p<0.0001), confirming the good predicting value of CRP with these aims. The optimal threshold maximizing both SE (0.820) and SPE (0.872) was 18.8 mg/l.
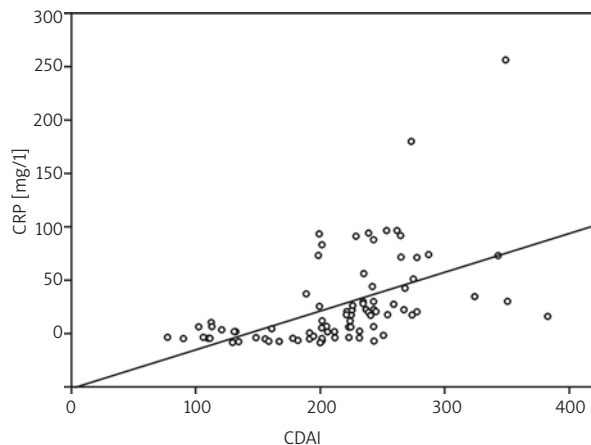
Fig. 1. Correlation between CRP and CDAI (r=0.783, p=0.000001)
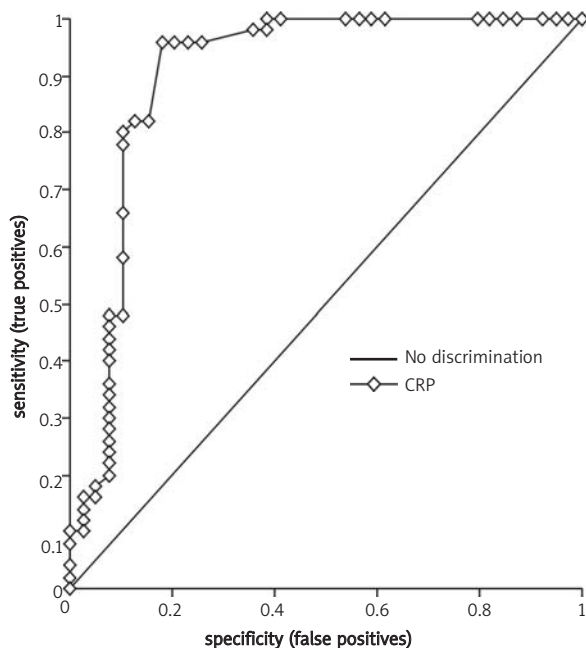*Ryc. 1. Korelacja CRP i CDAI (r=0,783, p=0,000001)*

Fig. 2. ROC curve – the relationship between sensitivity and specificity in determining the predictive value of CRP for active CD. The area under ROC curve is large – 0.902 (95% CI, 0.826-0.979; p<0.0001)
Ryc. 2. Krzywa ROC – zależność między czułością i swoistością, określająca znaczenie predykcyjne CRP dla aktywnej postaci CD. Duże pole powierzchni pod krzywą ROC – 0,902 (95% CI, 0,826-0,979; p<0,0001)

Positive predictive values of CRP to predict moderate or high Crohn's disease activity for different CRP level were also calculated. PPVx was the probability that CDAI was >220 if CRP was >x (mg/l). This calculation allowed us to relate the PPVx to the corresponding percentage of patients belonging to the population studied and selected in this way; the number nx was the patient number with CRP>x. PPVx increased when x increased: PPV5 = 0.772 (95% CI, 0.679-0.857, n5=66 [74.1%]), PPV45=0.947 (95% CI; 0.839-0.998, n45=19 [21.3%]).

Discussion

Clinical course of Crohn's disease (CD) is usually intermittent with periodic fluctuations of activity [1]. Acute flares of inflammation alternate with remissions. Assessment of the clinical activity of CD is often difficult and numerous symptomatic, endoscopic and laboratory indices have to be applied to monitor the disease and to predict future prognosis. Measurement of activity is important not only in everyday practice, but also in clinical trials to evaluate the patient's response to the new, studied therapeutic methods. Multiple indices including quantitative subjective symptoms, laboratory tests and endoscopic appearances are usually required for this purpose [8]. Complex and time-consuming numeric CD activity indices are not widely adopted by clinicians and therefore a simple, reproducible marker would be extremely desirable in the monitoring of the disease.

Since its discovery CRP has been studied as a screening device for occult inflammation, as a parameter of disease activity and a diagnostic tool [12]. It was found useful in monitoring exacerbations in chronic inflammatory conditions like rheumatoid arthritis or inflammatory bowel disease [13].

In contrast to the sedimentation rate (ESR) CRP rises more rapidly and returns to normal more quickly upon resolution of inflammatory stimuli. The levels of CRP are not affected by anaemia, polycythaemia, protein levels, patient's age or gender [12]. CRP has been described as a good diagnostic parameter in the differentiation of inflammatory bowel disease from functional bowel disorders [14]. CRP was also a marker of outcome and risk of surgery in ulcerative colitis [15].

We found that CRP is a reliable index of CD activity. The levels of CRP in our patients with CD were much higher when CDAI exceeded 220 than in the patients with CDAI <220 and the difference was highly significant (p<0.000001). Similarly, the diagnostic value of low level of CRP to predict lack or low activity was high.

CRP has not only been previously found as a marker of CD clinical activity [16], but also CRP elevation has appeared to be associated with endoscopic and

histological mucosal lesions [17]. Measurement of CRP is a fast, inexpensive test and much easier to use than multi-parametric and time-consuming scores in everyday practice.

Conclusions

We conclude that the determination of CRP levels provides a simple objective index of inflammatory activity which may be useful in the assessment, management and study of inflammatory bowel disease.

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