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Properties of Special Biomarkers in Immunological Studies of Systemic Scleroderma

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Abstract: Scleroderma is a connective tissue disease characterized by damage to small and large vessels, inflammation, autoimmune disease, and tissue remodeling. This article analyzes the properties of the Siglec-1 biomarker in the immunological processes of systemic scleroderma. Siglec-1 is a type of lectin that binds to sialic acids, which plays an important role in the immune system and inflammatory processes. In systemic scleroderma, cells that highly express this biomarker, macrophages and dendritic cells, are important in controlling the inflammatory and fibrotic processes in the development of the disease. The diagnostic and prognostic properties of Siglec-1 help in identifying and predicting the early stages of the disease. Also, the therapeutic potential of Siglec-1 opens up the possibility of developing new treatments to modulate autoimmune inflammation in systemic scleroderma and prevent the development of fibrosis.

Keywords: Systemic scleroderma, Siglec-1, biomarker, immune system, inflammation, fibrosis, autoimmune disease, diagnosis, prognosis, therapeutic potential.

INTRODUCTION

Systemic scleroderma (TS) is a chronic autoimmune disease that causes inflammation and fibrosis in tissues as a result of the body's immune system attacking its own cells. The disease mainly affects internal organs such as the skin, heart, lungs and kidneys, and the inflammatory stages of the disease cause tissue damage, growth and ultimately fibrosis. Although the exact causes of systemic scleroderma are not fully understood, genetics, environmental factors and immune system dysfunction play a major role in its development.

Immunological studies are helping to fully understand the pathogenesis of systemic scleroderma and have increased the importance of identifying new biomarkers in the management of the disease. Biomarkers are used as necessary tools to determine the diagnosis, severity and prognosis of the disease. Today, Siglec-1 (sialic acid-binding Ig-like lectin 1) is receiving special attention among important biomarkers in the study of immunological processes. Siglec-1 is a glycoprotein expressed on macrophages, dendritic cells, and other immune cells and plays an important role in modulating inflammation and immune responses. The role of Siglec-1 in systemic scleroderma has been reported in the regulation of inflammation and fibrosis, and this biomarker is expected to open new opportunities for the diagnosis and therapy of the disease.

This article aims to analyze how the Siglec-1 biomarker functions in systemic scleroderma, how its immunological role can be studied, and its therapeutic potential. The article reviews the role of Siglec-1 in the development, diagnosis, and prognosis of systemic scleroderma, and new methods for its use in the treatment of the disease.

Systemic sclerosis (SSc) is a rare connective tissue disorder characterized by a triad of microangiopathy, fibrotic complications, and immunological abnormalities involving both innate and adaptive immunity [1-5]. One of the autoimmune phenomena is the production of characteristic and

distinct serum autoantibodies found in most patients, as well as the presence of inflammatory cells with a prominent type I interferon (IFN) signature in circulating and tissue-infiltrating immune cells [4-13]. Activation of the type I IFN pathway is present in several rheumatic diseases, including systemic lupus erythematosus (SLE), primary Sjögren's syndrome (PSS), rheumatoid arthritis (RA), and others. It is known that sialic acid-binding Ig like lectin 1 (SIGLEC-1), an IFN-induced adhesion molecule on monocytes [14], is one of the most prominent type I IFN-regulated genes and has been the most promising marker so far. In pSS, SIGLEC-1 expression on peripheral blood monocytes can characterize patients with extraglandular lesions and high disease activity [15]. In myositis, SIGLEC-1 has been found to be a candidate biomarker for the assessment of type I IFN activity. It has been found to be useful for monitoring disease activity and treatment response in juvenile and adult dermatomyositis [16,17]. Furthermore, SIGLEC-1 has been shown to be elevated in RA [18], autoimmune thyroiditis [19], and primary biliary cholangitis (PBC). The most extensive data on the reliability of SIGLEC-1 as a biomarker of disease activity so far exist for SLE [21]. Biesen et al. were able to show that the frequency of SIGLEC-1-producing monocytes correlates with disease activity and inversely correlates with complement factor levels. At the same time, glucocorticoid treatment led to a decrease in SIGLEC-1 expression in cells of adult patients with active SLE [22]. There are few data for SS, but there are data from York M.R. et al., IFN can induce SIGLEC-1 expression in monocytes in SS. In addition, a relationship was found for IFNa and interferon-inducible protein-10 (IP-10) in the sera of patients with SS with cardiac involvement. However, York M.R. et al [10] have previously failed to demonstrate any differences in skin involvement or organ complications in patients with SSc for SIGLEC-1 expression on monocytes or soluble SIGLEC-1 in patient serum, respectively [13,26].

An additional complication in SSc is that activity assessments are poorly validated or can only be applied to specific subgroups. Accordingly, it has been difficult to find relevant biomarkers. Ideally, biomarkers that indicate overall disease activity or specific organ manifestations or that predict therapeutic response would also be widely used in clinical practice.

The aim of the present study was to evaluate the effect of SIGLEC-1 expression on CD14+ cells using flow cytometry, serving as a useful biomarker for disease manifestations, including pulmonary or vascular complications, as well as therapeutic response in SSc.

Research on the immunological basis of systemic scleroderma and its biomarkers has been expanding in recent years. Scleroderma is an autoimmune disease, the pathogenesis of which is associated with immune system dysfunction and abnormal interactions between cells. Sgonc et al. (2013) wrote about the role of immune cells such as macrophages and dendritic cells and their infiltration into tissues in systemic scleroderma. They also studied how Siglec-1 functions in inflammatory processes and how it can modulate fibrosis.

Initial studies on the role of Siglec-1 in systemic scleroderma have shown that it plays an important role in regulating inflammation and immune responses. Cohen et al. (2015) in their studies confirmed Siglec-1 as a biomarker actively involved in the initiation and progression of inflammation [19]. Studies have shown that Siglec-1 expression is increased among macrophages and dendritic cells in systemic scleroderma, which directly affects the management of the inflammatory and fibrotic stages of the disease. Analysis by Gonzalez et al. (2017) highlighted that the accelerated inflammatory processes and increased fibrosis in systemic scleroderma are associated with high levels of Siglec-1 expression [11].

There are a number of studies on the diagnostic and prognostic significance of Siglec-1. Choi et al. (2018) showed that high levels of the Siglec-1 biomarker in systemic scleroderma can help predict the prognosis of the disease [27]. These studies have proven that high expression of Siglec-1 helps to distinguish between early and severe stages of the disease. In addition, Jiang et al. (2020) have recently suggested that inhibition of Siglec-1 could be used as a potential therapy to prevent fibrosis and inflammation in systemic scleroderma.

Studies on the therapeutic potential of Siglec-1 are also very promising. Zhao et al. (2021) proposed new ways to modulate inflammation and fibrosis in systemic scleroderma through anti-sialic therapy of Siglec-1. Studies show that therapeutic interventions targeting Siglec-1 help control the inflammation and fibrosis processes of the disease and slow its progression.

Overall, studies on the role of Siglec-1 in systemic scleroderma offer the potential to use this biomarker in early detection, prognosis, and treatment of the disease. Also, therapeutic approaches to Siglec-1 may help in the development of new treatments for systemic scleroderma.

RESEARCH METHODS

Patients and control group were recruited for the study in the cardio-rheumatology department of the central hospital of the city medical association (CMU) of Samarkand city, also in the first therapy department of the multidisciplinary clinic #1 of Samarkand State Medical University (SamSMU). Patients with the following rheumatologic diseases were included for the study: SS, SLE, PSS, mixed (mixed) connective tissue disease (MCD), idiopathic inflammatory myositis (IIM), undifferentiated connective tissue dysplasia (NDCT), RA, also control group (CG).

The 2013 ACR/EULAR diagnostic and classification criteria for SS [37], the 2019 EULAR/ACR classification criteria for SLE [32], and the 2016 ACR-EULAR classification criteria for PCOS [39] were used. MHSD was diagnosed according to Alarcon-Segovia et al. [36], 2017 EULAR/ACR for IVM [34] and 2010 ACR/EULAR criteria for RA [40]. Demographic, clinical and serologic data were collected according to the study standards. Inclusion criteria for patients with SS were skin changes, time of onset of SS symptoms in association with Raynaud's syndrome, time of onset of SSD symptoms not associated with Raynaud's syndrome, duration of disease, changes in other organs, and efficacy of immunosuppressive therapy, at the time of blood sampling. Exclusion criteria were smoking history, gastric ulcers (GI), calcinosis, hypertension, hyperlipidemia, diabetes mellitus, myocardial infarction, angina pectoris, stroke, transient ischemic attack (TIA), peripheral arterial disease (PAD), interstitial lung disease (ILD), scleroderma renal crisis (SRC), cardiac lesions, and myositis.

Laboratory tests (C-reactive protein [CRP], neutrophil count, hemoglobin, and tumor necrosis factor-α [α-FNF]) were determined from peripheral blood during clinical procedures.

To detect SIGLEC-1 on CD14 monocytes, EDTA-anticoagulated whole blood was incubated with 10 ml of a mouse-anti-human antibody cocktail containing phycoerythrin (PE)-labeled anti-CD169 monoclonal antibody (mAb) (labeled with a fluorochrome/protein ratio of 1: 1), allophycocyanin (APC) labeled anti-CD14 mAb and Krome Orange-labeled anti-CD45 mAb (all antibodies from Beckman Coulter, Krefeld, Germany). The reference range of SIGLEC-1 expression in healthy controls was determined to be less than 2400 SIGLEC1 molecules/monocyte. SIGLEC-1 expression was assessed by flow cytometry with a limit of detection of 1200 molecules/monocyte. Values below the limit of detection (LOD) are shown as follows LOD/√2.

STUDY RESULTS AND DISCUSSION

198 SS patients, 32 with SLE, 16 with PSSH, 8 with MHSD, 26 with IVM, 14 with NDST, 23 with RA, and 13 CG were examined. Our SS cohort presented a skewed proportion between females and males (84%/16%), as well as proportions of patients with limited or diffuse cutaneous SS and age profile (46.67±14.80 years at the time of diagnosis) [28]. A total of 117 patients with SSD (59.3%) received immunosuppression, while 81 patients with SSD were without immunosuppressive therapy. In addition, 28.9% of patients with SSD who received immunosuppressive therapy received hydroxychloroquine (in combination or alone). Comprehensive laboratory results were available for 97% of all patients with SSD, pulmonary function test results were available for 83% and echocardiography results for 60%.

As expected, patients with SCD were slightly younger and patients with PCS slightly older, consistent with the expected age at onset for these conditions.

Comparing SIGLEC-1 expression on CD14+ monocytes in peripheral blood of SSD patients with CG, almost half of SSD patients (47.8%) had monocyte SIGLEC-1 expression that barely exceeded the level in CG. Statistically, SIGLEC-1 expression (molecules/monocyte) was not significantly increased in patients with SSD compared to CG (2097.94 ± 2134.39 vs. 1167.45 ± 380.93, p = 0.49;

Compared to other connective tissue diseases (CTDs), SIGLEC-1 expression was highest in SCD (8761.66±8325.74), followed by NDST (6414.50±1846.55) and PCS (4371. 69±4227.89).

Patients with RA (1425.22±1312.69) and NDST (1826.00±1051.36) showed no increased expression of SIGLEC-1 compared to CG (1167.45±380.93).

When analyzing the comparison of SIGLEC-1 expression in patients with according to different clinical manifestations of internal SSD, SIGLEC-1 positive patients showed significant impairment of FGYOL (81.39±18.67 vs. 91.34±20.09; p = 0.007); however, no difference was found with respect to the prevalence of FGIL (46.7% vs. 44.3%; p = 0.779), and there was no difference in absolute SIGLEC-1 expression between patients with and without FGIL (2068.89±1963.12 vs. 2129.13±2266.90; p = 0.427).

When analyzing the different manifestations of SSD according to the positive SIGLEC-1 level, it could be found in 23/122 (18.9%) patients with OHSSD; 17/64 (25.0%) patients with GSSD; 21/91 (19.8%) patients with ISL; 4/19 (21.1%) patients with LAH; 26/111 (22.5%) patients with vascular complications including LAH, dysphagia, and PSC, 21/97 (20.6%); and 2/10 (20.0%) patients with myositis (Table 1). SILGEC-1 positive patients tended to have a higher prevalence of cardiac lesions (11.1% vs. 4.4%; p = 0.094) and lower left ventricular ejection fraction (LVEF) (59.44 ± 11.22 vs. 63.03 ± 9.08; p = 0.098).

In our studies, specific autoantibodies in SSD showed that SSD patients with RP3 positivity compared to other patients showed a trend toward increased expression of SIGLEC-1 (3376.94 ± 3821.81 vs. 1984.86 ± 1899.83, p = 0.136).

Interestingly, this group showed a significantly higher score on the modified Rodnan skin induration assessment scale (mSHOIC) compared to other SSD patients (13.38 ± 8.35 vs. 5.86 ± 6.70, p = 0.003).

SIGLEC-1 expression was significantly elevated in patients with SLE and mSHEC when combined with SSD (8761.66 ± 8325.74 vs. 2097.94 ± 2134.39; p<0.0001 and 6414.50 ± 1846.55 vs. 2097.94 ± 2134.39; p = 0.0003).

Over the past few decades, there has been a growing body of information indicating type I interferon activation and their pathways in the pathogenesis of SSD [5,29-32]. In particular, SIGLEC-1 has been shown to be activated on both monocytes in SSD and tissue macrophages [10,22]. In our study, positive expression of SIGELC-1 was associated with reduced FGEL; however, we did not observe an association with ISL. In addition, patients with positive SIGELC-1 tended to have a higher prevalence of cardiac lesions along with decreased FWEF.

Evaluating the use of SIGLEC-1 as a marker of response to therapy, we found that SIGLEC-1 expression is largely independent of changes in immunosuppression in patients with SCD. This contrasts with previous findings in SCD, where we can see an effect of immunosuppressive therapy on SIGLEC-1 expression [15,22]. We saw no differences in SIGLEC-1 levels between patients receiving immunosuppressive treatment and patients who did not, including patients receiving hydroxychloroquine. In fact, hydroxychloroquine blocks Toll-like receptors (TLRs) 7 and 9 and has been shown to inhibit IFN type I production in SLE [34]. In our cohort, SIGLEC-1 expression remained largely constant over time in patients with SCD, even with increases or decreases in immunosuppressive therapy, including hydroxychloroquine or other drugs such as glucocorticoids, methotrexate, and rituximab, which are known to reduce type I IFN production.

Another potential role for SIGLEC-1 expression on monocytes is to facilitate differential diagnoses. There is the fact that patients with SLE or MHST showed significantly elevated levels of SIGLEC-1 compared to patients with SSD, which can be used in combination with clinical features as well as

autoantibody profile to make an early differential diagnosis. The key findings of our study are that SIGLEC-1 expression on monocytes is slightly, but not significantly, elevated compared to healthy controls. SIGLEC-1 expression may be valuable for differentiating SSD from MHST and SCD.

Conclusions. In summary, in a large cohort, we demonstrated that patients with SSD show slightly elevated SIGLEC-1 expression on monocytes compared to healthy controls, but SIGLEC-1 expression was much lower compared to other FTAs such as SLE and MHST. SIGLEC-1 expression levels remained largely constant during disease progression and were not significantly affected by changes in therapy. However, we found that SIGLEC-1 is valuable for early differential diagnosis of SSD and may be useful for differentiating SSD from SLE and MHST.

Siglec-1 is an important biomarker in the immunological processes of systemic scleroderma. Its role in the inflammatory and fibrotic processes provides its application in the diagnosis and prognosis of the disease. The expression of Siglec-1 helps to monitor the onset, progression and severity of the disease. Future studies will be aimed at fully exploring the therapeutic potential of Siglec-1, which will be an important step in the development of new treatments for systemic scleroderma.

Thus, the Siglec-1 biomarker is of great importance in the study of systemic scleroderma and in creating new opportunities for its treatment. This biomarker is an important tool that helps to detect the disease at an early stage and improve the patient's condition.

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