Soluble ST2: A new and promising activity marker in ulcerative colitis

David Díaz-Jiménez, Lucía E Núñez, Caroll J Beltrán, Enzo Candia, Cristóbal Suazo, Manuel Álvarez-Lobos, María-Julieta González, Marcela A Hermoso, Rodrigo Quera

AIM: To correlate circulating soluble ST2 (sST2) levels with the severity of ulcerative colitis (UC) and serum levels of pro-inflammatory cytokines, and to demonstrate the predictive power of sST2 levels for differentiation between active and inactive UC.

METHODS: We recruited 153 patients: 82 with UC, 26 with Crohn’s disease (CD) and 43 disease controls (non-inflammatory bowel disease (IBD)). Subjects were excluded if they had diagnosis of asthma, autoimmune diseases or hypertension. The serum levels of sST2 and pro-inflammatory cytokines [pg/mL; median (25th-75th)] as well as clinical features, endoscopic and histological features, were subjected to analyses. The sST2 performance for discrimination between active and inactive UC, non-IBD and healthy controls (HC) was determined with regard to sensitivity and specificity, and Spearman’s rank correlation coefficient (r). To validate the method, the area under the curve (AUC) of receiver-operator characteristic (ROC) was determined (AUC, 95% CI) and the total ST2 content of the colonic mucosa in UC patients was correlated with circulating levels of sST2.

RESULTS: The serum sST2 value was significantly higher in patients with active [235.80 (90.65-367.90) pg/mL] rather than inactive UC [33.19 (20.04-65.32) pg/mL], based on clinical, endoscopic and histopathological characteristics, as well as compared with non-IBD and HC (P < 0.001). The median level of sST2 in CD patients was 54.17 (35.02-122.0) pg/mL, significantly higher than that of the HC group only (P < 0.01). The cutoff was set at 74.87 pg/mL to compare active with inactive UC in a multicenter cohort of patients. The AUC of the ROC curve to assess the ability of this molecule to discriminate between active vs inactive UC was 0.92 (0.86-0.97, P < 0.0001). The serum levels of sST2 in patients with UC significantly correlated with endoscopic and histo-
INTRODUCTION

Inflammatory bowel diseases (IBDs) belong to the group of chronic diseases that cause intestinal inflammation. Ulcerative colitis (UC) and Crohn’s disease (CD) are the two most important diseases in this group. Their characteristics are mainly episodes of active inflammation or remission. In order to provide a differential diagnosis of these diseases, it is necessary to know the clinical, endoscopic, histological, radiologic and serologic characteristics, as well as their course throughout time.

Currently, classifications of IBD are based on epidemiologic (age, gender, race), clinical (activity rate, localization and phenotype) and genetic [single nucleotide polymorphism (SNP)] parameters, and the presence of biological markers. However, due to the high percentage of non-classifiable IBD (10%-15%) and the difficulty of a differential diagnosis, it has become necessary to search for new markers for these diseases.

One ideal characteristic of an IBD biomarker is the ability to identify individuals at risk of developing the disease, detect the activity, monitor the effect of the treatment and, finally, have a prognostic value for the reactivation of the disease. Current biomarkers for IBD include serological levels of specific antibodies (ASCA, ANCA, anti-OmpC, anti-Chir, anti-glycans), serum (CRP and cytokines) and fecal proteins (calprotectin and lactoferrin). Nevertheless, the majority of these markers show a low sensitivity and/or specificity, and they cannot reflect the real intestinal damage.

In this context, sST2 protein has recently been identified as a new and reliable biomarker of heart failure. High serum levels of sST2 have been described in patients with chronic inflammatory diseases, such as autoimmune diseases and asthma.

ST2 belongs to the interleukin (IL)-1R super-family, is coded in human chromosome 2 and is expressed as two splice variants: one membrane bound, ST2L, which is a receptor of IL-33; and a soluble protein, sST2.

Recently, in our laboratory, we have described for the first time increased levels of sST2 in serum and total ST2 in the colon in UC patients, and in another cohort of UC patients whether serum sST2 and intestinal total ST2 levels correlate with the severity of the disease, based on endoscopic and histological activity rates, and with serum levels of pro-inflammatory cytokines.

BIOMARKER

sST2 belongs to the IL-33/ST2 system. ST2 is a chemoattractant that is secreted by T cells and may be involved in the recruitment of T cells to the inflammatory site. ST2 can be found as a membrane-bound receptor (ST2L) or as a soluble protein (sST2), which is a ligand for IL-33. ST2 is expressed in various immune cells, such as T cells, macrophages, and dendritic cells, and is involved in the regulation of immune responses.

sST2 has been shown to play a role in the development of IBD, and to be correlated with disease severity and activity. It has been suggested that sST2 levels are increased in IBD patients compared to healthy controls, and that these levels are correlated with disease activity.

CONCLUSION: sST2 levels correlated with disease severity and inflammatory cytokines, are able to differentiate active from inactive UC and might have a role as a biomarker.

© 2011 Baishideng. All rights reserved.

Key words: Inflammatory bowel disease; Ulcerative colitis; Soluble ST2; Biomarkers

Peer reviewers: Dr. Christoph Reichel, Priv.-Doz., Head of the Gastroenterological Rehabilitation Center Bad Brückenau, Clinic Hartwald, German Pension Insurance Federal Office, Schlüchterner Str. 4, 97769 Bad Brückenau, Germany; Dr. Takayuki Yamamoto, Department of Inflammatory Bowel Disease Center, Yokkaichi Social Insurance Hospital, 10-8 Hazuyamacho, 510-0016 Yokkaichi, Japan

Díaz-Jiménez D, Núñez LE, Beltrán CJ, Candia E, Suzuo C, Álvarez-Lobos M, González MJ, Hermoso MA, Quera R. Soluble ST2: A new and promising activity marker in ulcerative colitis. World J Gastroenterol 2011; 17(17): 2181-2190. Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i17/2181.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i17.2181
Exclusion criteria were: non-classifiable inflammatory disease, indeterminate colitis, infectious ileocolitis, asthma, history of autoimmune diseases, celiac disease and hypertension.

Patients were grouped based on endoscopic and histological criteria: Group UC \((n = 84)\) and CD \((n = 26)\), and non-IBD controls (irritable bowel syndrome, colorectal cancer, family history of colorectal cancer, diverticular disease and chronic diarrhea; \(n = 43)\). In addition, a group of healthy subjects \((n = 40,\) between 18 and 45 years old) was included to determine reference levels of sST2.

A 5 mL blood specimen was obtained from each patient, and 3 to 4 biopsies were immediately frozen in liquid nitrogen and stored at -80°C until analysis. From the healthy subjects, only a blood sample was obtained for analysis.

In the case of UC, endoscopic activity was determined in the most swollen area using the endoscopic Mayo Score\(^{[37]}\). In the case of CD, clinical activity was determined according to the Harvey-Bradshaw Index (HBI)\(^{[38]}\), and for endoscopic activity, we used the Simple Endoscopic Score for Crohn’s Disease (SES-CD)\(^{[39]}\). Histopathological score was used for the evaluation of intestinal inflammation in both diseases. Each biopsy was graded on a scale of 0-3 (0 = normal; 1 = mild; 2 = moderate; 3 = severe and included those patients with active ulceration) according to Gomes et al\(^{[40]}\).

**Quantification of serum sST2 and total intestinal ST2 levels**

Levels of sST2 and total intestinal ST2, in serum and protein extract of colonic mucosa, respectively, were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit for human ST2 (DuoSet, R&D Systems, Minneapolis, MN, USA) according to the manufacturer’s instructions. Serum samples obtained from 5 mL of blood were subjected to a treatment with protein A/G PLUS-Agarose (Santa Cruz Biotechnology, Santa Cruz, CA, USA). Protein extracts were obtained from each sample by homogenization using a lysis buffer supplemented with a protease inhibitor cocktail (Complete Mini, Roche Diagnostics, Basel, Switzerland) and subsequent disruption by sonication. Levels of total intestinal ST2 were adjusted to the total protein concentration determined by Bradford protein assay. All samples were analyzed in duplicate and each determination was expressed in pg/mL. The detection limit of the technique, provided by the kit’s manufacturer, is 20 pg/mL.

**Measurement of serum inflammatory cytokines**

Serum levels of IL-33 (Apotech, Geneva, Switzerland), IL-6 (Human IL-6 ELISA Ready-Set-Go, eBioscience, San Diego, CA, USA) and tumor necrosis factor (TNF)-α (Human TNF-α ELISA Ready-Set-Go, eBioscience) were measured using an ELISA kit, according to the manufacturer’s instructions. The detection limits provided by the kit manufacturers are 5 pg/mL, 2 pg/mL and 4 pg/mL for IL-33, IL-6 and TNF-α, respectively. Samples were prepared as previously described for ST2 determination.

**Statistical analysis**

Data were analyzed using the statistical software GraphPad Prism4 (La Jolla, CA) and are presented as average ± SD for variables with a normal distribution, and as a median (25th-75th) in the case of non-parametric distributions. Differences and significances among analyzed groups were established by multiple comparisons using the non-parametric Kruskal-Wallis tests. Further comparisons of individual groups vs control were performed by using Bonferroni-Dunn statistics and a 5% significance level. Sensitivity and specificity for levels of sST2, and their respective confidence intervals of 95%, were calculated according to endoscopic activity and compared to a non-inflammatory condition. The best cut-off value for sST2 that discriminated between inactive UC and active UC patients and the different levels of endoscopic activity was determined by area under the curve (AUC). Uni and bivariate analyses were carried out to determine the risk factors associated with each one of the following demographic and clinical parameters: gender, age, extent of the disease and medication at endoscopy. The associations between serum levels of sST2 and total intestinal ST2, and serum cytokines, were analyzed using Spearman’s rank correlation coefficient \((r)\). For each statistical test that was used, values of \(P \leq 0.05\) were considered significant.

**RESULTS**

**Main characteristics of IBD patients**

During the study period, a total of 153 patients were recruited. Of these, 84 (54.9%) corresponded to UC, 26 (16.9%) to CD and the other 43 (28.1%) to non-IBD controls. Table 1 summarizes the main characteristics of IBD patients following the Montreal classification and also indicates gender and age distribution among groups, as well as medication at endoscopy. At the time of the procedure, 40 UC (47.6%) and 12 CD patients (46.1%) were active according to endoscopic Mayo and SES-CD criteria, respectively.

**Determination of reference levels and cut-off value for sST2 in patients with IBD**

The reference level of sST2 in serum, determined in the healthy subject group (HC), was 32.40 (19.00-49.00) pg/mL; in the case of the non-IBD, CD and UC groups, levels were 46.33 (26.00-74.66) pg/mL, 54.17 (35.02-122.0) pg/mL and 67.59 (30.78-199.1) pg/mL, respectively, with significant differences \((P < 0.001)\) between UC vs HC and CD vs HC (Figure 1A). Due to the low number of patients with each of the CD phenotypes, such as inflammatory, penetrating and stenosing, we decided to focus on the analysis of sST2 levels restricted to the group of UC patients. Analysis of the levels of sST2 in the serum of the UC group, according to the Mayo Score of endoscopic activity (active ≥ 2) resulted in concentrations of...
Levels of sST2, IL-33, TNF-α and IL-6 in serum and their correlation with disease activity

The range of serum sST2 concentrations for the different UC sub-groups, according to endoscopic Mayo score, is shown in Figure 2 and Table 3. Significant differences were observed among groups with moderate (Score 2) and severe activity (Score 3) compared to inactive (Score 0) and mild activity (Score 1) sub-groups ($P<0.001$) (Figure 2A). Regarding the histopathological compromise of the mucosa, the serum sST2 levels were significantly higher in the severe (Score 3) and moderate (Score 2) inflammation groups compared to both normal (Score 0) and mild (Score 1) sub-groups ($P<0.001$ and $P<0.01$, respectively) (Figure 2B). Endoscopic and histopathological scores directly correlated with serum sST2, with $r=0.76$ and $r=0.67$, respectively (Table 3).

Levels of serum TNF-α in the different UC sub-groups were directly proportional to endoscopic and histopathological scores. When comparing serum sST2 and cytokine levels, only TNF-α significantly correlated, both
with endoscopic \((r = 0.69, P < 0.0001)\) and histopathological scores \((r = 0.61, P < 0.0001)\) (Table 3).

Uni and bivariate analyses of serum levels of sST2, with reference to demographic and clinical parameters such as age, gender, localization of the disease and medication at the endoscopy for each one of the analyzed groups, are shown in Table 4. In addition to the activity score, significant differences were observed for localization \((P = 0.0061)\) and medication \((P = 0.0067)\) of the UC group (Table 4). These results show the same trend observed in Figure 2A and B, based on endoscopic and histopathological scores, regarding gender \((P < 0.0001)\), localization \((P < 0.0001)\) and medication with 5-aminosalicylic acid (5-ASA) \((P = 0.0005)\) (data not shown). These findings demonstrate that ST2 values exclusively depend on the severity of the disease.

**Levels of total intestinal ST2 correlate with disease activity scores and serum levels of sST2 in UC patients**

In order to determine if the findings observed at the systemic level reflect the local damage, total intestinal ST2 was measured in colonic mucosa. Similarly to the serum sST2 levels, total intestinal ST2 levels in UC are closely distributed to activity endoscopic \((P < 0.0001)\) (Figure 2C) and histopathological score \((P < 0.0001)\) (Figure 2D). Significant differences were observed between moderate and severe activity sub-groups compared to inactive and mild (Figure 2C and D). Similarly, total intestinal ST2 levels significantly correlated with endoscopic \((r = 0.62, P < 0.0001)\) and histopathological scores \((r = 0.60, P < 0.0001)\) (Table 3), as seen for serum sST2 levels (Figure 2A and B).

Furthermore, serum sST2 levels and total intestinal ST2 directly correlate, according to endoscopic Mayo activity score, in the severe \((r = 0.82, P = 0.0027)\), moderate \((r = 0.59, P = 0.0020)\) and mild \((r = 0.44, P = 0.0045)\) sub-groups (Figure 3).

**DISCUSSION**

Our group first reported that the ST2/IL-33 system, described in other inflammatory diseases, could be involved in the pathogenesis of IBD, because levels of ST2 and IL-33 in IBD patients were higher than in healthy subjects.
Figure 2 Analysis of serum sST2 and total intestinal ST2 levels in ulcerative colitis patients according to endoscopic and histopathological activity. Distribution of serum sST2 and total intestinal ST2 levels in ulcerative colitis (UC) patients according to the 4 rank Endoscopic Mayo Activity Score (A and C) (Activity: 0 = inactive; 1 = mild; 2 = moderate; 3 = severe) and histopathological score (B and D) (Degree of inflammation: 0 = normal; 1 = mild; 2 = moderate; 3 = severe with active ulceration). Data are represented as median and percentiles (25th-75th). Serum sST2 levels are significantly different among UC patient sub-groups of moderate and severe activity in relation to inactive and mild activity, independent of the score used. Total intestinal ST2 levels directly correlate with endoscopic activity (C) and degree of mucosal inflammation (D). A: \( P < 0.001 \), vs 0 and 1; B: \( P < 0.01 \), 2 vs 0 and 1; C: \( P < 0.001 \), 2 vs 0 and 1; D: \( P < 0.001 \), 2 vs 1; \( P < 0.001 \), vs 0 and 1.

Table 4 Baseline serum sST2 levels according to clinical characteristics of patients

| Clinical Characteristic       | Serum sST2 (pg/mL), median (Percentiles 25th-75th) |
|------------------------------|---------------------------------------------------|
|                              | UC                       | Non-IBD                  | HC                        |
| Gender                       |                         |                         |                           |
| Female                       | 55.5 (29.3-150.1)        | 43.9 (22.1-73.1)         | 29.4 (17.0-40.3)          |
| Male                         | 99.7 (34.0-216.4)        | 59.7 (35.6-74.9)         | 36.2 (27.0-53.2)          |
| Age (yr)                     |                         |                         |                           |
| 18-24                        | 190.8 (52.6-489.6)       | 63.2 (31.7-74.9)         | 29.0 (17.0-45.0)          |
| 25-34                        | 66.2 (30.4-313.3)        | 46.3 (18.5-116.6)        | 32.4 (16.9-40.8)          |
| 35-44                        | 125.4 (37.0-182.9)       | 48.1 (32.2-67.8)         | 44.3 (27.9-59.6)          |
| 45-54                        | 48.2 (24.9-116.4)        | 43.6 (26.0-72.4)         | 51.0 (35.7-65.0)          |
| ≥ 55                         | 51.3 (19.9-90.5)         | 53.0 (25.9-78.8)         | 0                         |
| Location of disease          |                         |                         |                           |
| Ulcerative proctitis, E1     | 56.5 (22.4-141.6)        | 35.8 (19.4-66.2)         |                           |
| Left-sided colitis, E2       | 35.8 (19.4-66.2)         | 35.8 (19.4-66.2)         |                           |
| Extensive colitis, E3        | 110.2 (34.0-345.8)       | 110.2 (34.0-345.8)       |                           |
| Medication at endoscopy      |                         |                         |                           |
| No medication                | 36.4 (19.6-105.6)        | 39.7 (20.4-75.7)         |                           |
| Topical 5-ASA                | 59.0 (23.6-141.7)        |                           |                           |
| Systemic 5-ASA               | 242.4 (124.9-349.1)      |                           |                           |
| Systemic steroids            | 125.4 (50.0-417.9)       |                           |                           |
| S-ASA + steroids             | 41.1 (68.9-109.0)        |                           |                           |
| Azathioprine                 | 0                       |                           |                           |

\( P < 0.05 \) vs other groups in the analysis. UC: Ulcerative colitis; HC: Healthy subjects; IBD: Inflammatory bowel disease; S-ASA: S-aminosalicylic acid derivatives.
degree of inflammation. Alternatively, sST2 would allow, as happens with fecal calprotectin, the differentiation between UC and functional diseases, such as irritable bowel syndrome, chronic diarrhea and abdominal pain. Many studies have shown that calprotectin significantly correlates with endoscopic and histological activity scores in CD and UC patients. Calprotectin level decreases during clinical remission, which could be related to endoscopic mucosal healing and consequently is considered a predictor of IBD reactivation. Serum sST2 levels allow for the differentiation between active and inactive UC with a high sensitivity and specificity. The cut-off value determined (74.87 pg/mL) permits the differentiation between active and inactive UC patients, as well as healthy subjects.

Similarly to fecal calprotectin, serum sST2 levels from UC patients significantly correlated with endoscopic (r = 0.76), as well as histopathological score (r = 0.67). Serum IL-33 level, another of the cytokines evaluated, did not show a direct relationship with disease activity; this might be due to the low levels detected compared to sST2, despite being the specific ligand of ST2. Serum sST2 levels in UC patients correlate with activity scores comparable with TNF-α, a commonly used serum inflammation marker. These characteristics result in the proposition of sST2 as an appropriate marker of inflammatory activity degree in UC. However, correlation of serum sST2 levels has to be achieved with other activity biomarkers previously associated with IBD, such as CRP or calprotectin.

In the case of CD patients, the analysis of serum sST2 values showed similar tendencies to those in UC, in relation to control patients (Figure 1A). The low incidence of CD in Chile, in addition to the exclusion criteria used in our study, account for the low number of CD patients included. Future studies will allow us to determine the association of sST2 with the inflammatory, stenosing and penetrating phenotypes of CD so as to support the concept that sST2 may also be applicable as a biomarker in CD.

Recently, sST2 has been described as a biomarker for heart failure, as serum levels correlate with hemodynamic variables, cardiac damage (BNP and pro-BNP) and inflammatory markers (CRP). In those studies, serum sST2 levels increase after myocardial infarction, hence patients with a history of cardiopathies and hypertension were excluded. In addition, 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.

In our study, serum sST2 levels in healthy subjects were similar to those described previously [32.4 (19-49) pg/mL vs 49 (4-89) pg/mL]. In addition, serum sST2 levels were higher in males than in females, and slightly increased between 18 and 24 years in age, as previously described. However, when considering serum sST2 levels together with endoscopic activity, adjusted by gender, the distribution remained the same; therefore, we conclude that sST2...
levels do not depend on these factors. Therapeutic strategies for IBD patients are determined according to severity and localization of the affected area. UC patients with pancolitis presented higher serum sST2 levels in relation to proctitis or left-sided colitis. UC patients receiving systemic corticoids showed an increased sST2 level when compared to other treatments. Due to the low number of patients, we were not able to determine whether corticoids affect the sST2 concentration and its correlation with activity scores. However, in UC patients, ST2 levels did not show an association with mesalazine (5-ASA) treatment and in those patients ST2 levels follow activity degree of the disease. One of the most important qualities of a biomarker is that it has to be used in clinical practice and not be affected by drug therapy\(^{[59,60]}\). One of the main limitations of calprotectin as an IBD marker is the influence of non-steroidal anti-inflammatory drugs on its level, as previously shown\(^{[59,60]}\). In our study, 66.3\% of IBD patients were receiving 5-ASA treatment, so measurement of calprotectin in those patients may be inconclusive.

Total ST2 levels in the colonic mucosa of UC patients significantly correlated with endoscopic and histopathological activity scores. In addition to the fact that total intestinal ST2 levels are directly associated with serum sST2 levels, these findings verify it as a new and promising UC activity biomarker. The relation between serum sST2 and inflammatory bowel activity would allow, in the future, the avoidance of a colonoscopic procedure in patients that do not require it. Association studies between ST2 and other biomarkers, such as calprotectin, may confirm its use.

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\(^{[65,66]}\), which causes polarization of naive T cells into Th2, and further, the production of IL-5 and IL-13 that are associated with UC\(^{[61,62]}\). On the other hand, ST2L activation with IL-33 stimulates TNF-\(\alpha\), IL-6 and IL-8 secretion in mast cells\(^{[63,64]}\) and, together with IgE, stimulates degranulation\(^{[65]}\). The increase of sST2 during periods of inflammation may be involved in the control of the immune response associated with IBDs such as UC.

In summary, we demonstrated that serum sST2 levels allow for the effective differentiation between the endoscopic activity degrees of UC. Determining whether serum sST2 levels could have any prognostic value for UC (and possibly for CD), whether sST2 levels could monitor the treatment impact on endoscopic mucosal healing, and whether they could predict the risk of complications in IBD course or need of surgery, are some of the questions that should be answered by further studies.

**ACKNOWLEDGMENTS**

We acknowledge the help of C Heine, F López-Kostner and C Figueroa in sample collection and thank D Waissbluth for helping in collection of data.

**REFERENCES**

1. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med 2009; 361: 2066-2078
2. Arnott ID, Nimmo ER, Drummond HE, Fennell J, Smith BR, MacKinlay E, Morecroft J, Anderson N, Kelleher D, O’Sullivan M, McManus R, Satsangi J. NOD2/CARD15, NOD2/CARD15, NOD2/CARD15, NOD2/CARD15, NOD2/CARD15, NOD2/CARD15, NOD2/CARD15, NOD2/CARD15. Gut 2006; 55: 749-753
3. Cho JH. Inflammatory bowel disease: genetic and epidemiologic considerations. World J Gastroenterol 2008; 14: 338-347
4. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006; 55: 749-753

**COMMENTS**

**Background**

Inflammatory bowel diseases (IBDs) belong to the group of chronic diseases that cause intestinal inflammation. Ulcerative colitis (UC) and Crohn’s disease are the two most important diseases in this group. Their characteristics are mainly episodes of active inflammation or remission. Currently, classifications of UC are based on epidemiologic, clinical and genetic parameters, and the presence of biological markers. Therapeutic strategies for UC patients are determined according to severity and localization of the affected area.

**Research frontiers**

To date, there are no studies that correlate levels of soluble ST2 (sST2) with severity of UC. It is possible that sST2 not only acts as a marker of UC activity; functions attributed to sST2 account for a role as immunomodulator in inflammatory processes. At the cellular level, sST2 has been described as an inhibitor of interleukin (IL)-33/ST2L signaling. The increase of sST2 during periods of inflammation may be involved in the control of the immune response associated with IBD.

**Innovations and breakthroughs**

Soluble ST2 protein has been identified as a new and reliable biomarker of heart failure. High serum levels of sST2 have been described in patients with chronic inflammatory diseases, such as autoimmune diseases and asthma. Recently, in their laboratory, the authors have described for the first time increased levels of sST2 in the serum and total ST2 in the colonic mucosa of UC patients. In this study, we show that serum sST2 levels significantly correlate with total ST2 levels in the colonic mucosa. Supporting our results, other groups have also shown evidence that the ST2/IL-33 system participates in the development of IBD.

**Applications**

The relation between serum sST2 and inflammatory bowel activity would allow, in the future, avoidance of colonoscopy procedures in patients that do not require them. In addition, some biochemical properties of sST2, such as its stability, support its characteristic as a reliable biomarker in UC. If sST2 levels decreased during clinical remission, these could be related to endoscopic mucosal healing, and therefore be considered a predictor of UC reactivation.

**Terminology**

ST2 belongs to the IL-1R super-family, is coded in human chromosome 2 and is expressed as two splice variants: one membrane bound, ST2L, which is a receptor of IL-33, and a soluble protein, sST2.

**Peer review**

The authors examined the expression of components of the ST2/IL-33 system in serum and colonic mucosa in UC patients and correlated levels of sST2 with severity of the disease. The study revealed that sST2 levels are able to differentiate active from inactive UC and correlate with endoscopic and histopathological activity scores. In addition to the fact that total intestinal ST2 levels are directly associated with serum sST2 levels, these findings verify that circulating sST2 levels may play an important role as a new and promising biological marker in UC.
CRP, and clinical indices. *Am J Gastroenterol* 2008; 103: 162-169

6. **Vermeire S**, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? *Gut* 2005; 55: 426-431

7. **Gisbert JP**, González-Lama Y, Matej J. [Role of biological markers in inflammatory bowel disease]. *Gastroenterol Hepatol* 2007; 30: 117-129

8. **Tibble JA**, Bjarnason I. Non-invasive investigation of inflammatory bowel disease. *World J Gastroenterol* 2001; 7: 460-465

9. **Jaskowski TD**, Litwin CM, Hill HR. Analysis of serum antibodies in patients suspected of having inflammatory bowel disease. *Clin Vaccine Immunol* 2006; 13: 655-660

10. **Rutgeerts P**, Vermeire S. Clinical value of the detection of antibodies in the serum for diagnosis and treatment of inflammatory bowel disease. *Gastroenterology* 1998; 115: 1006-1009

11. **Gisbert JP**, Gomollón F, Matej J, Pajares JM. The role of anti-neutrophil cytoplasmatic antibodies (ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) in inflammatory bowel disease. *Gastroenterol Hepatol* 2003; 26: 312-324

12. **Li X**, Conklin L, Alex P. New serological biomarkers of inflammatory bowel disease. *World J Gastroenterol* 2008; 14: 5115-5124

13. **Solem CA**, Loftus EV Jr, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Correlation of C-reactive protein with clinical, endoscopic, histologic, and radiographic activity in inflammatory bowel disease. *Inflamm Bowel Dis* 2005; 11: 707-712

14. **Karoui S**, Ouerdiane S, Serghini M, Jomni T, Kallel L, Fekih M, Boughalier J, Filali A. Correlation between levels of C-reactive protein and clinical activity in Crohn's disease. *Dig Liver Dis* 2007; 39: 1006-1010

15. **Papp M**, Norman GL, Altorjay I, Bellini M, Romano MR, Mumolo MG, Ceccarelli L, Bellini M, Romano MR. Utility of serological markers in inflammatory bowel diseases: gadget or magic? *World J Gastroenterol* 2007; 13: 2028-2036

16. **Konikoff MR**, Denson LA. Role of fecal calprotectin as a biomarker of intestinal inflammation in inflammatory bowel disease. *Inflamm Bowel Dis* 2006; 12: 524-534

17. **Raseth AG**, Schmidt PN, Fagerhol MK. Correlation between faecal excretion of indium-111-labelled granulocytes and calprotectin, a granulocyte marker protein, in patients with inflammatory bowel disease. *Scand J Gastroenterol* 1999; 34: 50-54

18. **Costa F**, Mumolo MG, Cecarelli L, Bellini M, Romano MR, Sterpi C, Richiutti A, Marchi S, Bottai M. Calprotectin is a stronger predictive marker of relapse than CRP, blood leukocytes, and EBV antibodies. *Inflamm Bowel Dis* 2008; 14: 32-39

19. **Schoepfer AM**, Trummer M, Scholzler P, Seibold-Schmid B, Seibold F. Discriminating IBD from IBS: comparison of the test performance of fecal markers, blood leukocytes, CRP, and IBD antibodies. *Inflamm Bowel Dis* 2008; 14: 32-39

20. **Schoepfer AM**, Beglinger C, Straumann A, Trummer M, Vavricka SR, Bruegger LE, Seibold F. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol* 2010; 105: 162-169

21. **Weinberg EO**, Shimp M, Hurwitz S, Tominga S, Rouleau JL, Lee RT. Identification of serum soluble ST2 receptor as a novel heart failure biomarker. *Circulation* 2003; 107: 721-726

22. **Januzzi JL Jr**, Peacock WF, Maisel AS, Chae CU, Jesse RL, Baggish AL, O'Donoghue M, Sukhria R, Chen AA, Van Kim Nielsen OH. IL-33 is upregulated in colonocytes of ulcerative colitis and induces T helper type 2-associated cytokines. *J Immunol* 2010; 185: 999-1007

23. **Seidelin JB**, Bjerrum JT, Coskun M, Widjaya B, Vainer B, Nielsen OH. IL-33 is upregulated in colonicocytes of ulcerative colitis. *Immunol Lett* 2010; 128: 80-85

24. **Lewis JD**, Chauai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008; 14: 1660-1666

25. **Harvey RF**, Bradshaw JM. A simple index of Crohn's disease activity. *Lancet* 1980; 1: 514

26. **Daperno M**, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, Sostegni R, Rocca R, Pera A, Gevers A, Mary JW, Colombel JF, Rutgeerts P. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastroenterology* 2004; 60: 505-512

27. **Gomes P**, du Boulay C, Smith CL, Holdstock G. Relationship between disease activity indices and colonoscopic findings in patients with colonic inflammatory bowel disease. *Gut* 1986; 27: 92-95

28. **Gisbert JP**, McNicholl AG. Questions and answers on the role of faecal calprotectin as a biological marker in inflammatory bowel disease. *Dig Liver Dis* 2009; 41: 56-66

29. **Freeman HJ**, Han V. Limitations in assessment of mucosal healing in inflammatory bowel disease. *World J Gastroenterol* 2010; 16: 15-20
Díaz-Jiménez D et al. Soluble ST2 activity marker in UC

43 Summerton CB, Longlands MG, Wiener K, Shreeve DR. Fecal calprotectin: a marker of inflammation throughout the intestinal tract. *Eu J Gastroenterol Hepatol* 2002; 14: 841-845

44 Tibble JA, Sigh hrsorsson G, Foster R, Forgaacs I, Bjarnason I. Use of surrogate markers of inflammation and Rome criteria to distinguish organic from nonorganic intestinal disease. *Gastroenterology* 2002; 123: 450-460

45 Pezzilli R, Barassi A, Morselli Labate AM, Finazzi S, Fantini L, Gizz L, Lotzniker M, Villani V, Melzi d’Erlig C, Corinaldesi R. Fecal calprotectin levels in patients with colonic polyposis. *Dig Dis Sci* 2008; 53: 47-51

46 Tibble J, Sigh hrsorsson G, Foster R, Sherwood R, Fagerhol M, Bjarnason I. Fecal calprotectin and faecal occult blood tests in the diagnosis of colorectal carcinoma and adenoma. *Gut* 2001; 49: 402-408

47 Limburg PJ, Devens ME, Harrington JJ, Diehl NN, Mahoney DW, Ahquist DA. Prospective evaluation of fecal calprotectin as a screening biomarker for colorectal neoplasia. *Am J Gastroenterol* 2003; 98: 2299-2305

48 Carroccio A, Vitale G, Di Prima L, Chifari N, Napoli S, La Russo C, Gulotta G, Averna MR, Montalto G, Mansueto S, Notarbartolo A. Comparison of anti-transglutaminase ELISA’s and an anti-endomysial antibody assay in the diagnosis of celiac disease: a prospective study. *Clin Chem* 2002; 48: 1546-1550

49 Sipponen T, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Crohn’s disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn’s disease activity index and endoscopic findings. *Inflamm Bowel Dis* 2008; 14: 40-46

50 Schoepfer AM, Beglinger C, Straumann A, Trummer M, Renzulli P, Seibold F. Ulcerative colitis: Correlation of the Rhamnolipid endoscopically normal index with fecal calprotectin, clinical activity, C-reactive protein, and blood leukocytes. *Inflamm Bowel Dis* 2009; 15: 1851-1858

51 Vieira A, Fang CB, Rolim EG, Klug WA, Steinwurz F, Rossin LG, Candelária PA. Inflammatory bowel disease activity assessed by fecal calprotectin and lactoferrin: correlation with laboratory parameters, clinical, endoscopic and histological indexes. *BMC Res Notes* 2009; 2: 221

52 van Assche G, Vermeire S, Rutgeerts P. Mucosal healing and treatment efficacy in IBD. *Inflamm Bowel Dis Monit* 2009; 1261-1270

53 Figueroa C C, Quera P R, Valenzuela E J, Jensen B C. Inflammatory bowel disease: experience of two Chilean centers. *J Am Coll Cardiol* 2002; 40-46

54 Bartunek J, Delrue L, Van Durme F, Muller O, Casselman F, De Wiest B, Croes R, Verstreken S, Goethals M, de Raedt H, Sarma J, Joseph L, Vanderheyden M, Weinberg EO. Nonmyocardial production of ST2 protein in human hypertrophy and failure is related to diastolic load. *J Am Coll Cardiol* 2008; 52: 2166-2174

55 Pascual-Figal DA, Ordonez-Llanos J, Tornel PL, Vázquez R, Puig T, Valdés M, Cinca J, de Luna AB, Bayes-Genis A. Soluble ST2 for predicting sudden cardiac death in patients with chronic heart failure and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2009; 54: 2174-2179

56 Weinberg EO, Shimpo M, De Keulenaer GW, MacGillivray C, Tominaga S, Solomon SD, Rouleau JL, Lee RT. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. *Circulation* 2002; 106: 2961-2966

57 Dieplinger B, Egger M, Poelz W, Halm mayer M, Mueller T. Long-term stability of soluble ST2 in frozen plasma samples. *Clin Biochem* 2010; 43: 1169-1170

58 Dieplinger B, Januzzi JL Jr, Steinmair M, Gabriel C, Poelz W, Halm mayer M, Mueller T. Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma—the Presage ST2 assay. *Clin Chim Acta* 2009; 409: 33-40

59 Meling TR, Aabakklen L, Roseth A, Osnes M. Fecal calprotectin shedding after short-term treatment with non-steroidal anti-inflammatory drugs. *Scand J Gastroenterol* 1996; 31: 339-344

60 Tibble J, Sigh hrsorsson G, Foster R, Scott D, Fagerhol MK, Roseth A, Bjarnason I. High prevalence of NSAID enteropa thy as shown by a simple faecal test. *Gut* 1999; 45: 362-366

61 Poullis A, Foster R, Mandal MA, Fagerhol MK. Emerging role of calprotectin in gastroenterology. *J Gastroenterol Hepatol* 2003; 18: 756-762

62 Hayakawa H, Hayakawa M, Kume A, Tominaga S. Soluble ST2 blocks interleukin-33 signaling in allergic airway inflammation. *J Biol Chem* 2007; 282: 26369-26380

63 Kurowska-Stolarska M, Kewin P, Murphy G, Russo RC, Stolarski B, Garcia CC, Komi-Koma M, Pitman N, Li Y, Niedbala W, McKenzie AN, Teixeira MM, Liew FY, Xu D. IL-33 induces antigen-specific IL-5+ T cells and promotes allergic-induced airway inflammation independent of IL-4. *J Immunol* 2008; 181: 4780-4790

64 Fuss IJ, Neurath M, Boirivant M, Klein JS, de la Mette C, Strong SA, Fiocchi C, Strober W. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn’s disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *J Immunol* 1996; 157: 1261-1270

65 Allakhverdi Z, Smith DE, Comeau MR, Delespesse G. Cutting edge: The ST2 ligand IL-33 potently activates and regulates of calprotectin in human cells. *Cytokine* 2007; 40: 216-225

66 Pushparaj PN, Tay HK, Hrng SC, Pittman N, Xu D, McKenzie A, Liew FY, Melendez AJ. The cytokine interleukin-33 mediates anaphylactic shock. *Proc Natl Acad Sci USA* 2009; 106: 9773-9778

S-Editor Sun H  I- Editor Logan S  E- Editor Zheng XM