LECTURE

From syndrome to disease: the evolution of the nomenclature of Sjögren's disease

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The article discusses current concepts of Sjögren's disease as an independent multisystem autoimmune disorder with a wide spectrum of organ manifestations and a high risk of lymphoproliferative complications. Special attention is given to new data on pathogenetic mechanisms based on B-cell hyperactivity. The most advanced approaches to monitoring and treatment are discussed, including the implementation of activity indices and the prospects of targeted therapy.

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More than 90 years have passed since the distinguished Swedish ophthalmologist Henrik Sjögren first described in his dissertation research the combination of clinical manifestations such as dry keratoconjunctivitis and chronic polyarthritis, and laid the foundation for the development of a diagnostic algorithm for the condition, which later became known as "Sjögren's syndrome" [1]. This syndrome was eventually recognized as a systemic autoimmune disease involving a wide range of extraglandular manifestations, and in the modern classification it belongs to the group of diffuse connective tissue diseases. Subsequently, clinicians and researchers, relying on clinical, serological and genetic data, introduced the terms "primary" and "secondary" Sjögren's syndrome into professional medical practice to stratify patients with sicca syndrome.[2]. The term "primary Sjögren's syndrome" was understood to mean an independent systemic autoimmune disease (AIDs) that develops in the absence of signs of other diffuse connective tissue diseases. In Russian rheumatology practice since the end of the 20th century, the term "Sjögren's disease" (SjD) has been used predominantly, which was already perceived as an independent nosological entity at that time. This pathology was characterized by chronic lymphocytic inflammation of the exocrine glands with the development of a pronounced sicca syndrome (xerostomia and xerophthalmia), as well as possible involvement of extra-glandular organs and tissues in the pathological process [3].

Later, this syndrome began to be detected as part of the symptom complexes of other diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and the concept of "secondary Sjögren's syndrome" was proposed as a concomitant condition against the background of other systemic AIDs [4]. Over the following decades, this conditional classification gained wide recognition and became a standard variation in the differential diagnosis and systematization of this disease. However, in recent years, in the global scientific community has been active discussion about the rationale of such a classification. Some researchers point to the potential inaccuracy of using the term "syndrome" to describe a clinically and pathogenetically independent disease [5].

In modern rheumatology, the terminological distinction between "primary" and "secondary" forms of Sjögren's syndrome has undergone a significant evolution, reflecting consistency with international classification approaches and in-depth understanding of the pathophysiological mechanisms underlying this disease [4, 6]. Morphological, molecular genetics, and serological studies, as well as biomarker analysis, have not revealed any significant differences between the forms of SjD. This has led to a change in concept: SjD is always a disease, but it can be independent (single) AIDs or be combined/associated with other AIDs (more often with SLE, RA, systemic scleroderma) [7].

SjD: the modern concept of pathogenesis

The observed changes in the terminology of SjD are based on new data obtained over the past 20 years and concern the causes, pathogenetic features, clinical manifestations, and long-term outcomes of the disease [8]. The current understanding of the pathogenesis of SjD is based on the results of recent molecular and clinical studies, which are rapidly expanding our understanding of the interaction between innate and acquired immunity, onset of autoimmune, inflammation, interferon activation, pathological B-cell hyperactivity, and epithelial homeostasis disorders [9]. The triggering mechanisms of SjD are formed under the influence of a combination of genetic, epigenetic, hormonal, and external factors, particular viral infections (Epstein-Barr virus, Coxsackie virus, cytomegalovirus, human T-cell leukemia virus type I, endogenous human retrovirus), as well as chemical substances. These factors initiate the activation of epithelial cells of the salivary and lacrimal glands, which begin to express molecules that ensure antigen presentation and secrete cytokines such as interleukin (IL) 6, interferon (IFN) I, BAFF, APRIL, and chemokines. These mediators induce immune cell homing, enhance IFN I expression by plasmacytoid dendritic cells, and promote B cell differentiation and survival [10].

Toll-like receptors 3, 7, and 9 on epithelial and dendritic cells play an important role in pathogenesis. Their activation causes the production of IFNα and IFNγ, forming a characteristic IFN- dependent disease pattern and inducing multiple ISG genes (interferon-stimulated genes) through JAK/STAT signaling pathways. These processes are accompanied by increased BAFF production, enhanced B-cell differentiation and survival, and the formation of ectopic germinal centers in the salivary glands. B-cell hyperactivity is expressed in the production of rheumatoid factor, autoantibodies to SSA/Ro and SSB/La, hypergammaglobulinemia, and local increase in BAFF production. In peripheral blood, there is a decrease in the pool of CD27 memory B cells due to their migration to the affected tissues.

In turn, persistent activation of B lymphocytes is associated with a high risk of developing MALT lymphoma [11].

The main BAFF receptors are BAFF-R, TACI, and BCMA, which are involved in maintaining plasma cell viability and APRIL production. Along with B cells, T helper cells of various subtypes are involved in pathogenesis: Th1, Th17, Tfh, Treg, with Tfh cells (CD4+CXCR5+) playing a special role in forming the microenvironment of germinal centers, ensuring the production of IL21, which contributes to hypergammaglobulinemia and the appearance of antibodies to SSA/Ro [11, 12].An imbalance between Th17 and Treg cells determines the severity of inflammation: Th17 cells damage acinar structures through matrix metalloproteinase 9 and IL22, stimulating the expression of chemokines CXCL13 and CXCL12, which enhances the recruitment of B cells to glandular tissue [13].

Genetic studies have revealed associations between SjD and HLA-DQB1 locus, as well as with IRF5, STAT4, BLK, IL12A, TNIP1, and CXCR5 genes—key regulators of interferon pathways and B-cell activation [14–16], which are characteristics of AID. Epigenetic mechanisms (such as DNA hypomethylation, histone acetylation, and microRNA expression) form a specific pattern of inflammation and interferon activation. DNA methylation varies in different cells and tissues under the influence of external factors, determining cell-specific activation of signaling pathways. Genetic and epigenetic data consistently point to the dominant role of the HLA locus and B-cell hyperactivity processes in the pathogenesis of SjD [17]. At the same time, a shift in normal IgA secretion in favor of IgG antibody production, including autoantibodies to Ro/ SSA, is observed in the glands. The number and maturity of B cells, plasmablasts, and plasma cells correlate with disease activity and reflect the degree of humoral hyperactivity. High maturity of the B cell pool is associated with an inflammatory phenotype and can be considered a biomarker [18].

Thus, SjD as an independent nosological entity represents a complex immunopathological process based on the interaction of epithelial, dendritic, T- and B-cell elements with pronounced IFN- dependent activation and disruption of immunological tolerance mechanisms.

The spectrum of organ damage in SjD

In SjD, in addition to active damage to the exocrine glands, a wide range of organ-specific, extra-glandular manifestations are observed, affecting virtually all organs and systems. According to current data, systemic manifestations often develop in the early stages of the disease, which is associated with higher values of the disease activity index developed by EULAR (European Alliance of Associations for Rheumatology), ESSDAI (EULAR Sjögren's syndrome disease activity index), and determines an unfavorable prognosis of the disease [19].

Respiratory tract involvement occurs in 9–24% of patients and may manifest as interstitial lung disease. The most common radiographic patterns are lymphocytic interstitial pneumonia and nonspecific interstitial pneumonia. In the early stages of SjD, lung involvement may be asymptomatic, but with prolonged disease, it leads to progressive fibrosis and restrictive respiratory disorders [20–22].

At the same time, kidney involvement in the pathological process is mainly characterized by chronic tubulointerstitial nephritis and distal renal tubular acidosis, often with a subclinical course, less often by membranoproliferative glomerulonephritis against the background of cryoglobulinemia. Kidney damage is associated with systemic disease activity and can lead to chronic renal failure [23, 24]. Pathology of the peripheral and central nervous system (CNS) occurs in approximately 10–30% of patients with SjD and includes sensory and sensorimotor polyneuropathy, ganglionopathy, and cranial neuropathies. In some cases, chronic inflammatory demyelinating polyneuropathy or demyelinating CNS lesions are observed [25]. Skin symptoms are noted in 15% of patients with SjD and can be quite diverse. The most common are erythematous changes, urticarial vasculitis, hypergammaglobulinemic vasculitis, and cryoglobulinemic purpura. Cryoglobulinemic vasculitis usually correlates with systemic activity and the risk of B-cell lymphoma [26, 27]. Lesions of the musculoskeletal system (arthralgia, non-erosive arthritis, myalgia, and inflammatory myopathies) are found in most patients with SjD. These manifestations often precede glandular symptoms and can be considered an early systemic phenotype of the disease. Cardiovascular disorders include SjD autoimmune pericarditis (extremely rare), manifestations of vasculitis, and an increased incidence of atherosclerosis. Systemic inflammation, hypergammaglobulinemia, and chronic B-cell activation are considered predictors of endothelial dysfunction and vascular complications [19].

The risk of lymphoproliferative complications in SjD is 5–44 times higher than in the general population. In the vast majority of cases, lymphomas of the lymphoid tissue marginal zone associated with mucous membranes (mucosa-associated lymphoid tissue, MALT) affecting the salivary glands are found. There is also a high incidence of diffuse large B-cell lymphomas and nodal lymphomas. In addition to the salivary and lacrimal glands, the lungs, stomach, spleen, lymph nodes, intestines, thymus, and bone marrow may also be involved. The risk of developing lymphoma is associated with persistent sialadenitis, cryoglobulinemia, hypocomplementemia, elevated rheumatoid factor levels, cytopenias, and remarkable lymphoplasmacytic infiltration of the minor salivary glands. The high incidence of B-cell non-Hodgkin lymphomas in Sjögren's disease once again highlights the pivotal role of B-cell hyperactivity in the pathogenesis of this condition [28, 29].

Pathology of the digestive system is represented by autoimmune hepatitis, primary biliary cholangitis, pancreatopathies, and chronic gastroenteritis. These manifestations are pathogenetically associated with cross-autoimmune activity and a general genetic predisposition [30].

The classification of SjD is far from perfect and has not yet taken its final form. At this stage, it is assumed that there are two main subtypes of SjD, which can transition into each other at different stages of the disease. In most patients, the clinical picture is dominated by manifestations of sicca syndrome, in some cases combined with joint damage and inflammatory activity. Formally, this course of the disease is considered mild. These patients expe-

rience a decline in quality of life due to severe dryness and serious complications associated with the progression of dry eye syndrome (adenitis, corneal ulcers, etc.). In addition, they are at high risk of developing lymphoproliferative diseases. In contrast to this group, 20% of patients have a severe course of SjD, characterized by multiple organ involvement, including severe forms of vasculitis [31].

The combined pathology of the lungs, kidneys, blood vessels, nervous and hepatobiliary systems necessitates early detection of systemic activity, multidisciplinary monitoring and mplementation of a "Treat-to-Target" (T2T) strategy to prevent severe complications and reduce the risk of developing lymphoma.

Evolution of the therapeutic approach

The main practical result of clarifying nomenclature concepts and changing the paradigm is not only the evolution of the therapeutic approach and strategy for patients management with SjD, but also the overall improvement of methods for assessing disease activity and developing new drugs. In turn, the new nomenclature sets a new clinical logic: from "symptomatic therapy" and non-selective immunosuppressants to the modern approach in the traditional rheumatology concept of T2T, aimed to reduce systemic immunological activity, prevent progressive destruction and loss of function of the salivary and lacrimal glands, prevent lymphoproliferative complications and, as a result, improv the quality of life of patients with Sjögren's syndrome [32, 33].

Until recently, there were no validated methods for quantitatively assessing the activity of SjD, which significantly hampered both scientific research and clinical observation of patients. In 2010, EULAR proposed an index that assesses the severity of disease symptoms as reported by the patient (EULAR Sjögren's Syndrome Patient Reported Index, ESSPRI), which, along with the ESSDAI index of disease activity in Sjögren's syndrome, can be used for standardized of symptomsassessment severity and systemic disease activity, respectively [34]. The ESSDAI and ESSPRI indices are important tools for determining the activity of SjD. ESSDAI allows for assessment of the inflammatory processes in different organs and systems of the body, which helps monitor the severity of systemic manifestations of the disease [35]. ESSPRI focuses on symptoms perceived by the patient, such as dryness, fatigue, and pain, and allows for the assessment of quality of life based on subjective feelings [36]. Due to the heterogeneous clinical picture of SjD, composite indices CRESS (Composite of Relevant Endpoints for Sjögren's Syndrome) and STAR (Sjögren's Tool for Assessing Response) were later developed, combining ESSDAI, ESSPRI, and additional clinical parameters for more accurate monitoring of treatment response, used primarily in scientific research [37]. Despite the importance of these indices for understanding and controlling the disease, their use in clinical practice remains limited, which highlights the need for further work on their implementation.

For a long time, clinical studies have demonstrated the low efficacy of drugs for SjD. Several clinical trials have failed to demonstrate the efficacy of classic basic anti-inflammatory drugs, such as hydroxychloroquine, methotrexate, and azathioprine, for sicca syndrome [38–41]. Attempts have also been made to study biologic disease-modifying anti-rheumatic drugs (bDMARDs) targeting various pathological molecules, but none of them have shown therapeutic efficacy. In particular, the use of the IL-6 inhibitor tocilizumab in patients with primary Sjögren's syndrome did not lead to a reduction in the severity of systemic involvement and symptoms during 24 weeks of treatment compared with placebo [42].

The TRIPSS clinical trial evaluated the efficacy of the tumor necrosis factor α inhibitor infliximab in patients with primary Sjögren's syndrome. No statistically significant differences were found between the infliximab and placebo groups in terms of improvement in sialometry and Schirmer's test results, pain and fatigue assessment on a visual analog scale, or ESSPRI scores. After analyzing the results, the authors suggested that one of the reasons for the failure may be the more significant role of B-cell hyperactivity and the humoral immune system, rather than classic pro-inflammatory cytokines. In addition, the heterogeneity of the disease, its varying duration and activity may have influenced the study results [43].

A randomized phase III clinical trial evaluated the efficacy of abatacept (CTLA-4-Ig, a T-cell costimulation inhibitor) in patients with active primary Sjögren's syndrome. The results showed no statistically significant differences in the reduction of the ESSDAI index between the abatacept and placebo groups. There were also no differences in secondary endpoints, including subjective symptoms on the ESSPRI index. A possible reason for the ineffectiveness of abatacept is the complexity of the disease pathogenesis. Although T cells are involved in the pathogenesis of SjD, their depletion does not allow control of the pathological process if the key driver of inflammation is B cell hyperactivation [44].

The TEARS study showed that rituximab (RTX) does not provide a statistically significant reduction in the main symptoms of primarySjögren's syndrome (fatigue, dryness, and pain) compared to placebo. At the same time, positive changes in individual parameters were noted meters, such as increased unstimulated salivation and improved ultrasound parameters of the salivary glands, clear positive dynamics of histological changes according to morphological examination of salivary gland biopsies. The partial failure of the study may have been due to the use of assessment methods that did not fully reflect the complexity of the clinical picture and were insufficiently sensitive to systemic and glandular symptoms of the disease [45]. These failures highlighted the need to stratify patients according to immunological and clinical phenotypes, search for specific biomarkers to assess disease activity, and develop new targeted pathogenetically based agents, including interferon pathway inhibitors, Toll-like receptor antagonists, BAFF/BAFF-R inhibitors, anti-B-cell drugs, T-cell costimulation, and neonatal Fc receptor (FcRn) inhibitors [46]. The first signs of efficacy were obtained in a study of a BAFF-specific monoclonal antibody, belimumab (BLM), which improved clinical indicators of disease activity in patients with SjD [47]. In addition, in a clinical study, combination therapy with BDM and RTX in patients with SjD showed long-term efficacy in reducing disease activity, especially in patients with BAFF overexpression and a risk of developing B-cell lymphoma. The combined approach improved the immunological profile and reduced the manifestations of sicca syndrome, which was not observed with RTX monotherapy and served as the basis for further research into the inhibition of B-cell activation factors [48]. Let us take a closer look at several promising molecules that have shown efficacy in Phase II clinical trials.

BAFF/BAFF-R inhibitors

Ianalumab is a fully human monoclonal IgG antibody to the BAFF-R receptor. Ianalumab has a dual mechanism of B-cell depletion: B-cell depletion through antibody-dependent cellular cytotoxicity (ADCC) and through BAFF-R blockade. Phase II

clinical trial data in SjD indicate that targeting BAFF-R in combination with B-cell depletion via ADCC causes rapid and profound B-cell depletion [49, 50]. The study achieved its primary endpoint, demonstrating a dose-dependent reduction in disease activity as measured by the ESSDAI index at week 24 and good tolerability of ianalumab [51]. Ianalumab is currently in Phase III clinical trials in patients with SjD.

Fc-receptor antagonists

Another promising therapeutic approach is to target diseasespecific circulating IgG by accelerating its catabolism without general immunosuppression. This is the mechanism of action of nipocaliumab, an IgG monoclonal antibody to FcRn. In the randomized, placebo-controlled, double-blind, multicenter Phase II DAHLIAS study evaluating the efficacy and safety of nipocaliumab in adults with primary Sjögren's syndrome, the primary endpoint was achieved, consisting of a significant reduction in the ESSDAI index compared to placebo. a dose- dependent decrease in total IgG levels and a marked reduction in systemic manifestations were observed [52].

Conclusion

Thus, the scientific rationale for the evolution of nomenclature of the SjD nomenclature consists of several factors: modern data convincingly prove that SjD is not an additional syndrome of other rheumatic diseases, but a pathogenetically and clinically independent disease, the immunopathogenesis of which includes clearly identified mechanisms: B-cell hyperactivity, activation of IFN-type I signaling pathways, and complex cascades of interaction between innate and acquired immunity, extending beyond the damage to the exocrine glands and determining the systemic activity of the disease. It is worth noting that the spectrum of systemic manifestations of the inflammatory process is represented not only by sicca syndrome, but also by damage to the joints, skin, respiratory organs, kidneys, liver, nervous system, and vascular bed, which makes SjD a truly multisystemic pathology. Of particular importance is the high risk of developing lymphoproliferative diseases, in particular MALT lymphoma. Such diversity allows us to speak of SjD as a full-fledged systemic pathology, which should occupy a worthy place in the modern nosological classification of rheumatic diseases.

REFERENCES

1. Jonsson R. Henrik Sjögren (1899-1986): the syndrome and his legacy. *Ann Rheum Dis.* 2021 Sep;80(9):1108-1109. doi: 10.1136/annrheumdis-2021-219942.
2. Moutsopoulos HM, Mann DL, Johnson AH, Chused TM. Genetic differences between primary and secondary sicca syndrome. *N Engl J Med.* 1979 Oct 4;301(14):761-3. doi: 10.1056/NEJM197910043011405.
3. Björk A, Mofors J, Wahren-Herlenius M. Environmental factors in the pathogenesis of primary Sjögren's syndrome. *J Intern Med.* 2020 May;287(5):475-492. doi: 10.1111/joim.13032.
4. Beydon M, McCoy S, Nguyen Y, et al. Epidemiology of Sjögren syndrome. *Nat Rev Rheumatol.* 2024 Mar;20(3):158-169. doi: 10.1038/s41584-023-01057-6.
5. Baer AN, Hammitt KM. Sjögren's disease, not syndrome. *Arthritis Rheumatol.* 2021 Jul; 73(7):1347-1348. doi: 10.1002/art.41676.
6. Ramos-Casals M, Baer AN, Brito-Zeryn MDP, et al. 2023 International Rome consensus for the nomenclature of Sjögren disease. *Nat Rev Rheumatol.* 2025 Jul;21(7): 426-437. doi: 10.1038/s41584-025-01268-z.
7. Mavragani CP, Moutsopoulos HM. Primary versus secondary Sjögren syndrome: is it time to reconsider these terms? *J Rheumatol.* 2019 Jul;46(7):665-666. doi: 10.3899/jrheum.180392.
8. Baldini C, Bartoloni E, Bombardieri M. Highlights of the 15th international symposium on Sjögren's syndrome. *Clin Exp Rheumatol.* 2022 Dec;40(12):2201-2210. doi: 10.55563/clinexprheumatol/yt6g9t.
9. Baldini C, Chatzis LG, Fulvio G, et al. Pathogenesis of Sjögren's disease: one year in review 2024. *Clin Exp Rheumatol.* 2024 Dec; 42(12):2336-2343. DOI: 10.55563/clinexprheumatol/i8iszc.
10. Liu Z, Chu A. Sjögren's Syndrome and Viral Infections. *Rheumatol Ther.* 2021 Sep;8(3): 1051-1059. doi: 10.1007/s40744-021-00334-8.
11. Li L, Shen S, Shao S, et al. The role of B cell-activating factor system in autoimmune diseases: mechanisms, disease implications, and therapeutic advances. *Front Immunol.* 2025 Jun 6:16:1538555. doi: 10.3389/fimmu.2025.1538555.
12. Пономарев АБ, Пашаева КР, Фейзиева НЮ. Сравнительный анализ механизмов развития криоглобулинемического васкулита и синдрома Шегрена. Архив патологии. 2024;86(1):52 56.
Ponomarev AB, Pashaeva KR, Feizieva NYu. Comparative analysis of the mechanisms of development of cryoglobulinemic vasculitis and Sjögren's syndrome. *Arkhiv patologii.* 2024;86(1):52 56. (In Russ.).
13. Verstappen GM, Kroese FGM, Bootsma H, et al. T cells in primary Sjögren's syndrome: targets for early intervention.*Rheumatology(Oxford).* 2021 Jul 1;60(7):3088 3098. doi: 10.1093/rheumatology/kez004.
14. Lessard C J, Li H, Adrianto I, et al. Variants at multiple loci implicated in both innate and adaptive immune responses are associated with Sjögren's syndrome. *Nat Genet.* 2013 Nov; 45(11):1284-1292. doi: 10.1038/ng.2792.
15. Khatri B, Tessneer KL, Rasmussen A, et al. Genome-wide association study identifies Sjögren's risk loci with functional implications in immune and glandular cells. *Nat Commun.* 2022 Jul 26;13(1):4287. doi: 10.1038/s41467-022-30773-y.
16. Thorlacius GE, Hultin-Rosenberg L, Sandling JK, et al. Genetic and clinical basis for two distinct subtypes of primary Sjögren's syndrome. *Rheumatology (Oxford).* 2021 Feb 1; 60(2):837-848. doi: 10.1093/rheumatology/keaa331.
17. Thorlacius GE, Bjork A, Wahren-Herlenius M. Genetics and epigenetics of primary Sjögren syndrome: implications for future therapies. *Nat Rev Rheumatol.* 2023 May; 19(5):288-306. doi: 10.1038/s41584-023-00932-6.
18. Bootsma H, Kroese FGM. Association of Circulating Antibody-Secreting Cell Maturity With Disease Features in Primary Sjögren's Syndrome. *Arthritis Rheumatol.* 2023 Jun; 75(6):973-983. doi: 10.1002/art.42422.
19. Baldini C, Fulvio G, La Rocca G, Ferro F. Update on the pathophysiology and treatment of primary Sjögren syndrome. *Nat Rev Rheumatol.* 2024 Aug;20(8):473-491. doi: 10.1038/s41584-024-01135-3.
20. Meudec L, Debray MP, Beurnier A, et al. Pulmonary involvement in Sjögren syndrome. *RMD Open.* 2024 Feb 29;10(1): e003866. doi: 10.1136/rmdopen-2023-003866.
21. Madej M, Proc K, Wawryka P, et al. The analysis of the pulmonary domain involvement in Sjögren's disease. *Ther Adv Musculoskelet Dis.* 2024 Dec 16:16:1759720X241305218. doi: 10.1177/1759720X241305218.
22. Чальцев БД, Васильев ВИ, Аветисов ИО и др. Поражение респираторного тракта при болезни Шёгрена, фокус на интерстициальное заболевание легких. Научно-практическая ревматология. 2022;60(2):214-227.
Chal'tsev BD, Vasil'ev VI, Avetisov IO, et al. Damage to the respiratory tract in Sjögren's disease, focus on interstitial lung disease. *Nauchno-prakticheskaya revmatologiya.* 2022;60(2):214-227. (In Russ.).
23. Aiyegbusi O, McGregor L, McGeoch L, et al. Renal Disease in Primary Sjögren's Syndrome. *Rheumatol Ther.* 2020 Dec 24;8(1): 63–80. doi: 10.1007/s40744-020-00264-x.
24. Porto Fuentes У. Renal involvement in primary Sjögren's syndrome: Beyond tubu-

lointerstitial nephritis. *Nefrologia (Engl Ed)*. 2025 Aug-Sep;45(7):501341. doi: 10.1016/j.nefroe.2025.501341.
25. Barsottin OGP, de Moraes MPM, Fraiman PHA, et al. Sjögren's syndrome: a neurological perspective. *Arq Neuropsiquiatr*. 2023 Dec 29;81(12):1077–1083. doi: 10.1055/s-0043-1777105.
26. Breillat P, Le Guern V, d'Humieres T, et al. Cutaneous Vasculitis in Primary Sjögren Disease. *JAMA Dermatol*. 2025 Aug 6;161(10):1057-62. doi: 10.1001/jamadermatol.2025.2665.
27. Торгашина АВ. Современный взгляд на лечение болезни Шегрена. Фарматека. 2020; 27(7):72 80.
Torgashina AV. A modern view on the treatment of Sjögren's disease. *Farmateka*. 2020; 27(7):72 80. (In Russ.).
28. Васильев МИ, Пробатова НА, Тупицын НН и др. Лимфопролиферативные заболевания при болезни Шегрена. Онкогематология. 2007;(3):16-26.
Vasil'ev MI, Probatova NA, Tupitsyn NN, et al. Lymphoproliferative diseases in Sjögren's disease. *Onkogematologiya*. 2007;(3):16-26. (In Russ.).
29. Rusinovich-Lovgach O, Plaza Z, Fernandez-Castro M, el al. High incidence of lymphoma in Sjögren's disease: predictors and mortality implications in a prospective cohort study. *Rheumatol Int*. 2025 Aug 6;45(8):184. doi: 10.1007/s00296-025-05935-y.
30. Shetler K. Management of Gastrointestinal Manifestations in Sjцgren's. In: Wallace DJ, editor. The Sjögren's Book 5. Oxford: Oxford University Press; 2022. P. 331–337.
31. Brito-Zeryn P, Kostov B, Solans R, et al. Systemic activity and mortality in primary Sjögren syndrome: Predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. *Ann Rheum Dis*. 2016 Feb;75(2):348-55. doi: 10.1136/annrheumdis-2014-206418.
32. Duarte C, Ferreira RJO, Santos EJF, da Silva JAP. Treating-to-target in rheumatology: Theory and practice. *Best Pract Res Clin Rheumatol*. 2022 Mar;36(1):101735. doi: 10.1016/j.berh.2021.101735.
33. Brito-Zeryn P, Ramos-Casals M, Benga G, et al. Efficacy and safety of topical and systemic medications: a systematic literature review informing the EULAR recommendations for the management of Sjögren's syndrome. *RMD Open*. 2019 Oct 28;5(2):e001064. doi: 10.1136/rmdopen-2019-001064.
34. Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjogren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis*. 2010 Jun;69(6):1103-9. doi: 10.1136/ard.2009.110619.
35. Seror R, Bowman SJ, Brito-Zeron P, et al. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. *RMD Open*. 2015 Feb 20;1(1):e000022. doi: 10.1136/rmdopen-2014-000022.
36. Ture HY, Kim NR, Nam EJ. EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and Other Patient-Reported Outcomes in the Assessment of Glandular Dysfunction in Primary Sjögren's Syndrome. *Life (Basel)*. 2023 Sep 29;13(10):1991. doi: 10.3390/life13101991.
37. Isenberg DA. CRESS: improving the assessment of disease activity in Sjögren's syndrome. *Lancet Rheumatol*. 2021 Aug;3(8):e534-e535. doi: 10.1016/S2665-9913(21)00150-8.
38. Fox PC, Datiles M, Atkinson JC, Macynski AA, et al. Prednisone and piroxicam for treatment of primary Sjögren's syndrome. *Clin Exp Rheumatol*. 1993 Mar-Apr;11(2):149-156.
39. Gottenberg JE, Ravaud P, Puechal X, et al. Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome the JOQUER randomized clinical trial. *JAMA*. 2014 Jul 16;312(3):249-58. doi: 10.1001/jama.2014.7682.
40. Skopouli FN, Jagiello P, Tsifetaki N, Moutsopoulos HM. Methotrexate in primary Sjögren's syndrome. *Clin Exp Rheumatol*. 1996 Sep-Oct;14(5):555-558.
41. Price E, Rigby S, Clancy U, Venables PA. Double blind placebo controlled trial of azathioprine in the treatment of primary Sjögren's syndrome. *J Rheumatol*. 1998 May;25(5):896-9.
42. Felten R, Devauchelle-Pensec V, Seror R, et al. Interleukin 6 receptor inhibition in primary Sjögren syndrome: a multicentre double-blind randomised placebo-controlled trial. *Ann Rheum Dis*. 2021 Mar;80(3):329-338. doi: 10.1136/annrheumdis-2020-218467.
43. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). *Arthritis Rheum*. 2004 Apr;50(4):1270-6. doi: 10.1002/art.20146.
44. Baer AN, Gottenberg JE, E St Clair W, et al. Efficacy and safety of abatacept in active primary Sjögren's syndrome: results of a phase III, randomised, placebo-controlled trial. *Ann Rheum Dis*. 2021;80(3):339-348. doi: 10.1136/annrheumdis-2020-218599.
45. Meletis J, Gottenberg JE, Mariette X, et al. Efficacy of Rituximab in Primary Sjögren's Syndrome: The TEARS Randomized, Placebo-Controlled Trial. *Ann Intern Med*. 2014 Feb 18;160(4):233-42. doi: 10.7326/M13-1085.
46. Ritter J, Chen Y, Stefansk AL, Dörner T. Current and future treatment in primary Sjögren's syndrome – A still challenging development. *Joint Bone Spine*. 2022 Nov;89(6):105406. doi: 10.1016/j.jbspin.2022.105406.
47. De Vita S, Quartuccio L, Seror R, et al. Efficacy and safety of belimumab given for 12 months in primary Sjögren's syndrome: the BELISS open-label phase II study. *Rheumatology (Oxford)*. 2015 Dec;54(12):2249-56. doi: 10.1093/rheumatology/kev257.
48. Mariette X, Barone F, Baldini C, et al. A randomized, phase II study of sequential belimumab and rituximab in primary Sjögren's syndrome. *JCI Insight*. 2022 Dec 8;7(23):e163030. doi: 10.1172/jci.insight.163030.
49. Dörner T, Posch MG, Li Y, et al. Treatment of primary Sjögren's syndrome with ianalumab, an anti-BAFF receptor monoclonal antibody. *Ann Rheum Dis*. 2019 May;78(5):641-647. doi: 10.1136/annrheumdis-2018-214720.
50. Bowman SJ, Everett CC, O'Dwyer JL, et al. Safety and efficacy of subcutaneous ianalumab (VAY736) in patients with primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled, phase 2b dose-finding trial. *Lancet*. 2022 Jan 8;399(10320):161-171. doi: 10.1016/S0140-6736(21)02251-0.
51. Dörner T, Bowman SJ, Fox R, et al. Safety and Efficacy of Ianalumab in Patients With Sjögren's Disease: 52-Week Results From a Randomized, Placebo-Controlled, Phase 2b Dose-Ranging Study. *Arthritis Rheumatol*. 2025 May;77(5):560-570. doi: 10.1002/art.43059.
52. Gottenberg JE, Sivils K, Campbell K, et al. Efficacy and Safety of nipocalimab, an anti-FcRn monoclonal antibody, in primary Sjögren's disease: Results from a phase 2, multicenter, randomized, placebo-controlled, double-blind study (DAHLIAS). *Ann Rheum Dis*. 2024;83(1):240.

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