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The positive effect of JAK inhibitor tofacitinib in the treatment of primary Sjögren's syndrome: a clinical case

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Abstract. Primary Sjögren's syndrome (pSS, Sjögren's disease) is a systemic autoimmune disease which develops in previously healthy individuals and characterized by damage to exocrine glands, mainly lacrimal and salivary glands, with gradual formation of their secretory insufficiency and various systemic manifestations. According to EULAR recommendation (2019) therapeutic management of pSS bases on symptomatic treatment of sicca syndrome and broad-spectrum immunosuppression for systemic manifestations. The perspective group for the treatment of autoimmune disease is Janus kinase inhibitors, which can block the signals from biologically active molecules (interferons, erythropoietins and cytokines) and providing a response to these target cell signals. Therefore, the use of JAK inhibitors in patients with pSS requires clinical confirmation of effectiveness. The article described the clinical case of the positive effect of tofacitinib with methotrexate combination in the treatment of patient with pSS. A 55-year-old female with sicca syndrome (confirmed by Schirmer's test), arthralgia, low-grade fever, weight loss and a positive test for the detection of specific antibodies (SS-A/Ro > 240 units/ml, SS-B/La 94 units/ml) was diagnosed with pSS. The total score of EULAR Sjögren's syndrome disease activity index (ESSDAI) was 9 (activity grade II). The treatment included symptomatic methods of sicca syndrome correcting (replacement therapy with artificial tear preparations and chewing gums with xylitol) in combination with immunosuppressive therapy. The addition of tofacitinib 5 mg twice daily to methotrexate (10 mg weekly) has been shown to significantly reduce disease activity after 6 months of treatment (ESSDAI = 0).
Keywords: primary Sjögren's syndrome; Janus kinase inhibitor; tofacitinib; clinical case

Introduction

Sjögren's syndrome is a systemic autoimmune disease which characterized by damage to exocrine glands, mainly lacrimal and salivary glands, with gradual formation of their secretory insufficiency and various systemic manifestations. Primary Sjögren's syndrome (pSS) develops in previously healthy individuals, unlike secondary Sjogren's syndrome, which can accompany a some of autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis) [1].

The spectrum of the disease manifestations extends from specific autoimmune disorders to a systemic process and is also associated with an increased risk of B-cell lymphoma, because B-cell activation is a consistent immunoregulatory abnormality [2]. Activation of B-cells leads to production of various autoantibodies. Anti-Ro and anti-La antibodies can be detected previous to the clinical onset of pSS [3], antinuclear antibodies are the most frequently detected autoantibodies, anti-Ro/SS-A are the most specific, and cryoglobulins and hypocomplementaemia are the main prognostic markers [4].

The main histomorphological feature includes lymphocytic and plasma cells infiltration of salivary, lacrimal and other exocrine glands — bronchial, intestinal, vaginal [5]. This process leads to sicca syndrome, which is the combination of dryness of the eyes (xerophthalmia), oral cavity (xerostomia), pharynx, larynx and/or vagina [6]. Xerostomia leads to secondary problems like oral candidiasis, dental carries and periodontal disease [7, 8]. Photosensitivity, chronic irritation and destruction of the corneal epithelium and ocular infections may be consequence of xerophthalmia. The most frequent systemic manifestations include lymphadenopathy, splenomegaly, myalgia, myositis, arthralgia, arthritis, skin vasculitis [9].

According to EULAR recommendation (2019) therapeutic management of pSS bases on symptomatic treatment of sicca syndrome and broad-spectrum immunosuppression for systemic manifestations [10, 11]. Unfortunately, there

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are not enough clinical trials, which demonstrated the benefit of efficacy and safety of any immunosuppressive agent. Therefore, it is necessary to search for the new pathogenic targets and more personalized therapeutic approach based on genetic, clinical, and immunological characteristics.

The perspective group for the treatment of autoimmune disease is Janus kinase (JAK) inhibitors. The function of JAK is to transmit signals from biologically active molecules (interferons, erythropoietins and cytokines) and providing a response to these target cell signals. JAK inhibitors administration leads to suppression of JAK-1, JAK-3 (to a lesser extend JAK-2 and tyrosin-kinase-2) which is accompanied by anti-inflammation effect [12, 13]. Currently, JAK inhibitors are included in international guidelines for the treatment of rheumatoid arthritis [14, 15], psoriatic arthritis (tofacitinib, upadacitinib) [16] and ulcerative colitis (tofacitinib) [17]. The clinical cases of pSS in which tofacitinib have used as immunosuppressive agent are episodic, so each case must be considered with clinical interest and collect for further modification of treatment guidelines.

Case report

A 55-years-old female with complains of dryness of the eyes, oral cavity, pain and morning stiffness in the small joints of the hands and left hip joint, low-grade fever, weight loss. The symptoms of sicca syndrome bothered the patient for a year. Low-grade fever, pain and morning stiffness for 1 hour in the joints appeared a month before visiting to rheumatologist. The patient also noted a weight loss of 5 kg during the last 3 months, not caused by diet and discomfort in the parotid areas. Physical examination revealed bilateral enlargement of tonsillar lymph nodes up to 1 cm. Signs of synovitis of the affected joints were not diagnosed, therefore complaints from the joints were considered as arthralgia. Laboratory findings: rheumatoid factor 25.5 IU/ml, C-reactive protein < 0.3 mg/l, antinuclear antibodies 1 : 1000, SS-A/Ro > 240 units/ml, SS-B/La 94 units/ml, antibodies to cyclic citrullinated peptides < 20.0 IU/ml and negative result for detection of hepatitis C and HIV. The patient underwent an MRI of the hands to rule out rheumatoid arthritis (as cause of morning pain, stiffness in the small joints and increase of rheumatoid factor) and osteoarthritis (as a cause of arthralgia). The indicated diagnoses were not confirmed. Among the available methods for diagnosing sicca syndrome, Schirmer's test was performed (OS = 1 mm, OD = 1 mm).

Based on the recommendations of the American College of Rheumatology (2016) was diagnosed pSS [18]. The patient had manifestations of sicca syndrome lasting more than 3 months, confirmed by the Schirmer's test (1 point), specific SS-A/Ro antibodies (3 points) and the absence of signs of another autoimmune disease or evidence of HIV/hepatitis C infection. The EULAR Sjögren's syndrome disease activity index (ESSDAI) was performed for assessing the disease activity with the definition of 12 domains [19]. The score of constitutional domain was 3 (included low-grade fever and weight loss up to 10 %), lymphadenopathy and lymphoma domain — 4 (bilateral enlargement of tonsillar lymph nodes up to 1 cm), glandular domain — 0 (enlargement of salivary glands was not detected during physical examination), articular domain — 2 (arthralgia), cutaneous — 0, pulmonary — 0, renal — 0, muscular — 0, hematological — 0, biological — 0, peripheral and central nervous system domain — 0. The total score was 9, which indicated the II degree of activity. The final diagnosis was primary Sjögren's syndrome, chronic course, II degree of activity (ESSDAI = 9).

The therapy was based on EULAR recommendation of pSS treatment [11]. The patient was prescribed replacement therapy with artificial tear preparations, and non-pharmacological methods (chewing gums without sugar with xylitol) for the correction of xerostomia. Methotrexate was prescribed in a dose of 10 mg weekly orally as an immunosuppressive agent, based on articular manifestations. To reduce the activity of the disease, the patient took 6 mg of methylprednisolone for 2 months with gradual withdrawal. NSAIDs recommended as rescue medication. After 6 months of treatment was observed a slight decrease of sicca syndrome manifestations, normalization of body weight, but complaints of moderate pain in the joints and low-grade fever persisted. According to the patient, the symptoms of the disease returned after some time after withdrawal of methylprednisolone. The Schirmer's test showed minimal positive effect (OS = 2 mm, OD = 2 mm). The score of constitutional domain of ESSDAI was 3 (low-grade fever), lymphadenopathy and lymphoma domain — 4 (enlargement of the right tonsillar lymph node up to 1 cm), glandular domain — 0, articular domain — 2 (arthralgia), cutaneous domain — 0, pulmonary — 0, renal — 0, muscular — 0, hematological — 0, biological — 0, peripheral and central nervous system domain — 0. The total score was 9, which indicated to the activity grade II.

Based on the results of the assessment of disease activity, we decided to correct the treatment. Due to the progress in the study of the effectiveness of JAK inhibitors in rheumatological pathology in recent years, the patient was offered off-label treatment with tofacitinib 5 mg twice daily in combination with methotrexate 10 mg weekly. Before starting therapy, potential risks from the use of this group of drugs, which have not yet been included in the official recommendations of leading expert groups, were discussed with the patient. After that, the patient signed the consent for off-label therapy. The patient also received methylprednisolone 6 mg per day orally for 1 month with gradual discontinuation. Recommendations for symptomatic treatment of sicca syndrome have not changed.

After 6 months of treatment, the patient's complaints about joint syndrome practically stopped (was not disturbed for more than 4 weeks) and the manifestations of sicca syndrome became much less. According to the patient, after withdrawal of methylprednisolone, her condition did not worsen. The score of constitutional domain of ESSDAI was 0, lymphadenopathy and lymphoma domain — 0, glandular domain — 0, articular domain — 0, cutaneous domain — 0, pulmonary — 0, renal — 0, muscular — 0, hematological — 0, biological — 0, peripheral and central nervous system domain — 0. The total score was 0 — absence of disease activity. The following changes were established: SS-A/Ro

160 U/ml, SS-B/La 28 U/ml, which indicated a decrease of immunological activity. The Schirmer's test (OS = 6 mm, OD = 4 mm) also showed the clinical improvement. There were no side effects from combined therapy with methotrexate and tofacitinib.

Discussion

The absence of standardized guideline for the treatment of pSS needs searching for the new clinical ways of influence. The aim of the pSS therapy is to reduce clinical symptoms, decrease clinical and immunological activity and prevent lymphoid proliferation with the development of lymphoproliferative diseases [10, 20]. According to EULAR recommendations (2019), correction of sicca syndrome may include non-pharmacological (grade I) and pharmacological methods (grade II), depending on the severity of manifestations and complications. In most cases, the choice of an immunosuppressive agent depends on the leading clinical syndrome and the degree of disease activity. Thus, short-term use of glucocorticoids (GC) is an effective means of reducing the degree of glandular proliferation, in case of systemic manifestations of the disease or in the form of sparring therapy in combination with cytostatics. But the long-term use of GCs is associated with the development of side effects and insufficient evidence base for the prevention of disease progression [11, 21]. The lack of head-to-head studies comparing the efficacy and safety profile of immunosuppressive agents (leflunomide, methotrexate, azathioprine, mycophenolate, cyclophosphamide) does not permit a recommendation on the use of one agent over another, except when patient characteristics or comorbidities are considered with respect to the safety profile. The use of B-cell targeted therapy in patients with pSS is advisable in cases of refractory, severe course of the disease [11]. In the presented clinical case, manifestations of sicca syndrome were combined with articular symptoms, constitutional disorders, and the absence of severe organ damage. Methotrexate is recommended in case with articular involvement [21], so the choice was stopped on this cytostatic drug. To quickly reduce the activity of the process, methylprednisolone was prescribed for 2 months with gradual withdrawal. After 6 months of the therapy, the patient showed the absence of disease activity dynamics (ESSDAI = 9).

The results of research in recent years have demonstrated the significant effectiveness of JAK inhibitors in patients with rheumatological diseases. The discovery of the pathogenetic links of pSS with the involvement of autophagy mechanisms and the participation of cytokines, such as the family of interferons (IFN) [22, 23], tumor necrosis factor (TNF), interleukin (IL) 1β [24], IL-6 [25], IL-10 [26], IL-17 [27], IL-23 [28] became the impetus for research the effectiveness of JAK inhibitors in patients with pSS.

One of mechanism which induces inflammation is deficiency of autophagy and is associated with accumulation of JAK-STAT components [29]. Altered homeostasis of salivary gland epithelial cells in pSS could be the initiating factor that leads to inflammation, secretory dysfunction and autoimmunity. Barrera M.J. et al. have demonstrated that labial salivary gland epithelial cells of pSS patients have an inverse correlation in the expression of autophagy proteins and components of the JAK-STAT pathway, evidenced by decreased ATG5 expression and high IL-6 and IFN-γ expression levels and with JAK-STAT pathway activation (pSTAT1 and pSTAT3) [30]. They have showed the improvement of mitochondrial morphology under tofacitinib treatment in submandibular glands of a murine model of pSS and suggest a potential use of this agent in mitochondrial alterations associated with inflammation [31, 32]. Author made a conclusion that tofacitinib acting as an anti-inflammatory agent may reduce the inflammation caused by altered autophagy in pSS patients.

Another randomized clinical trial demonstrated the effectiveness of the topical form of tofacitinib in the correction of ophthalmic manifestations of pSS, which was associated with a decrease in the expression of HLA-DR in conjunctival cells and infiltration by CD11+ cells and a decrease in the content of TNF, IL-23, and IL-17 in the cornea [33].

In 2021, the National Institute of Dental and Craniofacial Research (USA) started a randomized, placebo-controlled phase Ib-IIa clinical trial to study the safety of tofacitinib in patients with pSS, which will end in 2023, and the results will be published in 2024. So, the interest in studying the effectiveness and safety of tofacitinib in patients with pSS is constantly increasing, therefore the clinical evidence base is growing.

Thus, the effect of tofacitinib in patients with pSS is realized through several pathogenetic pathways and provides a positive clinical response. In the described clinical case, addition of tofacitinib to methotrexate provided a reliable reduction of clinical and immunological activity of disease. At the time of the creation of EULAR recommendation (2019), the evidence base regarding the effectiveness and safety of JAK inhibitors in patients with pSS was insufficient, therefore the JAK inhibitors group was not recommended by the EULAR experts. But medicine does not stand still, and in the last few years there have been studies (including randomized ones) that have demonstrated the effectiveness of JAK inhibitors in patients with pSS. We believe that in the next recommendations of the EULAR/ACR expert group, JAK inhibitors will be indicated as one of the recommended for the treatment of pSS.

Conclusions

Treatment of primary Sjögren's syndrome should be comprehensive, include non-pharmacological and pharmacological methods of sicca syndrome correction and be combined with immunosuppressive therapy. A combination of methotrexate 10 mg weekly with tofacitinib 5 mg twice daily may be recommended as cytostatic therapy for reducing the disease activity.

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Позитивний ефект JAK-інгібітору тофацитинібу в лікуванні первинного синдрому Шегрена: випадок із клінічної практики

Резюме. Первинний синдром Шегрена (пСШ, хвороба Шегрена) — системне автоімунне захворювання, що розвивається в попередньо здорових осіб та характеризується ураженням екзокринних залоз, переважно слізних і слинних, із поступовим формуванням їх секреторної недостатності й різними системними проявами. Згідно з рекомендаціями EULAR (2019), основними методами лікування пСШ є симптоматична терапія проявів сухого синдрому та застосування різних імуносупресивних агентів залежно від конкретного клінічного випадку. Перспективною при лікуванні автоімунних захворювань є група інгібіторів янус-кінази (JAK-інгібіторів), механізм дії яких полягає в блокуванні ферменту янус-кінази, що відповідальна за реакцію клітин-мішеней на зовнішні сигнали від біологічно активних молекул (інтерферони, еритропоетини та цитокіни) і забезпечує протизапальний ефект. Тому дослідження ефективності JAK-інгібіторів у хворих на пСШ є актуальним та потребує клінічного підтвердження. У статті представлено клінічний випадок позитивного впливу тофацитинібу в комбінації з метотрексатом у лікуванні пацієнтки із пСШ. У хворої 55 років із проявами сухого синдрому (підтвердженого пробою Ширмера), артралгією, субфебрилітетом, схудненням та позитивним тестом на специфічні антитіла (SS-A/Ro > 240 ОД/мл, SS-B/La 94 ОД/мл) було діагностовано пСШ. Згідно з індексом ESSDAI (EULAR Sjögren's syndrome disease activity index), активність хвороби до початку терапії була II ступеня (ESSDAI = 9). Лікування хворої включало симптоматичні методи корекції сухого синдрому (замісна терапія препаратами штучної сльози й жувальні гумки без цукру з ксилітом) та прийом імуносупресивних агентів. Продемонстровано, що додавання тофацитинібу 5 мг двічі на добу до терапії метотрексатом (10 мг щотижня) забезпечувало вірогідне зменшення активності хвороби через 6 місяців лікування (ESSDAI = 0).

Ключові слова: первинний синдром Шегрена; інгібітори янус-кінази; тофацитиніб; клінічний випадок