C-Reactive Protein Level Predicts the Severity but Not Response of Immune-Mediated Diarrhea and Colitis

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Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target down-regulators of the anti-cancer immune response: Cytotoxic T-lymphocyte antigen-4, programmed cell death protein-1, and its ligand programmed death-ligand 1.

Immune mediated diarrhea and colitis (IMDC) is the resultant GI immune related adverse effect of ICIs.

CRP is an acute phase reactant primarily produced by the liver when stimulated by cytokines during infection or inflammation.

CRP is non-specific for bowel inflammation and is widely influenced by systemic factors, unlike fecal calprotectin which has been found to be specific to bowel inflammation and predictive of disease in IMDC.

CRP has been found to be predictive of severity and outcome in IBD. Its use in IMDC has not yet been studied.

We aimed to study the utility of CRP as a predictor of disease severity and of response in IMDC, as well as its relation to fecal calprotectin in IMDC.

Methods

Retrospective cohort study of patients who received ICI therapy at a tertiary cancer center between January 2016 and February 2022.

Patients with CRP level checked at IMDC diagnosis and after treatment were included. Patients with concurrent infections or without CRP levels measured during disease course were excluded.

Independent sample and paired-sample T-tests were used to compare the mean CRP levels between different groups after testing for normality. Finally, univariate logistic regression was used to test the association between CRP levels and different types of remission.

Table 1. The association between clinical characteristics and C-reactive protein levels at first biologic infusion after IMDC diagnosis (N=74).

Characteristic	N	Initial CRP Levels [mg/L] Mean±SEM	P
Diarrhea grade, – no. (%)			0.049
1-2	25	27.0 ±9.4	
3-4	46	53.3±9.2	
Colitis grade, – no. (%)			0.04
1	28	12.7± 2.8	
2-4	63	66.7±13.3	
Endoscopic presentation, – no. (%)			0.012
Active inflammation (ulcer + non-ulcer inflammation)	53	67.1±9.2	
Normal	**19**	**16.0±3.7**	

Characteristic	N	CRP Levels at IMDC onset [mg/L] Mean±SEM	P	N	Last CRP Levels post IMDC treatment [mg/L] Mean±SEM	P
Clinical remission, – no. (%)			0.552			0.701
Yes	57	48.9±8.0		84	17.1±4.3	
No	15	38.0±16.0		17	14.3±5.9	
Endoscopic remission, – no. (%)			0.696			0.446
Yes	12	53.9±20.2		23	18.2±12.2	
No	19	44.5±12.2		33	8.4±3.6	
Histological remission, – no. (%)			0.275			0.309
Yes	18	57.9±15.9		33	16.3±8.8	
No	15	35.9±11.7		24	6.6±3.3	
Recurrence IMDC, – no. (%)			0.912			0.751
Yes	16	45.8±11.7		26	17.4±5.4	
No	**55**	**47.4±8.7**		**77**	**19.9±5.8**	

Table 2. The Association between IMDC outcome and C-reactive protein levels at IMDC onset and post-biologic IMDC treatment (N=105).

Results

At the time of IMDC diagnosis, there was significant difference in initial CRP level between grade 1-2 diarrhea and grade 3-4 diarrhea (27 and 53 respectively, p=0.049).

There was significant difference in initial CRP level and colitis grade 1 and colitis grade 2-4 (12.7 and 66.7, p=0.04).

There was significant difference in initial CRP and endoscopic presentation of IMDC between those with active inflammation or normal colon (67.1 vs 16.0, p=0.012).

There is no significant difference between clinical remission and CRP level at IMDC onset compared to CRP level post IMDC treatment.

There is no significant difference between endoscopic, histologic, or recurrence of IMDC with CRP levels before and after IMDC treatment either.

The mean CRP level has no correlation with the mean FCal level at IMDC onset or post medical treatment (correlation coefficient 0.088, p=0.511; correlation coefficient=0.1, p=0.379).

Conclusions

CRP may be a useful biomarker when evaluating initial disease severity in IMDC.

CRP has poor correlation with IMDC disease clinical, endoscopic, or histologic remission or recurrence, thus is not a useful marker for monitoring of IMDC disease progression or response to treatment.

Limitations of our study are that CRP elevations may be confounded by the presence of underlying malignancy, ICI which itself augments the immune system, or other underlying systemic inflammation.

Future studies should be directed toward the use of fecal calprotectin or other biomarkers to monitor IMDC disease progression and response.

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