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THE ROLE OF INTERLEUKINE-33 AND sST2 IN INFLAMMATORY BOWEL DISEASE

*Ahmed Abdul-Hassan Abbas[1], Raghad Raad Hwyidii[1] and Khalid A. AL-Khazraji[2]
[1]Department of Microbiology, Medical College, Al-Nahrain University, Iraq
[2]Medical College, Baghdad University, Iraq

ABSTRACT

The etiopathogenic hypothesis for inflammatory bowel disease (IBD) suggests an immune mediated process originates from an inappropriate response of immune system. This study was performed to evaluate the role of IL-33 and sST2 in pathogenesis of IBD and to correlate their levels with the disease activity and with serum levels of p-ANCA and ASCA. Fifty five patients with IBD (41 UC patients and 14 CD patients) and 25 subjects as controls were participated in this study. Blood samples were collected from all patients and controls to assess serum concentrations of IL-33, sST2, p-ANCA and ASCA by enzyme-linked immune-sorbent assay. There was significant elevation in serum level of IL-33 among UC and CD patients as compared to controls, where a serum level of sST2 was increase significantly only in UC patients when compared to controls. In addition the serum level of IL-33 was lower in treated patients with infliximab than patients on other treatments but statistically not significant. While the comparison between patients who receive infliximab versus patients with other treatment revealed significant differences in serum level of sST2. High positively of p-ANCA in UC patients and ASCA in CD patients were found as compared with control. Another important result in UC patients there was positive correlation between serum IL-33 and sST2 and the disease activity, also IL-33 level was positively correlated with each of sST2 and p-ANCA. IL-33 and sST2 might be a crucial mediator in pathogenesis of IBD. In addition, the increased levels of IL33 and sST2 correlated with disease activity of UC possibly reflect an acute response due to inflammation. Also, in particular, IL-33 may regulate by TNF-α in UC.

Keywords: IBD, IL-33, soluble ST2, ulcerative colitis.

INTRODUCTION

Inflammatory Bowel Disease (IBD) is a chronic, relapsing, inflammatory disorder of the gastrointestinal tract that includes two entities, namely crohn's disease (CD) and ulcerative colitis (UC) (Cosnes *et al*., 2011).The exact cause of these diseases is unknown, but several researches suggest that they may be caused by a malfunction in the body's immune system. Certain environmental factors may also increase an individual's risk for CD and UC, IBD has become one of the most common chronic inflammatory conditions only after rheumatoid arthritis, with millions of patients all over the world (Russel, 2000).

The Cytokines act as key players in communication among different cell types; balance among pro and anti-inflammatory cytokines critical for gut immune homeostasis. Broad studies explain the importance of cytokine dys-regulation in the onset of inflammation of the gastrointestinal tract. IBD is characterized by modulation of cytokine production, in general, an excess of pro-inflammatory mediators (Kaser *et al*., 2010). IL-33 is a robust activator of the innate immune system. IL-33 and its receptors are portion of the IL-1 family, and their interactions encourage a diversity of actions from different cell types (Schmitz *et al*., 2005; Dinarello, 2010; Mirchandani *et al*., 2012; Nakae *et al*., 2013). IL-33 interacting with ST2 on variety leukocytes stimulates number of inflammatory pathways (Tago *et al*., 2001; Latiano *et al*., 2013). A soluble form of the IL-33R (sST2) is able to neutralize IL-33. Soluble ST2 acts as a decoy receptor functionally inhibit IL-33 in vitro and in vivo (Hayakawa *et al*., 2009).

IL-33 and its receptor ST2 are the potential targets for the treatment of allergic and autoimmune inflammatory diseases. However, their exact roles in these diseases still remained poorly understood (Zhao and Chen, 2014). In patients with acutely decompensated heart failure, elevated concentrations of sST2 are strongly associated and predict increased risk of heart failure complications or death, independent of natriuretic peptides and other established or emerging biomarkers (Januzz *et al*., 2015).

The use of Peri-nuclear anti-neutrophil cytoplasmic (pANCA) and anti-saccharomyces cerevisiae antibodies

*Corresponding author e-mail: ahmed26770@yahoo.com

(ASCA) has been suggested as a valuable and noninvasive diagnostic approach in the differentiation of UC and CD (Papp *et al*., 2007). The present study was performed to evaluate the role of IL-33 and sST2 in pathogenesis of IBD and to correlate their levels with the disease activity and/or severity, and with serum levels of pANCA and ASCA.

MATERIALS AND METHODS

Fifty five patients with IBD (41 UC patients and 14 CD patients) were enrolled in this study, their age range from (16-65) years. They were among patients attending to gastroenterology out patient's clinic at Baghdad Teaching Hospital in medical city and AL Kadmyia Teaching Hospital in Baghdad from December 2012 to June 2013. The diagnosis of each case was established by clinical examination done by a gastroenterologist and confirmed by colonoscopy and biopsy investigations. The UC patients were divided into two groups: Group I consisted of 15 recently diagnosed UC patients (untreated), while group II consisted of 26 patients on treatment.

All the cases had no complain of other chronic or systemic diseases, hence patients with a history of cardio-pathies and hypertension were excluded. The Ethical Committee of College of Medicine, Al-Nahrain University approved this study, and all samples were obtained with informed consent in accordance with the Baghdad Teaching Hospital declaration and AL Kadmyia Teaching Hospital.

Twenty five subjects whose ages and sexes were matched with patients group were considered as control (Negative finding endoscopy). All of them received no treatment with no complaint of other chronic or systemic diseases; their age range was (18 to 64) years. Whole blood from patients and control individuals was collected. Serum samples were separated from the whole blood, aliquated and kept at -20ºC until used. The levels of IL-33, sST2, p-ANCA and ASCA were determined by using commercially available enzyme-linked immunosorbent assay (ELISA) kits and performed as recommended in leaflet with kits (IL-33/ Ray Bio/USA; sST2/ Critical Diagnostics/USA; p-ANCA/Cusabio/China, ASCA Kit/ Gentaur).

Statistical Analysis

Data were presented by frequency, percentage, mean, standard error, and range (minimum-maximum values). The significance of difference of different means was tested using t-test. The significance of difference of different percentages was tested using Chi-square test (χ^2-test).

RESULTS AND DISCUSSION

The demographic characteristics of patients and controls groups are presented in table 1. The present results revealed no significant differences ($p>0.05$) among the three studied groups according to age and gender. The differences in clinical parameters in patients groups are summarized in table 2. The present study revealed significant elevation ($P<0.05$) in serum levels of IL-33 in UC and CD patients as compared with control group, whereas serum level of sST2 was significantly increase in UC patients ($P<0.05$), but in CD patients there was no significant elevation when compared to control group ($p>0.05$), these findings were in accordance with the observations of the other study Pastorelli *et al*. (2010). Moreover, there were no significant differences ($p>0.05$) in the mean ratio of IL-33/ST2 in the study groups, as clearly shown in table 3. Concerning the relation between serum levels of (IL-33 and sST2) with clinical parameters, the current study revealed positive correlation between serum IL-33 and sST2 with the disease activity in UC ($P=0.41$, <0.001) respectively. As regards to disease location, IL-33 was significantly higher ($P<0.001$) in UC patients with pan-colitis (E3) as compared to those patients with E1 and E2. Meanwhile, serum level of sST2 did not show any significant differences ($p>0.05$) in UC patients with proctitis disease (E1) and left side of colon (E2) or pan-colitis (E3) as shown in table 4.

Serum IL-33 and sST2 levels were elevated in UC patients compared with controls, while anti-TNF treatment (infliximab) decreased circulating IL-33 and increased sST2, thus favorably altering the ratio of the cytokine with its decoy receptor (Pastorelli *et al*., 2010). Diaz-Jimenez *et al*. (2011) observed that the serum sST2 value was significantly higher in patients with active rather than inactive UC based on clinical, endoscopic and histo-pathological characteristics; as well as compared with non-IBD and healthy control the mean level of sST2 in CD patients was significantly higher than that of the healthy control group. So they concluded that sST2 levels correlated with disease severity are able to differentiate active from inactive UC and might have role as a biomarker. On the other hand, another study (Ajdukovic *et al*., 2010) denoted that serum concentrations of IL-33 were low or did not differ between UC patients and controls.

The variation that showed among different studies might relating to race, ethnicity, sample size, patient selection and differences in methodology. In UC, IL-33 could be released by injured epithelial cells to induce pro-inflammatory cytokines production through activation of ST2L in mast cells, macrophages, eosinophils and neutrophils (Luthi *et al*., 2009).As well as the stimulation of ST2L in dendritic cells may participate in the polarization to IL-5 and IL-13-producing Th2 cells (Rank

Table 1. Demographic characteristic in three study groups.

Demographic Parameters		Control group	UC patients	CD patients	P-value
Age (years)	Age Range	18-64	16-65	23-63	
	Age Mean ± SD	38.72±2.28	35.24± 2.09	37.71±3.04	0.522NS
Gender Type	Male	15 (60.00%)	23 (56.10%)	7 (50.00%)	0.833NS
	Female	10 (40.00%)	18 (43.90%)	7 (50.00%)	

Significant difference: ($p<0.05$).

Table 2. Clinical characteristic in patients groups.

Clinical Parameters		UC patients	CD patients
Disease behavior	Inflammatory	-	4 (29.00%)
	Stenosing	-	3 (21.00%)
	Penetrating	-	7 (50.00%)
Disease location	Proctitis disease (E1)	10 (24.39%)	-
	Left side of colon (E2)	19 (46.34%)	-
	Pan-colitis (E3)	12 (29.27%)	-
	Ileal disease (L1)	-	1 (7.14%)
	Colon (L2)	-	9 (64.29%)
	Ileocolonic (L3)	-	4 (28.57%)
Disease activity (Endoscopy grade)	Grade 1	12 (29.26%)	-
	Grade 2	16 (39.02%)	-
	Grade 3	7 (17.07%)	-
	Grade 4	6 (14.63%)	-

et al., 2009) and in basophiles the stimulation of IL-13-dependent fibrosis (Pecaric-Petkovic *et al*., 2009). The cytokines that induced by IL-33, mostly IL-13 may have injurious effects on epithelial barrier function (Heller *et al*., 2005). The effects induced by IL-33 could magnify the local inflammation, and contributing to prolongation of pathogenic inflammatory process that is characteristic of the UC (Palmer and Gabay, 2011).

The present study demonstrates a direct association between serum levels of sST2 protein and the grade of endoscopic disease activity in UC. This fact is reported by Pastorelli *et al*. (2010) and Diaz-Jimenez *et al.* (2011). They reported that serum sST2 is superior to other markers in the direct correlation with endoscopic disease activity like calprotectin which is fecal molecule reflects the intestinal damage pathology, and TNF alpha which is common inflammatory marker during inflammation. This would be helpful for the management and prognosis of IBD patients.

The use of a serum inflammation marker that reflects the intestinal damage would be helpful for the management and prognosis of IBD patients. Fecal molecules, such as calprotectin and lactoferrin, represent an inflammatory neutrophilic process of the intestinal mucosa. However, these are also non-specific markers of inflammation, which are increased in organic intestinal diseases such as diverticular disease (Tibble *et al*., 2002) polyposis (Pezzilli *et al*., 2009) and colorectal cancer (Limburg *et al*., 2003). Some biochemical properties of sST2 support its characteristic as a reliable biomarker in UC, mainly based on its stability and limited dependence on epidemiological and clinical factors, such as age, gender and diet (Dieplinger *et al*., 2010). It is possible that sST2 not only acts as a marker of UC activity; functions attributed to sST2 account for a role as an immunomodulator in inflammatory processes. At the cellular level, sST2 has been described as an inhibitor of IL-33/ST2L signaling (Hayakawa *et al*., 2007). The increase of sST2 during periods of inflammation may be involved in the control of the immune response associated with IBDs such as UC. The relation between serum sST2 and inflammatory bowel activity may be allowed, in the future, the avoidance of a colonoscopic procedure in patients that do not require it.

Other important results in the present study were the high positively of p-ANCA in UC patients and ASCA in CD patients ($p<0.001$) when compared with control group. However; this prevalence of p-ANCA was significantly higher ($p<0.001$) among UC patients when compared with CD patients, while seroprevalence of ASCA in UC patients was significantly lower ($p<0.001$) than those in CD patients (Table 5). On the other hand the correlation among immunological parameters in this study indicate that there was significant positive linear correlation between IL-33 with each of sST2 and p-ANCA ($r= 0.408$, $P= 0.008$; $r=0.355$, $P=0.023$) respectively in UC (Tables 6, 7).

Table 3. Descriptive statistics of serum IL-33, sST2 and IL-33/sSt2 ratio among studied groups.

	Control group	UC patients	CD patients	P-value (ANOVA)
Serum IL-33 (pg/ml)				
Mean± SE	15.43± 1.95	28.47±2.97	30.92±6.27	p<0.05
P (Bonferroni t-test)				
Control vs. UC <0.05*				
Control vs. CD =0.010*				
UC vs. CD =0.654NS				
Serum sST2 (ng/ml)				
Mean± SE	4.86±0.39	11.30 ±1.60	10.05±2.51	p<0.05
P (Bonferroni t-test)				
Control vs. UC =0.003*				
Control vs. CD =0.068Ns				
UC vs. CD =0.634Ns				
Serum ratio IL-33/sST2				
Mean± SE	4.32±5.61	5.43±6.19	5.08±3.54	p>0.05
P (Bonferroni t-test)				
Control vs. UC = 0.438NS				
Control vs. CD = 0.684 NS				
UC vs. CD = 0.843 NS				

Table 4. Distribution of serum IL33 and sST2 levels according clinical parameters in UC and CD patients.

Clinical parameters		UC patients		CD patients	
		IL-33	sST2	IL-33	sST2
Disease behavior	Inflammatory			24.46±8.70	7.27±2.73
	Stenosing			15.27±1.37	3.01±.95
	Penetrating			41.32±10.44	14.66±4.14
	P-value			0.234 NS	0.155 NS
Disease location	proctitis disease (E1)	14.69±1.96	8.91±3.03		
	left side of colon (E2)	25.37±3.52	12.18±2.54		
	pan-colitis (E3)	44.85±5.91	11.89±2.89		
	P-value	0.001**	0.708NS		
	ileal disease (L1)			13.40	4.90
	colon (L2)			28.31±6.81	11.81±3.56
	ileocolonic (L3)			41.19±15.90	7.39±3.51
	P-value			0.526 NS	0.661 NS
Disease activity (Endoscopy grade)	Grade 1	18.72±2.09	3.55±0.8		
	Grade 2	27.46±4.57	7.79±1.53		
	Grade 3	33.89±9.07	19.08±3.38		
	Grade 4	44.31±9.3	27.08±2.92		
	P-value	0.041*	<0.001**		

Although individually ASCA and p-ANCA tests have moderate sensitivity and specificity, the combination of these markers may be helpful in patients in whom a distinction between CD from UC is not obvious from diagnostic tools based on clinical data, endoscopic and histopathologic examination. The current study showed that p-ANCA was strongly associated with UC and ASCA with CD. The prevalence of p-ANCA in patients with UC and ASCA in CD patients was high (82.93% and 78.5%) respectively. This prevalence is comparable with those previously reported (Peeters *et al*., 2001; Conrad *et al.,* 2002; Lerner and Shoenfeld, 2002; Kaila *et al*., 2005). Elevated levels of serum p-ANCA in UC patients are believed to be caused by p-ANCA production in the colonic mucosa. ASCA is an antibody that reacts to a component of yeast commonly found in food. ASCA has been detected in serum of a majority of CD, but fewer UC patients. The origin of ASCA antibody is not clear. As well as, this study showed high specificity for serological markers; the higher specificity was found for ASCA (88%) for distinguishing CD from healthy controls, whereas p-ANCA (86%) for distinguishing UC from

Table 5. Descriptive analysis of p-ANCA and ASCA among the study groups.

		Control group	UC patients	CD patients
Serum p-ANCA	Negative	24	7	12
	%	96.00%	17.07%	85.71%
	Positive	1	34	2
	%	4.00%	82.93%	14.29%
	Sensitivity		83%	14%
	Specificity		86%	17%
Serum ASCA	Negative	23	36	3
	%	92.00%	87.80%	21.43%
	Positive	2	5	11
	%	8.00%	12.20%	78.57%
	Total	25	41	14
	Sensitivity		12%	79%
	Specificity		21%	88%

Table 6. Correlation coefficient among various parameters in UC patients.

		IL-33	sST2	pANCA	ASCA
IL-33	R	1.000	0.408	0.355	-0.097
	P	-	0.008	0.023	0.545
sST2	R	0.408	1.000	-0.098	-0.067
	P	0.008	-	0.542	0.679
p-ANCA	R	0.355	-0.098	1.000	-0.029
	P	0.023	0.542	-	0.857
ASCA	R	-0.097	- 0.067	-0.029	1.000
	P	0.545	0.679	0.857	-

Table 7. Correlation coefficient among various parameters in CD patients

		IL-33	sST2	p-ANCA	ASCA
IL-33	R	1.000	0.373	0.057	-0.123
	P		0.189	0.846	0.676
sST2	R	0.373	1.000	0.486	-0.123
	P	0.189		0.078	0.676
p-ANCA	R	0.057	0.486	1.000	-0.284
	P	0.846	0.078		0.325
ASCA	R	-0.123	-0.123	-0.284	1.000
	P	0.676	0.676	0.325	

healthy controls. However; the present results showed rather low sensitivity for two serological markers (83% for p-ANCA and 79.0% ASCA), these values are consistent with previous reports (Lerner and Shoenfeld, 2002; Kaila *et al*., 2005). These findings have shown that serological markers have accuracy in differentiating IBD from non-IBD patients and CD patients from UC patients. This is very important in day-to-day clinical practice in making decision about performing invasive diagnostic procedures like ileocolonoscopy.

The current results showed statistically non significant elevation of serum levels of IL-33 and sST2 in early diagnosed UC patients (untreated) as compared with patients on treatment (p= 0.138, p=0.202) respectively (Table 8). However, table 9 shows that the serum level of IL-33 was significantly higher in UC patients without treatment than those patients who treated with infliximab. On the other hand, the comparison between patients without treatment and patients who receive treatment other than infliximab showed non-significant differences in the level of IL-33. In addition the serum level of IL-33 was lower in treated patients with infliximab than patients on other treatments but statistically not significant. Concerning the level of sST2 according to type of treatment the comparison between patients who receive infliximab versus patients with other treatment revealed significant differences (p=0.001).

Table 8. Mean serum level of IL IL-33 and sST2 in UC patients with and without treatment.

	Early diagnosed (no treatment) n=15	On treatment n=26	P Value
IL-33	34.30±5.95	25.10±3.10	0.138
sST-2	14.01±2.78	9.73±1.93	0.202

Table 9. Mean serum level of IL33 and sST2 according to type of treatment.

	IL-33	sST-2
Early diagnosed (No treatment)	34.30±5.95	14.01±2.78
Infliximab (biological agents therapy)	15.87±2.02	20.42±3.53
Other treatment (pentasa,salazopyrin,prednisone)	28.47±4.15	5.95±1.61
ANOVA	0.109	0.002
No treatment vs Infliximab	0.036*	0.089NS
No treatment vs other treatments	0.390NS	0.022*
Infliximab vs other Treatments	0.133NS	0.001**

Depending on the current study, in total UC patients (treated and untreated) the circulating IL-33 and sST2 revealed significant increased levels as compared with control group and correlated with disease severity. Also there was statistically non-significant elevation in the serum level of IL-33 and sST2 in recently diagnosed UC patients (untreated patients) as compared with patients on treatment. In addition, the comparison between patients who receive infliximab versus patients with other drugs revealed significant differences, these results agree with other study (Pastorelli *et al*., 2010). The UC patients who treated with infliximab (anti-TNF) treatment showed decreased circulating IL-33 and increased sST2. Taken together, the IL-33/ST2 system may play an important role in UC and is modulated by anti-TNF therapy, and may represent a specific biomarker for active UC.

CONCLUSION

These results indicated that IL-33 and its receptor (sST2) might be a crucial mediator in pathogenesis of IBD. In addition, the increased levels of IL33 and sST2 correlated with disease activity of UC possibly reflect an acute-phase response due to inflammation. Also, in particular, IL-33 may regulate by TNF-α in UC.

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