İSTANBUL ÜNİVERSİTESİ YAYINEVİ

RESEARCH / ARAŞTIRMA
DOI: 10.26650/IUITFD.2020.0090
İst Tıp Fak Derg 2021 / J Ist Faculty Med 2021

THE RELATIONSHIP BETWEEN sTREM-1 AND ACTIVATION OF INFLAMMATORY BOWEL DISEASES

İNFLAMATUAR BARSAK HASTALIKLARI AKTİVASYONU İLE sTREM-1 ARASINDAKİ İLİŞKİ

Yasin KUTLU[1], İlkim Deniz TOPRAK[2], Yasemin GÖKDEN[1], Hasan ERUZUN[3], Yücel ARMAN[1], Şengül AYDIN YOLDEMİR[1], Zeki TOPRAK[4], Tufan TÜKEK[5]

[1]Sağlık Bilimleri University, Okmeydani Training and Research Hospital, Department of Internal Medicine, Istanbul, Turkey
[2]Sağlık Bilimleri University, GOP Training and Research Hospital, Department of Internal Medicine, Istanbul, Turkey
[3]Ondokuz Mayıs University, School of Medicine, Department of Gastroenterology, Samsun, Turkey
[4]Sağlık Bilimleri University, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Nephrology, İstanbul, Turkey
[5]Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medicine, Istanbul, Turkey

ORCID IDs of the authors: Y.K.0000-0003-2184-634X; İ.D.T. 0000-0002-9320-1252; Y.G. 0000-0001-6767-3072; H.E. 0000-0003-0355-1820; Y.A. 0000-0002-9584-6644; Ş.A.Y. 0000-0003-4236-1181; Z.T. 0000-0002-7411-3628; T.T. 0000-0002-4237-1163

Cite this article as: Kutlu Y, Toprak ID, Gokden Y, Eruzun H, Arman Y, Aydin Yoldemir S, et al. The relationship between sTREM-1 and activation of inflammatory bowel diseases. J Ist Faculty Med 2021;84(3):318-23. doi: 10.26650/IUITFD.2020.0090

ABSTRACT

Objective: In inflammatory bowel disease (IBD), there is no reliable biomarker, yet. We aimed to determine whether Serum Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) could be useful as a marker for the diagnosis and/or the determination of disease activity in patients with IBD.

Material and Method: A total of 47 patients with ulcerative colitis (UC) and 25 patients with Crohn's disease (CD) were prospectively enrolled. Clinical disease activity was analyzed using the Crohn's Disease Activity Index (CDAI) for CD and the Truelove-Witts index for UC.

Results: sTREM-1 levels were significantly lower in patients with IBD compared to healthy controls (p=0.001). In comparison of the levels of sTREM-1 between the different groups (CD, UC, and healthy controls) the difference was statistically significant. No considerable differences in sTREM-1 levels were determined in patients with active versus quiescent disease. The sTREM-1 levels negatively correlated with C-reactive protein, blood neutrophil-lymphocyte ratio, and positively with haemoglobin levels.

Conclusion: sTREM-1 levels are decreased in IBD patients compared with the healthy individuals. It may, therefore, be useful for the diagnosis of IBD. However, it does not seem to be a precise marker of disease activity in IBD and cannot be suggested for assessing disease activity in these patients.

Keywords: sTREM-1, inflammatory bowel diseases, Crohn's disease, ulcerative colitis

ÖZET

Amaç: İnflamatuar barsak hastalıkları (İBS) tanısında henüz uygun bir biyobelirteç bulunmamıştır. Çalışmamızda STREM-1 molekülünün bir belirteç olarak, İBS tanısında ve hastalık aktivitesini belirlemede uygunluğunu belirlemeyi amaçladık.

Gereç ve Yöntem: Toplam 47 ülseratif kolit ve 25 Crohn hastalığı tanılı vaka çalışmaya dahil edildi. Crohn hastalığı için aktiviteyi belirlemede Crohn Hastalığı Aktivite İndeksi (CDAI), ülseratif kolit için ise Truelove-Witts indeksi kullanıldı.

Bulgular: Sağlıklı grupla kıyaslandığında, sTREM-1 molekülü, İBS hastalarında anlamlı derecede düşük saptandı. Ülseratif kolit, Crohn hastalığı ve sağlıklı grup arasında sTREM-1 molekülü kıyaslandığında ise fark istatiksel olarak anlamlıydı. Aktif ve remisyonda olan hastalarda sTREM-1 düzeylerinde önemli bir fark bulunmamıştır. sTREM-1 seviyeleri C-reaktif protein, nötrofil-lenfosit oranı ve hemoglobin düzeyleri ile negatif korelasyon gösterdi.

Sonuç: sTREM-1 seviyeleri İBS'de sağlıklı bireylere göre daha düşüktür. İBS tanısı için yararlı olabilir. Ancak, İBS'de hastalık aktivitesinin belirlemede doğru bir belirteç gibi görünmemektedir ve bu hastalarda hastalığın aktivitesini değerlendirmek için önerilemez.

Anahtar Kelimeler: sTREM-1, inflamatuar barsak hastalıkları, Crohn hastalığı, ülseratif kolit

Corresponding author/İletişim kurulacak yazar: hasaneruzun@gmail.com

Submitted/Başvuru: 15.07.2020 • **Revision Requested/Revizyon Talebi:** 03.09.2020 •
Last Revision Received/Son Revizyon: 25.09.2020 • **Accepted/Kabul:** 01.11.2020 • **Published Online/Online Yayın:** 05.07.2021

INTRODUCTION

In general, inflammatory bowel disease (IBD) refers to two major diseases: Ulcerative colitis (UC) and Crohn's disease (CD). Though UC and CD have different pathologic and clinical characteristics, the exact pathogenetic mechanisms of IBDs are still not understood in detail.

The triggering receptor expressed on myeloid cells-1 (TREM-1) is a cell surface receptor expressed on monocytes/macrophages and neutrophils during acute inflammation. It is a member of the immunoglobulin superfamily (1). During inflammation, sTREM-1 is released from the membrane-bounded TREM-1. Studies have shown that bacteria such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and fungi such as *Aspergillus fumigatus* may up-regulate TREM-1 expression in the cell culture, peritoneal lavage fluid, and tissue samples obtained from infected patients (2, 3).

However, increased levels of sTREM-1 have also been reported in non-infectious inflammatory diseases such as systemic lupus erythematosus (4), acute pancreatitis (5), and chronic kidney disease (6). Thus, sTREM-1 is not only defined as a diagnostic marker for bacterial or fungal infections but also potentially a new marker for diagnosing and evaluating the severity of the disease in other inflammatory diseases.

Thus, the aims of the present study were: 1) to analyse and compare sTREM-1 levels in UC and CD patients and healthy individuals and 2) to search for an answer to the question of whether sTREM-1 could be used as a possible biomarker in IBD for the diagnosis and evaluation of disease activity.

MATERIAL AND METHODS

Patients and clinical data collection

In the gastroenterology and internal medicine departments of the University of Health Sciences Okmeydanı Training and Research Hospital, 72 outpatient or hospitalized adult patients with an estimated GFR greater than 90 (mL/min)/(1.73 m^2) and with endoscopically and histopathologically confirmed IBD (47 UC, 25 CD) were included. This study was approved by the Ethics Committee of Health Sciences University, Okmeydanı Training and Research Hospital (Date: 28.02.2017, No: 602). Sixteen healthy controls matched for age and sex with these patients were included in the study. Their disease activities were recorded [CD: clinically Crohn's Disease Activity Index (CDAI), UC: clinically Truelove-Witts index] at the time of blood collection (7, 8). Age, gender, type and duration of the disease, area of involvement of the disease in the bowel, medical treatments, and surgical operation history were recorded at the time of blood collection. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and complete blood count results were recorded.

Clinical remission in UC was defined as 1 or 2 stools per day without blood, absence of fever and tachycardia, normal hemoglobin levels, and weight gain. Active patients were categorized as mild, moderate, or severe according to the Truelove-Witts index.

For CD, active and/or inactive time points were based on the disease activity scores (active: CDAI>150 points; moderate activity: CDAI:221-450; severe activity: CDAI>450 points; inactive: CDAI≤150 points).

Measurement of sTREM-1

The serum sTREM-1 levels were analysed in all participants. Blood samples were collected from all of the participants and left to stand for 30 min at room temperature, centrifuged for 10 min at 4000 rpm, and the obtained serum was preserved at –80°C. All stored blood samples were thawed only once on the analysis day. Enzyme-linked immunosorbent assay (ELISA) kits were used with a standardized protocol.

Data analysis and statistics

The Statistical Package for Social Sciences (SPSS) version 24 was used to analyse the data. It has been determined by the Kolmogorov-Smirnov test that the data differ significantly from the normal distribution. Therefore, non-parametric methods have been used in the analysis of data. Descriptive statistics (frequency, mean, standard deviation, and minimum, maximum, median) of the variables were calculated. Significant differences were calculated using the Mann–Whitney U test and Kruskal Wallis test for continuous variables. To determine the relationship between two continuous variables, Spearman's rank correlation was used. P values of less than 0.05 were considered statistically significant.

RESULTS

Patients' characteristics

Seventy-two IBD patients (25 CD, 47 UC) and 16 healthy controls were included in the study. The detailed demographic and clinical characteristics of the study participants are presented in Table 1.

Table 1: Characteristics of IBD patients and healthy controls

	UC	CD	Control
Number of individuals (n)	47	25	16
Males	25	12	8
Age (years) (range)	49.8 (18-69)	35.8 (25-55)	42.2 (24-62)
Active/ remission (n)	28/19	19/6	
Smokers	20	15	9

The sTREM-1 levels in IBD patients and healthy controls

The patients with CD and UC were evaluated as a single disease group (IBD) and compared with healthy controls (Table 2, Figure 1). As shown in Figure 1 and Table 2, sTREM-1 levels were significantly lower in patients with IBD (mean:221±228 pg/ml) compared to healthy controls (mean:502±404 pg/ml) (p=0.001). There was also a statistically significant difference between patient and control groups regarding serum CRP (p<0.0001) and ESR (p<0.0001) levels, blood neutrophil-lymphocyte ratio (NLR) (p=0.003), platelet counts (p=0.004), and haemoglobin (p<0.0001) levels.

In comparison of the sTREM-1 levels between the different disease groups and controls (CD:mean=169±105, UC: mean=249±269 and healthy controls: mean=502±404 pg/ml) the difference was also statistically significant (p=0.004) (Table 3, Figure 2).

When using the Spearman's rank correlation to study the correlation of sTREM-1 levels with several variables (Table 4), it was found that s-TREM-1 levels negatively correlated with CRP (r=-0.387, p<0.0001) and ESR (r=-0.235, p=0.028) levels, NLR (r=-0.377, p<0.0001), platelet count (r=-0.258, p=0.015) and positively with the haemoglobin levels (r=0.300, p=0.004). There was no correlation between sTREM-1 and CDAI (p=0.57).

DISCUSSION

Fluctuating disease course is the characteristic feature of both CD and UC with active disease and remission episodes. Objective evaluation of disease activity is essential for tailoring the best treatment approach and evaluating treatment response. A trustworthy biomarker for IBD would be an extremely helpful guide for physicians.

In IBD patients, extensive efforts have been undertaken to evaluate non-invasive biomarkers and disease activity indices (2, 9, 10). Among laboratory parameters, CRP and ESR are routinely analysed, but they exhibit low specificity for IBD (2, 7). A precise laboratory biomarker that truthfully reflects the disease activity of IBD has not been defined yet. Inflammatory markers can be used as a rational marker for the IBD group where the main pathogenetic mechanism is intestinal inflammation. Therefore, the current study aimed to analyse the serum sTREM-1 levels in IBD patients in diagnosis and evaluation of disease activity. Park JJ et al. reported that the mean sTREM -1 level in healthy controls (0.6±1.4 pg/ml) was significantly lower than that of the patients with either UC (60.4±41.8 pg/

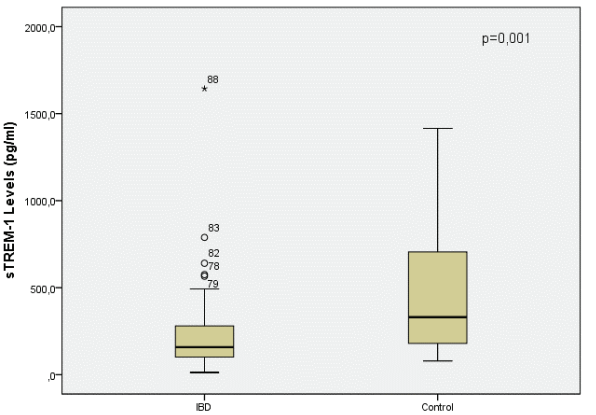

Figure 1: The distribution of sTREM-1 levels in IBD and control groups

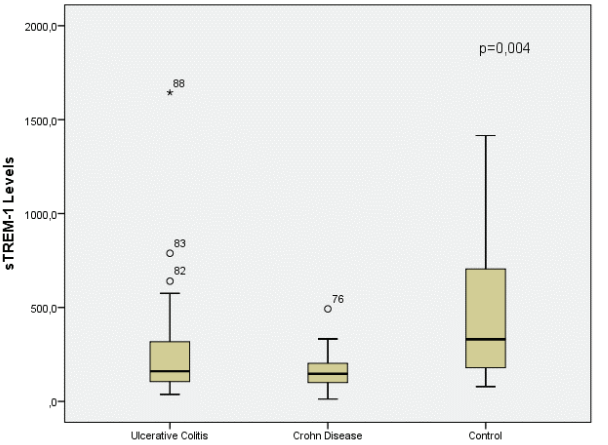

Figure 2: The distribution of sTREM-1 levels in ulcerative colitis, Crohn disease and control groups

Table 2: The distribution of sTREM-1, CRP, ESR, NLR, platelet and haemoglobin levels in active and quiescent IBD

Group	STREM-1 (pg/mL)	CRP (mg/L)	ESR (mm/s)	NLR	Platelet (10^3/uL)	Haemoglobin (g/dL)
Remission (n=25)	251±175 (12-640)	4.8±3.7 (0.3-7.7)	18±12 (2-54)	2.3±1.2 (1-7)	280±44 (201-351)	13.5±1.2 (11.7-17)
Active (n=47)	206±252 (31-1644)	42±58 (2.1-320)	40±23 (2-92)	3.3±1.6 (1.2-7.5)	390±162 (163-835)	11.1±2.3 (5.8-15.5)
p value	**0.098**	**<0.0001**	**<0.0001**	**0.003**	**0.002**	**<0.0001**

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil lymphocyte ratio

Table 3: The distribution of sTREM-1, CRP, ESR, NLR, platelet and haemoglobin levels in the CD, UC and healthy controls

Group	STREM-1 (pg/mL)	CRP (mg/L)	ESR (mm/s)	NLR	Platelet (10^3/uL)	Haemoglobin (g/dL)
Control (n=16)	502±404 (79-1415)	2.7±1.8 (0.3-7.7)	12±7.7 (1-28)	2.04±1.3 (0.9-7)	258±62 (198-342)	14.0±0.9 (12.9-14.9)
IBD (n=72)	221±228 (12-1644)	29±50 (1.3-320)	32 ± 22 (2-92)	2.9±1.6 (1–7.5)	352±143 (163-835)	11.9±2.2 (5.8–17.1)
UC (n=47)	249±269 (37-1644)	18.9±29.7 (1.3-138)	27±20 (2-92)	2.6±1.2 (1–6.5)	352±152 (202-835)	12.1±2.4 (5.8–17.1)
CD (n=25)	169±105 (12.5-492)	48.2±71.2 (2.1-320)	42±25 (6-84)	3.5±2.0 (1.24-7.5)	351±129 (163-617)	11.6±2.0 (8.0-14.5)
p value	0.004	<0.0001	<0.0001	0.003	0.016	0.001

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil lymphocyte ratio

Table 4: The correlation of sTREM-1 levels with CRP, ESR, NLR, platelet and haemoglobin

STREM-1 (pg/mL)	CRP (mg/L)	ESR (mm/s)	NLR	Platelet (10^3/uL)	Haemoglobin (g/dL)
Correlation coefficient	-0.387	-0.235	-0.377	-0.258	0.300
p value	<0.0001	0.028	<0.0001	0.015	0.004

ml) or CD (66.5±42.4 pg/ml) of the) (11). Similarly, Tzivras M et al. reported that sTREM-1 values in healthy individuals (53.31±32.93) were significantly lower than that of the CD (735.10±197.17) and UC (435.82±279.71) group. Interestingly, in the same study, it was also reported that the sTREM-1 concentrations were significantly lower in patients with moderately active CD (CDAI 150-400) (16.03±4.19), remission of CD (4.91±3.21), remission of UC (7.09±4.9), and with mildly active UC (18.91±15) than the healthy control group (10). Also in a study by Billioud V et al. the sTREM-1 level was higher in the CD group than that of the healthy controls (12). Some other recent studies indicate that sTREM-1 levels were nearly undetectable in healthy controls (13, 14).

In our study, we conversely detected significantly lower levels of sTREM-1 in the plasma of IBD patients than in the matched healthy controls. However, we should state that our study's sample size was higher than that of the three other previous studies. Similarly, Bouchon A et al. have shown that TREM-1 was not up-regulated in patients with non-infectious inflammatory diseases caused by immune complexes such as psoriasis, ulcerative colitis, or vasculitis. However, the expression of TREM-1 was up-regulated on neutrophils and monocytes both in cell culture and tissue samples obtained from the patients in the presence of bacterial infections (15). The cause of this discrepancy among the studies is unclear, but it may be because of the different sTREM-1 quantification techniques used in different studies or cross-reactivity with other immunoglobulins. Also, the expression of TREM 1 may vary between races. Moreover, high numbers of bacteria within intestinal mucus have been associated with IBD (16). The fact that the group of patients with severe activation is less in our study (29/72) may have resulted in lower intestinal bacterial overload. So, unlike other studies, we may find the sTREM-1 levels lower in the patients.

Furthermore, we found CRP, ESH, NLR, haemoglobin, and platelet counts statistically significantly different between the groups. The levels of sTREM-1 in UC and CD patients separately were also significantly lower than the healthy individuals.

From this point of view, the data presented here demonstrate that sTREM-1, which acts as a negative acute phase reactant, may be useful for the diagnosis of IBD.

The innate immune system is composed of myeloid-derived cells (neutrophils, monocytes, dendritic cells, and macrophages), natural killer cells, and innate lymphoid cells. These cells, express pattern recognition receptors, which bind stereotypic microbial products. In combination, these cells provide the initial response to either pathogenic or commensal micro-organisms. sTREM-1 may have a role in regulating the responsiveness to the intestinal flora. However, there is currently insufficient data to assess this role. Further studies are needed. But, based upon the results of recent studies and the current study, conditions such as sepsis may increase the STREM-1 levels to manage the bacterial response, but it may not increase in IBD because of the possible defective

function of the sTREM-1 molecule. Another point of view is that sTREM-1 could be suppressed in IBD because of the activation of other proinflammatory pathways.

Moreover, Billoud V et al. reported that sTREM-1 was neither correlated with CDAI nor with CRP. Also, there was no significant difference in sTREM-1 levels between the active and remission groups. So, Billioud et al. concluded that plasma sTREM-1 does not seem to be a precise marker of disease activity in CD and cannot be suggested for analysing disease activity in these patients (12). In our study, when sTREM-1 levels in active and remission groups were compared, the mean of the sTREM -1 levels in the active group was lower, but unfortunately this trend did not reach statistical significance. There was a significant difference between the other inflammatory markers (CRP, ESR, NLR, Haemoglobin, and Platelet counts). This finding suggests that while sTREM-1 may be useful as a negative acute phase reactant in IBD diagnosis, we concluded that sTREM-1 does not seem to be a precise marker of disease activity in IBD and cannot be suggested for analysing disease activity in these patients. Serum sTREM-1 levels were negatively correlated with *CRP*, ESR, NLR, platelet levels, and positively correlated with haemoglobin levels.

Another possible explanation about the lower sTREM-1 levels in the patients involves the pathophysiological mechanisms. In the pathophysiology of IBD, massive neutrophil infiltration is involved and the degree of neutrophil migration into intestinal crypts correlates with the mucosal injury and the patients' symptoms. Moreover, migrated neutrophiles have been concerned in the impairment of epithelial barrier function, tissue destruction, and the maintenance of inflammation by the release of inflammatory mediators (17). Soluble TREM-1 could have been measured lower because of the neutrophil adhesion and also migration to the tissue, even if TREM-1 levels were higher in IBD patients.

Another issue we need to mention is that in UC, the oxidative injury theory is one of the pathogenic mechanisms. TREM-1 is expressed on neutrophils and its engagement stimulates rapid degranulation of neutrophiles and oxidative burst; thus sTREM-1 could more exactly show the disease activity in UC than CD(11). Hence, in our study higher sTREM-1 levels were found in UC (mean=249, range=37-1644) compared with CD (mean:169, range=12.5-492). However, the difference was not statistically significant (p=0.504). If the sample size was larger, this difference could be significant.

Limitations of the study

Our study has some limitations. Firstly, our study is limited by its small sample size. Most probably, because of this small sample size, we were unable to display any associations between serum sTREM-1 levels and activity scores. A larger cohort study is warranted to confirm our data. Secondly, this study was not aimed at elucidating the pathophysiological pathways of sTREM-1 regulation in IBD but was rather designed to evaluate its possible clinical significance in IBD. Third, by choosing a cross-sectional design we cannot rule out excess circulating sTREM-1 as a consequence rather than the driving factor. Fourth, our results were obtained in samples from Turkish people and should be investigated in other ethnic groups. Finally, we did not examine whether the sTREM-1 level could be a predictor of future relapse or not.

CONCLUSION

In conclusion, our results indicate that the sTREM-1 levels are down-regulated in the serum of IBD patients compared with healthy controls. The sTREM-1 drew attention as a negative acute phase reactant, in the current study. The presence of a negative correlation with CRP suggests that this molecule can be used as a negative acute phase reactant, especially in non-bacterial inflammatory diseases. However, it does not appear to be an accurate marker of disease activity in IBD and cannot be recommended for assessing disease activity in these patients. Further larger-scale studies of sTREM-1 in diverse clinical spectrums of IBD patients are warranted.

Ethics Committee Approval: This study was approved by the Ethics Committee of Health Sciences University, Okmeydanı Training and Research Hospital (Date: 28.02.2017, No: 602).

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Y.K., Y.G.; Data Acquisition- Y.K., Z.T.; Data Analysis/Interpretation- İ.D.T., H.E., Y.A., T.T.; Drafting Manuscript- Y.K., İ.D.T., Y.G.; Critical Revision of Manuscript- H.U., Y.A., Z.T., T.T.; Final Approval and Accountability- Y.K., İ.D.T., Y.G., H.E., Y.A., Ş.A.Y.,Z.T., T.F.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Etik Komite Onayı: Bu çalışma için etik komite Sağlık Bilimleri Üniversitesi, Okmeydanı Eğitim ve Araştırma Hastanesi Etik Kurulu'ndan alınmıştır (Tarihi: 28.02.2017, No: 602).

Bilgilendirilmiş Onam: Katılımcılardan bilgilendirilmiş onam alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Çalışma Konsepti/Tasarım- Y.K., Y.G.; Veri Toplama- Y.K., Z.T.; Veri Analizi/Yorumlama- İ.D.T., H.E., Y.A., T.T.; Yazı Taslağı- Y.K., İ.D.T., Y.G.; İçeriğin Eleştirel İncelemesi- H.U., Y.A.,

Z.T., T.T.; Son Onay ve Sorumluluk- Y.K., İ.D.T., Y.G., H.E., Y.A., Ş.A.Y.,Z.T., T.F.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

REFERENCES

1. Bouchon A, Dietrich J, Colonna M. Cutting edge: inflammatory responses can be triggered by TREM-1, a novel receptor expressed on neutrophils and monocytes. J Immunol 2000;164(10):4991-5. [CrossRef]
2. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut 2006;55(3):426-31. [CrossRef]
3. Scaldaferri F, Fiocchi C. Inflammatory bowel disease: progress and current concepts of etiopathogenesis. J Dig Dis 2007;8(4):171-8. [CrossRef]
4. Bassyouni IH, Fawzi S, Gheita TA, Bassyouni RH, Nasr AS, El Bakry SA, et al. Clinical Association of a Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) in Patients with Systemic Lupus Erythematosus. Immunol Invest 2017;46(1):38-47. [CrossRef]
5. Liu M, Wu W, Zhao Q, Feng Q, Wang W. High expression levels of Trigger Receptor Expressed on Myeloid Cells-1 on neutrophils associated with increased severity of acute pancreatitis in mice. Biol Pharm Bull 2015;38(10):1450-7. [CrossRef]
6. Essa ES, Elzorkany KM. sTREM-1 in patients with chronic kidney disease on hemodialysis. APMIS 2015;123(11):969-74. [CrossRef]
7. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70(3):439-44. [CrossRef]
8. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J 1955;2(4947):1041-8. [CrossRef]
9. Desai D, Faubion WA, Sandborn WJ. Review article: biological activity markers in inflammatory bowel disease. Aliment Pharmacol Ther 2007;25(3):247-55. [CrossRef]
10. Tzivras M, Koussoulas V, Giamarellos-Bourboulis EJ, Tzivras D, Tsaganos T, Koutoukas P, et al. Role of soluble triggering receptor expressed on myeloid cells in inflammatory bowel disease. World J Gastroenterol 2006;12(21):3416-9. [CrossRef]
11. Park JJ, Cheon JH, Kim BY, Kim DH, Kim ES, Kim TI, et al. Correlation of serum-soluble triggering receptor expressed on myeloid cells-1 with clinical disease activity in inflammatory bowel disease. Dig Dis Sci 2009;54(7):1525-31. [CrossRef]
12. Billioud V, Gibot S, Massin F, Oussalah A, Chevaux JB, Williet N, et al. Plasma soluble triggering receptor expressed on myeloid cells-1 in Crohn's disease. Dig Liver Dis 2012;44(6):466-70. [CrossRef]
13. Radsak MP, Taube C, Haselmayer P, Tenzer S, Salih HR, Wiewrodt R, et al. Soluble triggering receptor expressed on myeloid cells 1 is released in patients with stable chronic obstructive pulmonary disease. Clin Dev Immunol 2007;2007:52040. [CrossRef]
14. Yasuda T, Takeyama Y, Ueda T, Shinzeki M, Sawa H, Takahiro N, et al. Increased levels of soluble triggering receptor expressed on myeloid cells-1 in patients with acute pancreatitis. Crit Care Med 2008;36(7):2048-53. [CrossRef]
15. Bouchon A, Facchetti F, Weigand MA, Colonna M. TREM-1 amplifies inflammation and is a crucial mediator of septic shock. Nature 2001;410(6832):1103-7. [CrossRef]
16. Schultsz C, Van Den Berg FM, Ten Kate FW, Tytgat GN, Dankert J. The intestinal mucus layer from patients with inflammatory bowel disease harbors high numbers of bacteria compared with controls. Gastroenterology 1999;117(5):1089-97. [CrossRef]
17. Brazil JC, Louis NA, Parkos CA. The role of polymorphonuclear leukocyte trafficking in the perpetuation of inflammation during inflammatory bowel disease. Inflamm Bowel Dis 2013;19(7):1556-65. [CrossRef]