

Importance of Interleukin 6 in Pathogenesis of Inflammatory Bowel Disease

Boris Takač¹, Silvio Mihaljević², Mario Štefanić¹, Ljubica Glavaš-Obrovac³, Aleksandar Kibel² and Marina Samardžija⁴

¹ »J. J. Strossmayer« University, University Hospital Centre Osijek, Clinical Department of Nuclear Medicine and Radiation Protection, Osijek, Croatia

² »J. J. Strossmayer« University, University Hospital Centre Osijek, Division of Gastroenterology, Internal Clinic, Osijek, Croatia

³ »J. J. Strossmayer« University, School of Medicine, Osijek, Croatia

⁴ »J. J. Strossmayer« University, University Hospital Centre Osijek, Department of Transfusion Medicine, Osijek, Croatia

ABSTRACT

Inflammatory bowel disease (IBD), encompassing ulcerative colitis (UC) and Crohn's disease (CD), is an uncontrolled chronic inflammation of the gastrointestinal tract caused by an interaction of diverse genes and environmental factors. There is growing evidence that cytokine production plays an important role in IBD. One of the key roles in signaling pathway in development of IBD is performed by interleukin 6 (IL-6), although molecular mechanism of this pathway is not yet fully understood. In order to assess the clinical relevance of IL-6 serum concentration in patients with CD and UC we performed cross-sectional, case-control study of IL-6 levels in patients' and healthy blood donors' sera. A total of 100 CD and UC patients and 71 healthy blood donors were investigated. Clinical activity of CD and UC was evaluated using the Crohn's disease activity index and Truelove-Witt's criteria, respectively. Quantitative assessment of serum IL-6 was performed with solid-phase, enzyme-labeled, chemiluminescent sequential immunometric assay. Our results indicate that serum IL-6 is a clinically relevant parameter for CD and UC that strongly correlates with inflammatory activity of disease. We confirmed and extended the role of cytokine production patterns for IBD presentation in Croatian population.

Key words: Interleukin 6, ulcerative colitis, Crohn's disease, C-reactive protein, signal transducer and activator of transcription, T cells, soluble interleukin 6 receptor, membrane bound interleukin 6 receptor, proinflammatory cytokines, Crohn's disease activity index

Introduction

Inflammatory bowel disease (IBD) is clinically and histopathologically categorized into two basic subgroups – Crohn's disease (CD) and ulcerative colitis (UC). Both are characterized by chronic relapsing bowel inflammation that responds to anti-inflammatory drugs such as glucocorticoides and immunosupresives¹. Continuous inflammation of the large intestine affecting both the colonic mucosa and submucosa is characteristic only for UC in contrast to CD which manifests itself most frequently in distal ileum and colon². IBD has been conceived of as multifactorial disorder caused by an interplay between environmental factors and multiple predisposing gene variants, such as nucleotide oligomerization domain 2/Caspase activation recruitment domains 15 (NOD2/CARD15)

polymorphisms, signal transducer and activator of transcription-6 (STAT6), INF γ , metalloproteinase (MMP18), Vitamin D receptor (VDR) Th17 and β 7 integrin family members³⁻⁶. In addition, several other pathologically relevant pathways have been recently identified in both disorders including, but not restricted to immunity defects, autophagy, epithelial barrier permeability defects and loss of detoxification of intestinal drugs.

IBD is characterized by a predominantly T helper (Th) 1 cellular profile, involving the up-regulation of cytokines such as IL-6, IL-8, IL-1 β and tumor necrosis factor (TNF) α ^{7,8}. Among these, IL-6 is a pleiotropic cytokine that functions in both innate and adaptive im-

immune process and has a role in multitude of immune and non-immune system reactions⁹. IL-6 production is generally correlated with cell activation and is normally kept in control by glucocorticoids, catecholamines and secondary sex steroids¹⁰. Disruption of IL-6 regulation has been related to several immune-mediated inflammatory diseases such as rheumatoid arthritis, systemic juvenile idiopathic arthritis, Castleman disease, various types of cancer and IBD¹¹. IL-6 plays a key role in acute phase response which leads to STAT3-dependent changes in concentrations of plasma proteins such as C-reactive protein, serum amyloid A, haptoglobin, fibrinogen, albumin and transferrin^{12,13}. IL-6 stimulates the proliferation of mature T cells, differentiation of cytotoxic T cells and B cells, activates the hypothalamic-pituitary-adrenal axis by releasing adrenocorticotrophic hormone¹⁴. Although IL-6 is mostly regarded as proinflammatory cytokine it also has many anti-inflammatory activities^{15,16}. In order to induce signal transduction, IL-6 first forms a complex with IL-6 receptor (IL-6R) and afterwards associates with gp130 whose cytoplasmic portion is sufficient to activate Janus kinase (JAK) and STAT signal cascade. Contrary to membrane-bound IL-6R (mbIL-6R) gp130 is ubiquitously expressed^{17–19}. However, IL-6 exerts its biological function not only by association with mbIL-6R but by forming a complex with the soluble IL-6R (sIL-6R) and afterwards binds to gp130²⁰.

Understanding cytokine production patterns in IBD may be critical to understanding IBD pathogenesis²¹. The aim of the present descriptive study is to provide insight into pathological roles of IL-6 in IBD, and to investigate the extent to which IL-6 is related to disease activity.

Materials and Methods

Patients

The study population consisted of 100 (32 CD, 68 UC) adult patients (52 males, median age 43, range 20–79 yrs) with IBD diagnosed at the Internal Clinic, Department of Urgent and Intervention Gastroenterology, University Hospital Centre Osijek and at Zagreb University Hospital Centre (Table 1). Seventy-one adult, otherwise healthy blood donors with no clinical signs or family history of autoimmune diseases or malignancy were recruited as controls. The median follow-up time for patients was 6 (interquartile range 3–12) years. Patients' age, sex and relevant clinical and biochemical data were extracted from medical records. IBD diagnosis was established on the basis of endoscopy findings, pathohistological and radiological criteria. Subjects with infective and nonspecific colitis, multiple sclerosis, confirmed autoimmune or malignant diseases were excluded from the study. There were 21 patients under treatment with corticosteroids (8 CD and 13 UC patients). They received either methylprednisolone (median dose 16, range 8–40 mg; N=9) or prednisone (median dose 17.5, range 5–40 mg, N=12). The following laboratory parameters were assessed: erythrocyte sedimentation rate (ESR), white

blood cell count (WCC), C reactive protein levels (CRP), serum albumin (ALB), alanin aminotransferase (AST), aspartate transaminase (ALT), and creatinine (CREAT). Serology for IL-6 was conducted at Clinical Department of Nuclear Medicine and Radiation Protection, Clinical Hospital Centre Osijek, Croatia. Seventy-one healthy blood donors were also investigated for IL-6 serum level. Prior approval of the institutional ethical committee, as well as patients' and healthy blood donors' informed consent was obtained.

Biochemical measurements

Tests were performed on Siemens Immulite 1000 in incubation cycles of 2x30 minutes according to company protocol. Immulite IL-6 (Siemens Healthcare Diagnostics, Llanberis, Gwynedd, United Kingdom) is a solid-phase, enzyme labeled, chemiluminescent sequential immunometric assay. Specimens were collected by venipuncture in blood collection vacutainers without clot-promoting additives (BD Vacutainers Systems, Bellerive Industrial Estate, Plymouth, UK). To prevent erroneous results due to the presence of fibrin, complete clot formation had taken place prior to centrifugation of samples. Centrifugation step was performed in Hettich rotina 380 R centrifuge 15 min at 3,000 rpm. Serum samples were aliquotted and stored at –20°C before analysis within one hour of venipuncture. Immulite IL-6 kit containing one bead coated with a monoclonal murine anti-IL-6 antibody, two IL-6 reagent wedges. First contains 7.5 ml of a protein/buffer matrix and second of 7.5 ml alkaline phosphatase (bovine calf intestine) conjugated to polyclonal sheep anti-IL-6 antibody in buffer and IL-6 low and high adjustors of lyophilized IL-6 in a protein buffer matrix. Calibration range is up to 1,000 pg/ml and high-dose hook effect is none up to 60,000 pg/ml. IL-6 assay was calibrated due to low and high adjustors both reconstituted with 3 ml distilled water and mixed by swirling until lyophilized material was fully dissolved. Both were run in tetraplicates. For positive test verification as an aid in monitoring performance of assays two controls contained different concentrations of selected lyophilized cytokines in a human serum matrix were used. Both were reconstituted with 5 ml distilled water inside of 30 minutes prior to use and mixed until lyophilized material was fully dissolved. The controls were assayed in the same manner as patient samples, in the context of an internal quality follow-up. The result for control one was 97.3 pg/ml (expected range was from 74 to 104 pg/ml). The result for control two was 422 pg/ml (expected range varying from 365 to 543 pg/ml).

Statistical analysis

Data are presented as medians (ranges) and counts (percentages) depending on the scale of the measure. Mann-Whitney and Kruskal-Wallis tests with Schaich-Hamerle post hoc procedures were used for group comparisons. Relations between variables were tested by Spearman rank test. All statistical analyses were performed with Statistical Package for Social Sciences, ver-

sion 17.0 SPSS Inc., Chicago, IL, USA. Two-sided p-values <0.05 were considered significant.

Results

Patients' characteristics and biochemical data are presented in Tables 1 and 2, respectively.

The majority of patients (N=79) were treated with mesalamine (median dose 2,500 mg, range 1,000–4,000 mg). IL-6 serum levels were separately assessed in CD (CDAI median: 109), UC (MTLWSI median: 6) patients and healthy controls (Table 3). In both CD patients and UC patients concentrations of IL-6 were significantly higher ($\chi^2=50.64$, $df=2$, $p<0.001$, Kruskal-Wallis test) when compared to healthy blood donors (Table 3). In either CD or UC patients there were no significant differ-

ences in concentrations of IL-6 between patients under corticosteroid treatment and patients receiving no corticosteroid therapy ($\chi^2=5.44$, $df=3$, $p=0.142$, Kruskal-Wallis test).

The relationship between IL-6, clinical and biochemical data was investigated using Spearman rank order correlation coefficient in CD and UC patients separately. In both CD and UC patients, a strong positive correlation was seen between ESR and IL-6 levels ($r=0.54$, $p<0.01$ and $r=0.67$, $p<0.01$, respectively), and CRP and IL-6 levels ($r=0.68$, $p<0.01$ and $r=0.78$, $p<0.01$, respectively). In both patients' groups a positive correlation between WCC and IL-6 levels was seen, more pronounced in UC patients ($r=0.53$ vs. 0.42 , $p<0.01$). In both groups, an inverse correlation between ALB and IL-6 levels was found (CD patients, $r=-0.42$, $p<0.05$; UC patients, $r=0.59$, $p<0.01$). In CD patients, CDAI correlated positively with IL-6 ($r=0.48$, $p<0.01$). Similarly, a highly significant positive correlation was found between MTLWSI and serum IL-6 ($r=0.66$, $p<0.01$) (Table 4). In UC patients, additional inverse correlations were found between HGB and IL-6 ($r=-0.43$, $p<0.01$), HCT and IL-6 ($r=-0.33$, $p<0.05$), and CREAT and IL-6 ($r=-0.28$, $p<0.05$).

Mann-Whitney test was conducted to compare the IL-6 serum level for CD patients with previous intestinal resections with other CD patients. There was no statistically significant difference between the two subgroups of CD patients ($p=0.313$).

TABLE 1
DEMOGRAPHIC CHARACTERISTICS OF STUDY POPULATION OF CD AND UC PATIENTS

Patients (N=100)	
Male	52
Female	48
Age (median, range)	42.5 (20–79)
CD patients	32
UC patients	68

TABLE 2
BIOCHEMICAL DATA OF CD (N=32) AND UC PATIENTS (N=68)

Parameter	CD patients (N=32)		UC patients (N=68)	
	Median	Range	Median	Range
Crohn's disease activity index	109	30–469	–	–
Modified Truelove & Witts Severity Index	–	–	6	0–17
Erythrocyte Sedimentation Rate	18	1–68	20	1–145
White Blood Cell Count	8.2	4.19–16.1	8.6	3.4–24.5
Erythrocytes	4.4	3.43–5.59	4.53	2.22–5.98
Hemoglobin	125	65–163	127	77–181
Hematocrit	0–36	0.31–0.47	0.38	0.21–0.51
Alanin Aminotransferasis	18	11–37	19	9–135
Aspartate Transaminase	15	2–54	19.5	6–167
Serum Albumin	40	26.4–51.1	38	19.9–51.5
Creatinine	74	42–100	76.5	37–135
C Reactive Protein	7.7	0.2–187.5	6.85	0.2–421

TABLE 3
IL-6 LEVELS IN CD AND UC PATIENTS AND HEALTHY CONTROLS

	CD patients (N=32)		UC patients (N=68)		Healthy controls (N=71)	
	Median	Range	Median	Range	Median	Range
Interleukin 6 (pg/ml)	3.25*	1.99–13.7	2.67**	1.99–118	1.99	1.99–4.03

* – CD vs. healthy controls, $p<0.001$, Schaich-Hamerle post-hoc test, ** – UC vs. healthy controls, $p<0.001$, Schaich-Hamerle post-hoc test

TABLE 4
SPEARMAN CORRELATIONS BETWEEN IL-6 AND PATIENTS' CLINICAL AND BIOCHEMICAL DATA

Parameter	IL-6					
	CD			UC		
	N	p	ρ	N	p	ρ
Crohn's disease activity index	28	0.481	0.009**	–	–	–
Disease duration	31	0.188	0.311	68	0.027	0.824
Age	32	0.115	0.532	68	0.019	0.877
Duration	31	–0.081	0.663	68	–0.096	0.437
Modified Truelove & Witts Severity Index	–	–	–	67	0.669	0.000**
Erythrocyte Sedimentation Rate	30	0.544	0.001**	60	0.671	0.000**
White Blood Cell Count	30	0.451	0.012*	65	0.536	0.000**
Erythrocytes	30	–0.211	0.261	62	–0.202	0.114
Hemoglobin	30	–0.324	0.081	61	–0.436	0.000**
Hematocrit	23	–0.139	0.525	46	–0.335	0.023*
Alanin Aminotransferasis	29	–0.037	0.848	60	–0.221	0.089
Aspartate Transaminase	29	–0.117	0.546	60	–0.083	0.526
Serum Albumin	27	–0.420	0.028*	53	–0.591	0.000**
Creatine	28	0.078	0.691	60	–0.281	0.029*
C Reactive Protein	30	0.682	0.000**	64	0.787	0.000**
Interleukin 23	32	0.171	0.349	67	–0.039	0.753

* – $p < 0.05$, ** – $p < 0.001$

Finally, Mann-Whitney test was conducted to compare the IL-6 serum level for inactive (CDAI < 150) CD patients (median = 1.99, range = 1.99–9.36, N = 17) with healthy blood donors (median = 1.99, range = 1.99–4.03, N = 71). There was a statistically significant difference between the two groups of participants ($z = -3.896$, $p = 0.000$).

Discussion and Conclusion

In the present study we explored the role of IL-6 in IBD and investigated whether serum IL-6 level is a representative parameter of CD and UC activity. Examined by single point measurement, serum IL-6 level was found to significantly correlate with severity and extent of inflammatory bowel disease. Similarly it has been shown that serum IL-6 level was substantially elevated in patients with IBD²² and positively correlated with inflammatory activity of disease²³. In addition, increased serum levels of sIL-6R and IL-6/sIL-6R complexes were reported, suggesting an active IL-6 trans-signaling mechanism operating through membrane-bound gp130 in IBD^{24–26}. This is crucial in mechanism of IL-6 activity because only small fractions of cells express mbIL-6R, mainly hepatocytes, macrophages, neutrophils and some lymphocytes^{17,27}. We have shown in our study that serum IL-6 levels in patients with active CD (CDAI > 150) were significantly higher when compared to patients with inactive CD (CDAI < 150), and that serum IL-6 levels in patients with inactive CD were significantly higher than those in healthy blood donors. CRP and ESR mirrored

IL-6 levels, possibly reflecting the existence of remaining lesions, activation of the mucosal immune system or abnormal intestinal permeability, all of which can stimulate IL-6 synthesis in inactive CD patients, but it could also be attributed to the existence of subclinical, yet relevant residual inflammatory activity of the disease. These biological abnormalities have also been reported to be associated with an increased risk of relapse assessed over a short to medium period of time, usually one year^{28–30}. Interestingly, in contrast to our study, some previous studies could not unequivocally disclose a relationship between serum IL-6 levels and scores of clinical activity which has been attributed to the effect of steroid medication which inactivates proinflammatory transcription factors and reduces half-lives and utility of cytokine mRNA thus inhibiting IL-6 synthesis^{21,31}.

CRP value was elevated in both CD and UC groups and positively correlated with IL-6 serum value. IL-6 is a principal cytokine that induces the production of acute phase reactants like the CRP. CRP is responsible for IL-6R shedding thus enhancing the effects of IL-6³². Furthermore, it has been reported that serum concentrations of various acute phase proteins anticipate clinical relapses, but only the combination of several laboratory tests provides a reliable predictive index^{14,33}.

Although a comparison of CD patients with intestinal resection with CD patients who did not have previous intestinal resections did not yield statistically significant differences, we believe that the observed lower IL-6 serum levels in patients with intestinal resection might have potential implications. Namely, substantial reduction of inflammatory tissue is performed by intestinal re-

section and thus inflammatory stimuli are diminished which could lead to decrease of intestinal IL-6 release to systemic circulation. Lack of statistical significance in the present study concerning intestinal resection may be attributed to the small sample size, although some differences may also be attributed to varying therapeutic modalities.

Measurement of serum IL-6 levels might be a useful tool to stratify patients with high risk of relapse. However, the present study is limited by a lack of longitudinal

measurement of serum IL-6 in steroid induced remission which we believe would yield a better insight into IL-6 dynamics and usefulness of IL-6 serum value as relapse predictive factor. This will be further explored in our future research. Our results demonstrated that serum IL-6 reflects inflammatory activity in patients with CD and UC, and overall seems to be a good predictor of IBD activity. Given a prominent role of IL-6 signaling in both CD and UC pathogenesis, IL-6 can be considered as an important target for cytokine specific therapies.

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B. Takač

»J. J. Strossmayer« University, University Hospital Centre Osijek, Clinical Department of Nuclear Medicine and Radiation Protection, Hutlerova 4, 31000 Osijek, Croatia
e-mail: btakac@gmx.net

VAŽNOST INTERLEUKINA 6 U PATOGENEZI UPALNIH BOLESTI CRIJEVA

SAŽETAK

Upalne bolesti crijeva (engl. inflammatory bowel disease – IBD) koje obuhvaćaju ulcerozni kolitis i Crohnovu bolest su nekontrolirane kronične upale gastrointestinalnog trakta uzrokovane interakcijom različitih genskih faktora i faktora okoliša. Sve je više dokaza da produkcija citokina ima važnu ulogu u upalnim bolestima crijeva. Jednu od ključnih

uloga u razvoju upalnih bolesti crijeva ima interleukin 6 (IL-6), iako molekularni mehanizmi djelovanja još nisu u potpunosti objašnjeni. Kako bismo procijenili kliničku važnost serumske koncentracije IL-6 u pacijenata oboljelih od ulceroznog kolitisa i Crohnove bolesti, proveli smo ispitivanje razine IL-6 u serumima oboljelih i zdravih donatora krvi. Istraživanje je obuhvatilo ukupno 100 pacijenata oboljelih od Crohnove bolesti i ulceroznog kolitisa i 71 zdravih donatora krvi. Klinička aktivnost Crohnove bolesti mjerena je pomoću indeksa aktivnosti Crohnove bolesti, a ulceroznog kolitisa pomoću Truelove-Wittsovih kriterija. Kvantitativno određivanje serumske koncentracije IL-6 učinjeno je kemiluminescentnim sekvencijalnim imunometričkim testom. Rezultati upućuju na zaključak da je serumski IL-6 klinički relevantan parametar za obje bolesti koji snažno korelira s upalnom aktivnošću bolesti. Potvrdili smo i proširili ulogu i značaj sinteze citokina u upalnim bolestima crijeva u hrvatskoj populaciji.