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Review Article

Insights on Sjögren's Syndrome: Beyond Dry Eye Symptoms

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ABSTRACT

Sjögren's Syndrome (SS), a systemic autoimmune condition, that is characterised by the presence of dry eyes along with dry mouth. However, it is important to note that the effects of this disorder are not limited to these primary symptoms. This dissertation examines the complex nature of SS, investigating its various forms, the underlying immunological processes involved, and the consequences for diagnosing and treating the condition. In addition to causing dryness in the eyes and mouth, SS can also impact various other organ systems, resulting in consequences such as systemic inflammation, tiredness, joint discomfort, and organ dysfunction. This article provides a thorough examination of the current literature and clinical observations to elucidate the intricate nature of SS pathophysiology. It explores the involvement of lymphocytic infiltration, autoantibody production, and hereditary predisposition. Moreover, it explores the difficulties in diagnosing SS, highlighting the significance of thorough evaluation and interdisciplinary cooperation. Treatment strategies involve a comprehensive strategy focused on alleviating symptoms, maintaining organ function, and enhancing quality of life. This abstract seeks to expand our comprehension of SS beyond its symptoms related to dry eyes, with the goal of improving therapeutic treatment and promoting increased recognition of this frequently neglected autoimmune disorder.

Keywords: Autoimmune condition, Dry eyes, Immunological processes, Systemic inflammation, Joint discomfort, Organ dysfunction, Lymphocytic infiltration.

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INTRODUCTION

Sjögren's Syndrome (SS), pronounced SHOW-grins, is named for Dr. Henrik Sjögren, a Swedish ophthalmologist who initially documented the condition in 1933. The characteristic symptoms include persistent dryness of the eyes, lips, or both. The lacrimal glands and saliva-producing glands are responsible for maintaining moisture in the eyes and mouth, respectively. In SS, these glands are the focus of an immune system that is not functioning properly (Fox, 1984). Leukocytes migrate from the bloodstream to the glands and impair the secretory function of the glandular cells, leading to a reduction in moisture secretion. This process remains poorly comprehended and is currently the subject of ongoing investigation. Approximately 50% of individuals with SS have an atypical protein, known as an autoantibody, present in their blood. This protein is also linked to another autoimmune disorder, rheumatoid arthritis. This implies a potential correlation between SS and other autoimmune disorders. Approximately half of patients diagnosed with SS have an underlying connective tissue condition, including rheumatoid arthritis or lupus (Reale, 2018). SS can manifest independently of any other medically acknowledged rheumatic condition. At that point, it is referred to as "primary" Sjögren's. Conversely, the term "secondary Sjögren's" is employed when SS manifests alongside another autoimmune disorder.

SS is a persistent autoimmune disorder characterised by the immune system's white blood cells attacking the exocrine glands responsible for producing saliva and tears. The predominant manifestations of SS are xerophthalmia and xerostomia resulting from diminished excretion of tears and saliva (Youinou, 2001). This autoimmune condition is highly common, affecting up to 2% of Americans, with a higher prevalence among women. There is an increasing level of public awareness regarding the disease. Nevertheless, a significant number of individuals lack comprehension regarding the profound influence that SS exerts on their physiological well-being, as well as the gravity of this ailment. The systemic characters of SS is what can render it a debilitating and potentially life-threatening condition. Damage

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to dermatological organs, such as the skin and vaginal tissues, can result in discomfort and agony. The presence of lymphocytes in the salivary and lacrimal glands causes swelling in those specific areas, and medicines like steroids and antimalarials are commonly used to suppress the immunological response throughout the body (Sáez, 2021).

Women over the age of 40 frequently have the issue of dry eye. SS, an autoimmune condition, can manifest as a symptom and has the potential to impact up to 4 million individuals in the United States. The objective of this series is to enhance knowledge and understanding of this intricate condition and to offer valuable information to patients and their families. The series will also benefit carers, healthcare practitioners, and the general public (Karnell, 2014).

SS is a common autoimmune condition that affects 0.1-4% of the population in the United States, with a higher occurrence in women. The illness is defined by the immune system's assault on the glands that produce tears and saliva, resulting in symptoms of dry eyes and mouth. Additionally, this illness can impact various other bodily systems like joints, thyroid, kidneys, liver, lungs, skin, and nerves. SS is more commonly diagnosed in those over the age of 40, and women are at a significantly higher risk of developing this ailment. Furthermore, persons with rheumatic illnesses, such as rheumatoid arthritis or lupus, are more likely to experience SS. Potential risk factors for Primary SS (pSS) comprise infections, a family history of autoimmune disorders in first-degree relatives, unfavourable stressful life situations, polymorphisms in the IRF5 gene, CGGGG deletion or insertion. There is no connection between a person's past smoking habits and the development of pSS. However, it has been found that present smoking has a detrimental effect on the beginning of pSS. SS can result in a range of difficulties, especially impacting the eyes and mouth. These issues include dental caries, fungal infections, and visual impairments (Nair, 2017).

CLINICAL AND SYSTEMIC MANIFESTATIONS

Dry Eye Symptoms

SS can lead to dry eyes, which can result in a burning or itchy sensation, as well as a feeling of having sand in the eyes (Nikolov, 2009; Christodoulou, 2008; Ambrus, 2016). The lack of moisture in the eyes can result in symptoms such as impaired vision, heightened sensitivity to light, redness, frequent blinking, and excessive tear production. Insufficient tear production can cause visual impairments, such as corneal ulcers, and if not effectively addressed, can potentially result in eye infections (Figure 1).

Dry Mouth Symptoms

Xerostomia, often known as dry mouth, can result in a mouth sensation that resembles chalk or cotton. This condition can lead to challenges in swallowing, speaking, and tasting. People may experience nocturnal thirst or increase their daytime fluid intake to facilitate the process of swallowing food. The absence of saliva's defensive properties can result in dental problems such as tooth decay and oral infections, including oral thrush.

Joint Pain and Swelling

SS often presents with joint pain and swelling, which typically affects numerous joints. This pattern of joint pain can be episodic, with times of intense pain (flares) followed by periods of minimal or no discomfort (Blaschek, 1988; Goëb, 2007; Mishra, 2024; Pessôa, 2023). SS primarily affects the fingers, wrists, and ankles, but it can also impact other joints such as the shoulders, hips, and knees. The pain can be attributed to either inflammatory arthritis, which is characterised by tenderness and swelling, or fibromyalgia, which originates from the muscles but is interpreted as originating from the joints (García-Carrasco, 2012). It is essential to differentiate between Osteoarthritis (OA) and inflammatory arthritis in SS to choose the appropriate treatment.

Fatigue and Weakness

Fatigue is a common and debilitating symptom in SS, affecting around 70% of patients and exerting a significant negative impact on their overall quality of life. The reason of fatigue in SS is not defined properly, and there is no known effective way to address it (Pillemer, 2001; Fauchais, 2010; Peen, 2009; Theander, 2006).

Skin Dryness

This disorder triggers an immune response that targets healthy cells, particularly those involved in the production of bodily moisture. As a consequence, dryness occurs, leading to the appearance of thin tissues, the disappearance of creases, and the presence of pale, dry skin in the affected area (Tobon, 2010; Barone, 2008; García-Carrasco, 2006; Binard, 2009). Engaging in pelvic floor exercises and using vaginal dilators can effectively mitigate the occurrence of rigidity in the vaginal muscles and gradually expand the vaginal canal.

Vaginal Dryness

Vaginal dryness is a prevalent symptom of SS, causing soreness, itching, pain, or discomfort during sexual intercourse, frequent urination, and urinary tract infections (Nazmul-Hossain, 2011). Effective natural therapies for alleviating vaginal dryness in individuals with SS include engaging in regular sexual activity, utilising coconut oil and aloe vera, employing vitamin E suppositories, increasing vitamin D intake, maintaining a healthy diet and exercise routine, and using water-based lubricants. Frequent sexual stimulation can enhance vaginal health by promoting increased blood circulation and vaginal secretions, thereby alleviating vaginal dryness. Coconut oil functions as a natural cleanser, hydrant, and moisturiser. However, it should not be employed as a lubricant due to its potential to harm condoms. Aloe vera gel helps alleviate vaginal dryness resulting from SS (Fragkioudaki, 2016). Vitamin D has the potential to reduce

vaginal dryness and enhance vaginal well-being. Pre-coital application of aqueous lubricants can effectively hydrate the vaginal region and alleviate any discomfort or pain resulting from vaginal dryness.

PATHOPHYSIOLOGY

SS is primarily an autoimmune illness defined by lymphocyte invasion and destruction of the salivary as well as lacrimal glands. It also induces autoantibodies to develop against ribonucleoprotein particles; SS-B/La and SS-A/Ro throughout body. The invasive lymphocytes, including T-cells, B-cells, along with dendritic cells, disrupt the function of the glands in many ways (Gulati, 2010). They collapse glandular elements through cell-mediated mechanisms, produce cytokines that triggers type 1 and 2 interferon pathways, produce autoantibodies those disrupt muscarinic receptors, and discharge metalloproteinases (MMPs) those block the interaction among glandular cells and their extracellular matrix, all of which are crucial for appropriate glandular functions. Pathogenesis is a multifaceted process driven by numerous causes (Figure 2). Environmental variables are thought to trigger inflammation in people who are genetically predisposed to the disorder (Hansen, 2010).

DIAGNOSTIC APPROACHES

Blood Tests for Autoantibodies

SS is characterised by the production of autoantibodies by the immune system, which specifically target the glands that generate moisture in the eyes and mouth. The autoantibodies; SS-B (La), SS-A (Ro), antinuclear antibodies including rheumatoid factors (Min, 2021). SS-A (Ro) antibodies have been identified in around 60-80% of those diagnosed with SS, while SS-B (La) antibodies have been found in approximately 30-50% of these individuals. These antibodies are non-specific to SS and can also be detected in individuals having SLE; Systemic Lupus Erythematosus and other autoimmune disorders. Antinuclear antibodies; ANAs are available in almost all of SS patients, but they are also commonly seen in healthy individuals.

Salivary Gland Biopsy

Salivary gland biopsy, namely labial salivary gland biopsy, is essential for diagnosing SS. Antinuclear antibodies; ANAs are found in practically all Sjögren's disease patients, but they are also frequent in healthy people. A verified ANA test is not restricted to SS and may reveal a diagnosis of other autoimmune diseases. Biopsies of the small salivary glands, which are conveniently positioned immediately beneath the inner surface of the lip, are frequently performed due to their easy accessibility. During a lip biopsy, a superficial cut is performed on both sides of the inner lip, and around 5-7 glands are delicately extracted for analysis (Chung, 2019). The defining histological feature regarding SS is "focal lymphocytic sialoadenitis," characterised by the availability of dense clusters of lymphocytes in close proximity to healthy glandular tissue, around a duct inside a specific region of the gland. The presence of these aggregates, referred to as foci, is measured using a "focus score" and serves as an indication of the condition. In addition, the lip biopsy can detect several forms of glandular inflammation that may indicate other diagnoses such as sarcoidosis, amyloidosis, or lymphoma.

COMPLICATIONS AND ASSOCIATED CONDITIONS

Lymphoma and SS

SS can lead to a serious and potentially life-threatening condition called lymphoma. Mortality rate in patients with this illness is primarily influenced by this factor. Extra nodal non-Hodgkin lymphomas with B cells are the most common type of lymphoma regarding SS, primarily impacting Mucosa Associated Lymphoid Tissue (MALT). The proliferation of B-cell lymphoma in case of SS is such a complex series of steps, where the cancerous B cells often originate from autoreactive clones, particularly B cells that produce RF. These cells suffer uncontrolled growth and evade the body's normal mechanisms to prevent malignancy. The main predictive indicators for lymphomas associated with SS include B-cell activation, disease activity, and reduced immunosurveillance. The association between primary SS (SS) and the development of Non-Hodgkin Lymphoma (NHL) is widely recognised, and it is particularly prominent compared to other systemic autoimmune illnesses.

Pulmonary Involvement

The pulmonary symptoms of SS encompass a wide range of conditions, including abnormalities in the airways and Interstitial Lung Disease (ILD). The primary risk factors for lung involvement are male gender, smoking, initiation of the disease at a later age, and a prolonged disease progression. The incidence of pSS lung illness with clinical significance has been documented to range from 9% to as high as 20%. Nevertheless, the prevalence estimates see a substantial increase (43-75%) when subjected to a thorough review using imaging techniques and pulmonary function testing, indicating a broader range of subclinical manifestations.

Renal and Gastrointestinal Manifestations

SS is an autoimmune condition that mostly impacts the exocrine glands, resulting in symptoms of dryness in the eyes and mouth. Nevertheless, this illness can also impact other areas of the body, such as the kidneys and gastrointestinal tract (Lee, 2019). The renal symptoms of SS arise from two separate pathophysiological mechanisms: epithelium disease characterised by extensive infiltration of lymphocytes, and non-epithelial disease that can cause glomerulopathy through an immune complex-mediated process. Epithelial diseases can cause a variety of illnesses, including electrolyte abnormalities

such as hypokalaemia, proximal renal tubular acidosis, Fanconi syndrome, diabetes insipidus, distal renal tubular acidosis, Gitelman syndrome, nephrolithiasis, nephrocalcinosis, and Tubulointerstitial Nephritis (TIN) (Zabotti, 2019).

THERAPEUTICAL MANAGEMENTS

Artificial Tears and Moisturizing Agents

Artificial tears and moisturising chemicals are frequently employed to treat the symptoms of dry eyes that are linked to SS. These drops are designed for stabilising the tear film, shield the eye surface, decrease tear evaporation, and improve the healing process and lubrication. Preserved artificial tears can be administered up to 4 times per day for mild dry eye disease, while preservative-free artificial tears should be injected 4 or more times per day for more severe disease (Vitali, 2002). Preservative-free eye drops are supplied in vials instead of bottles and should be refrigerated for a maximum of 2 days after opening. Applying a topical gel or ointment before going to bed can also be helpful. During the day, if tears alone are not enough, a gel formulation of tears can be utilised. Prescription drops, such as topical steroids, cyclosporine, and lifitegrast, are effective in reducing ocular inflammation. Topical steroids are used for limited durations because to the potential risks of developing cataracts and increased pressure within the eye. Supplementing with omega-3 fatty acids may potentially alleviate dry eye condition, while the evidence is inconclusive. The tear volume can be increased by inserting removable plugs into the tear ducts in the eyelids and by taking specific oral drugs that promote tear production, such as pilocarpine and cevimeline (Zhang, 2015). Proper usage of artificial tears is crucial to prevent contamination and the risk of eye infections that may lead to blindness or severe disease.

Saliva Stimulants and Substitutes

Saliva stimulants and replacements have a crucial role in treatment of dry mouth symptoms in individuals having Sjögren's disease. Pilocarpine (Salagen) and cevimeline (Evoxac) are medications that can enhance the production of saliva and occasionally tears. These drugs function by activating the salivary glands to generate an increased amount of saliva, which can effectively reduce symptoms of dry mouth (Youinou, 2010). Saliva substitutes are employed to replenish the absence of saliva in the oral cavity. They are available in several formulations, including sprays, gels, or lozenges, and can alleviate mouth dryness by providing lubrication. Aside from saliva stimulants and replacements, there are several strategies that can aid in the management of dry mouth symptoms in SS. These measures encompass augmenting the consumption of fluids, refraining from specific food and drink items that may exacerbate dry mouth symptoms, encouraging saliva production through the use of sugar-free gum or sweets, and utilising artificial saliva products (Figure 3).

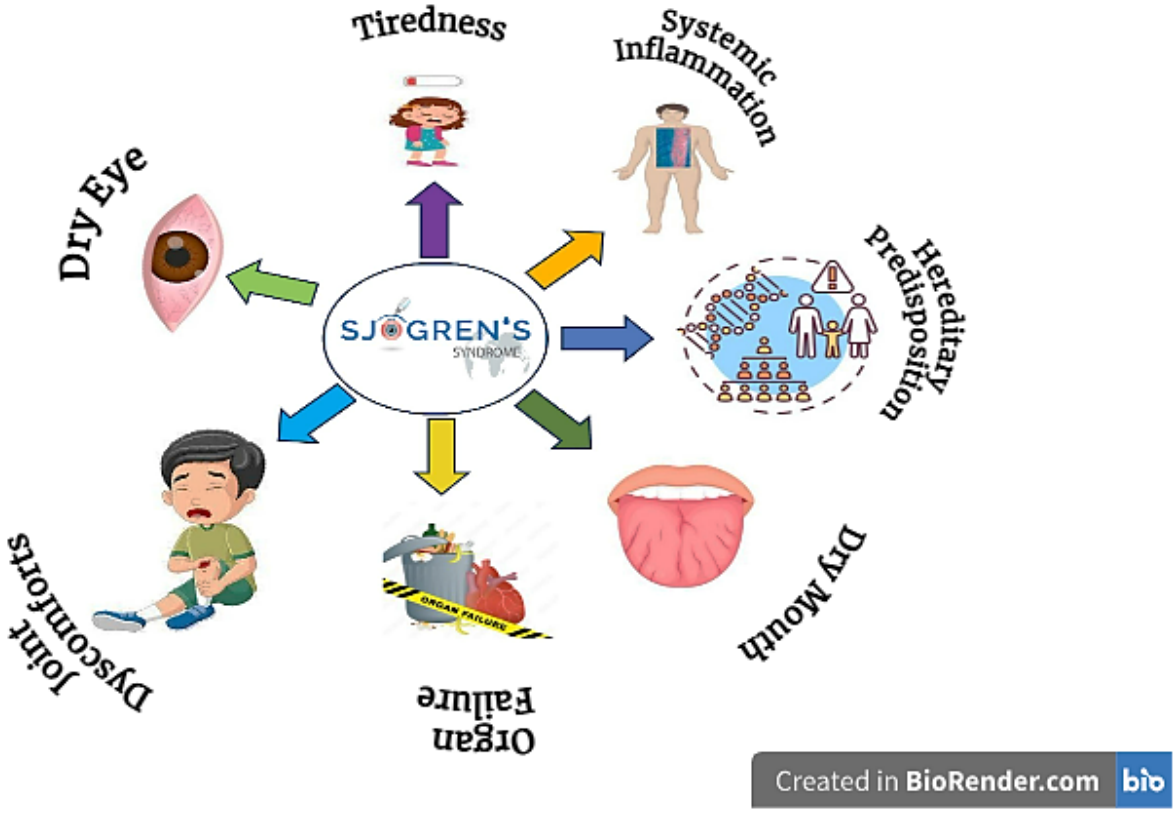

Figure 1: Clinical Representation of SS.

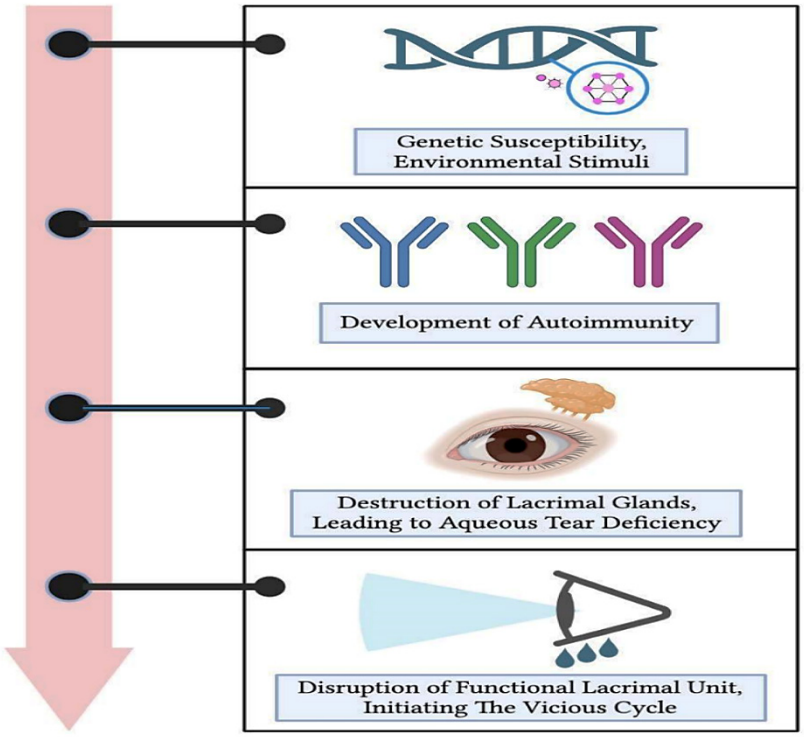

Figure 2: Pathophysiology of Dry Eye.

Immunomodulatory Drugs

Immunomodulatory medicines have a crucial role in treating SS (SS), a long-term autoimmune condition that largely influences the exocrine glands, leading to symptoms of dry eyes as well as dry mouth. The management of this disorder has not progressed beyond mitigating the conditional symptoms regarding glandular dysfunction along with regulating any systemic consequences (Baer, 2016). The measurement of systemic activity and patient symptoms in recent clinical trials has predominantly utilised the EULAR SS Disease Activity Index (ESSDAI) and ESSPRI as validated outcome measures. The ESSDAI, a comprehensive index that integrates the weighted scores of ten clinical items, a haematologic item, and a biological item to yield a single score (Tanaka, 2017). So far, medications for SS have mostly been chosen basing on their efficacy in case of other autoimmune disorders, alike SLE; Systemic Lupus Erythematosus (SLE) or RA; Rheumatoid Arthritis. Nevertheless, this approach has clear disadvantages, as SS probably possesses distinct immunological systems in action, especially considering the significant involvement of epithelial cells in the development of this illness (Alam, 2020). When evaluating new therapy for SS, it is important to assess their scientific justification and how they relate to the development of the disease.

IMMUNOTHERAPY IN SS

Current Therapeutic Approaches

Corticosteroids

Topical corticosteroids are widely used to suppress inflammation in SS. They inhibit cytokine production and immune cell activation but are associated with long-term side effects such as glaucoma and cataracts (Bron, 2017).

Cyclosporine A (CsA)

CsA, an immunomodulator, inhibits T-cell activation and cytokine release by blocking calcineurin. It is approved for treating moderate-to-severe DED and has demonstrated efficacy in reducing inflammation and improving tear production (Sall, 2000).

Lifitegrast

Lifitegrast inhibits T-cell activation as well as adherence to the ocular surface by blocking lymphocyte function-associated antigen-1 (LFA-1). Clinical trials have revealed substantial improvements in symptoms and markers of DED, particularly in the NSDE (Gottenberg, 2019).

EMERGING IMMUNOTHERAPIES

Janus Kinase (JAK) Inhibitors

JAK inhibitors target the signaling pathways of type I and II interferons. By reducing the inflammatory cascade, these

inhibitors show promise in managing SSDE, particularly in patients with high interferon signatures (McCoy, 2020).

Tumor Necrosis Factor-α; TNF-α Inhibitors

TNF-α inhibitors, such as infliximab and etanercept, have been explored in autoimmune diseases, including SSDE. They suppress inflammatory cytokines and ameliorate glandular dysfunction (Almulhim, 2024).

IL-17 and IL-23 Inhibitors

Interleukin (IL)-17 and IL-23 play crucial roles in Th17-mediated inflammation. Their inhibitors, such as secukinumab, have shown potential in reducing corneal and conjunctival inflammation in animal models of DED (Negrini, 2022).

Mesenchymal Stem Cell Therapy

Mesenchymal Stem Cells (MSCs) exert immunomodulatory effects by secreting anti-inflammatory cytokines and promoting tissue repair. Preliminary studies suggest their potential in regenerating lacrimal gland tissue and reducing inflammation in both SSDE and NSDE (Kelly, 2022).

Anti-B-cell Therapies

Rituximab, a monoclonal antibody that targets CD20 on B cells, has demonstrated effectiveness in systemic SS. It reduces autoantibody production and immune cell infiltration, potentially benefiting SSDE-associated DED (Phadatare, 2015).

Biologic Therapies

Biologic therapy are essential in the treatment of SS, a systemic autoimmune condition that mostly impacts the exocrine glands, resulting in symptoms such as dry eyes and mouth. These therapies selectively focus on particular elements of the immune system to regulate the immune response and diminish inflammation linked to the disease. Various biologic medicines have demonstrated potential in the management depicted in Figure 4.

FUTURE RESEARCH AND ADVANCEMENTS

Novel Therapeutic Targets

Biologic treatments, including rituximab, belimumab, and other immunomodulatory drugs, have demonstrated potential in treating the immunological dysregulation and inflammation linked to SS. Additional investigation and rigorous clinical trials are necessary to reveal innovative treatment options that can target the intricate immunological pathways involved in SS and enhance patient outcomes.

Precision Medicine Approaches

The application of precision medicine in the treatment of SS entails the utilisation of tailored therapies that are customised to address the individual patient's unique requirements and attributes. Implementing this molecular classification approach can improve understanding the underlying mechanisms of diseases and accelerate the development of specialised treatments. Furthermore, a precision medicine strategy for SS may include the utilisation of biological therapies that selectively target immune system components to regulate the immune response

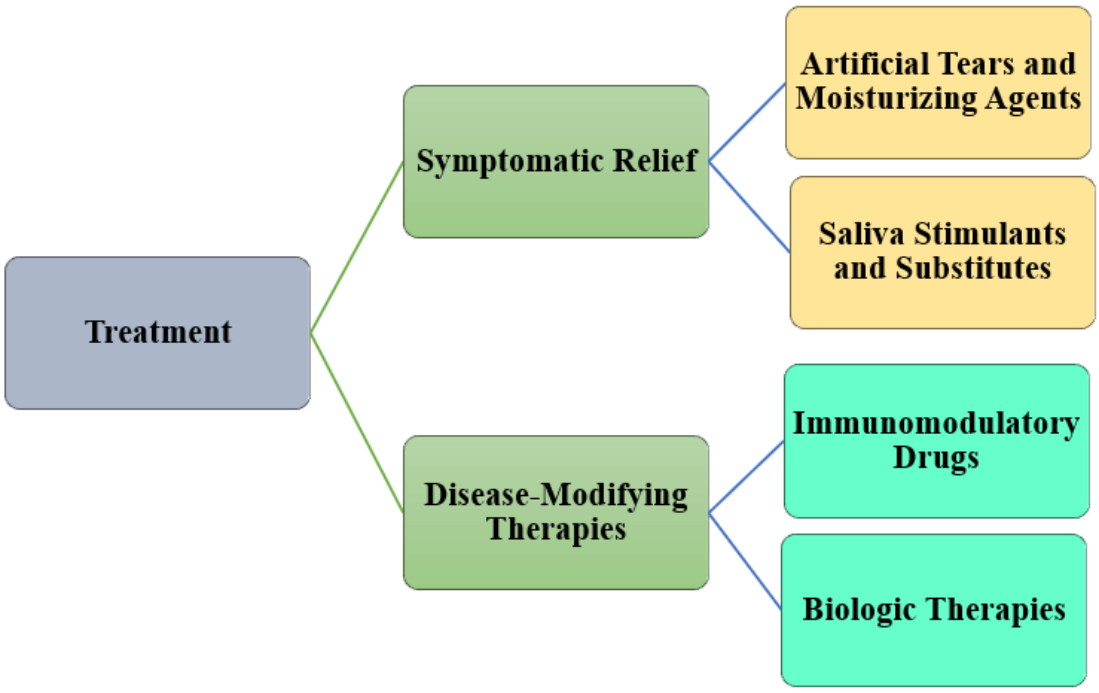

Figure 3: Types of Treatment or therapies.

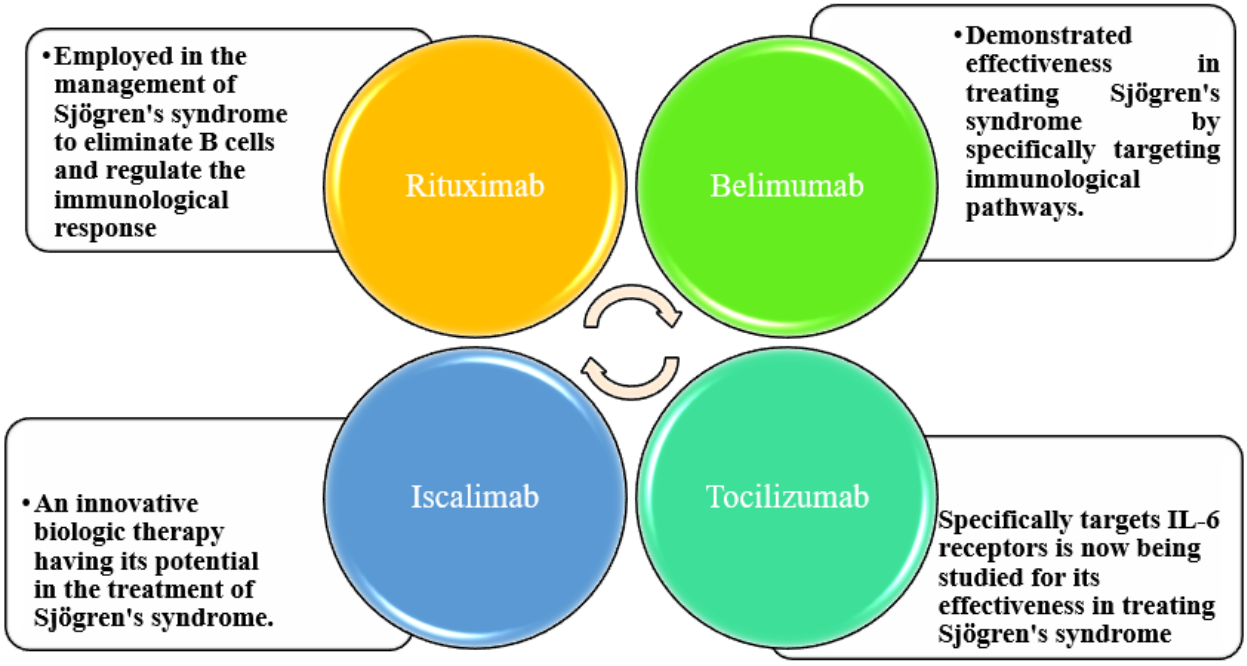

Figure 4: Predicted Therapies.

and mitigate disease-related inflammation. Some examples of these medicines are rituximab, belimumab, and other specific immunomodulatory drugs. In addition, precision medicine can encompass the application of salivary gland gene therapy, which seeks to administer therapeutic genes directly to the salivary glands, stimulating the production of moisture and alleviating symptoms. This technique is now in its preliminary stages of development, but it shows potential for a more focused and enduring therapy alternative.

Biomarkers and Early Detection

Effective care of SS, a complex autoimmune condition that causes dry eyes and mouth symptoms, relies heavily on biomarkers and early identification. Biomarkers play a crucial role in early illness detection, disease activity monitoring, and complication prediction. At now, there is no singular biomarker available for diagnosing SS. However, other biomarkers have been developed that potentially provide support for the diagnosis. These include Antinuclear Antibodies (ANA), anti-Ro/SS-A, anti-La/SS-B, Rheumatoid Factor (RF), and hypocomplementemia. These biomarkers lack specificity for SS and are also present in other autoimmune disorders. Hence, a comprehensive diagnosis requires the integration of clinical symptoms, laboratory investigations, and imaging studies. Current research has prioritised the identification of novel biomarkers to enhance the timely detection and treatment of SS.

CONCLUSION

SS is a multifaceted autoimmune condition that impacts the exocrine glands, resulting in symptoms of dry eyes and mouth. Furthermore, research has studied the effects of immunological surveillance on the success of biologic therapy for SS, highlighting the need for future studies in this sector. Regarding treatment, the latest guidelines from the EULAR propose that both topical and systemic medicines can be efficacious in the management of SS. These treatments encompass B-cell depletion therapy, modulation of co-stimulatory and co-inhibitory pathways, and inhibition of T cell co-stimulation. Nevertheless, further investigation is necessary to comprehensively comprehend the repercussions of these medicines and their influence on patient outcomes. In order to effectively manage SS, it is important to adopt a comprehensive approach that acknowledges the intricate relationship between immunological dysregulation and inflammation that is at the core of this disorder.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SS: Sjogren's Syndrome; **pSS:** Primary Sjogren's syndrome; **OA:** Osterarthritis; **SLE:** Systemic Lupus Erythematosus; **ANA:** Antinuclear Antibodies; **MALT:** Mucosa Associated Lymphoid Tissue; **NHL:** Non-Hodgkin Lymphoma; **ILD:** Interstitial Lung Disease; **TIN:** Tubulointerstitial Nephritis; **RA:** Rheumatoid ArthritisCsA: Cyclosporine A; **LFA1:** Lymphocyte Function Associated Antigen-1; **JAK:** Janus Kinase; **TNF:** Tumor Necrosis Factor; **IL:** Interleukin; **MSCs:** Mesenchymal Stem Cells; **RF:** Rheumatoid factor.

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