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Review

Emerging Trends and Management for Sjögren Syndrome-Related Dry Eye Corneal Alterations

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Abstract: Background: Sjögren's syndrome (SS) is a systemic autoimmune condition marked by significant dry eye disease (DED), leading to considerable corneal changes. These modifications, encompassing punctate epithelial erosions, chronic epithelial abnormalities, and corneal ulcers, significantly impact eyesight and quality of life. Progress in comprehending the corneal pathophysiology associated with SS has prompted innovative diagnostic and treatment approaches. Aim: This narrative review aims to examine developing trends in the pathogenesis, diagnostic methods, and treatment strategies for Sjögren's syndrome-associated corneal changes. Methods: The study was based on a narrative review of the current literature available on PubMed and Cochrane from Jan 2000 to December 2024. Results: Corneal changes associated with Sjögren's syndrome result from a multifactorial interaction of ocular surface inflammation, tear film instability, and epithelium degradation. Recent research underscores the significance of immune-mediated pathways, such as T-cell-induced inflammation and cytokine dysregulation, as crucial factors in corneal disease. Innovations in diagnostic instruments, including in vivo confocal microscopy and tear proteomics, provide earlier and more accurate identification of subclinical alterations in the corneal epithelium and stroma. Therapeutic developments concentrate on meeting the specific requirements of SS-related DED. Biological treatments, especially tailored inhibitors of interleukin-6 and tumor necrosis factor-alpha, show potential in mitigating inflammation and facilitating epithelial repair. Moreover, regenerative approaches, such as autologous serum tears and mesenchymal stem cell therapies, provide innovative methods to repair ocular surface integrity. Advanced drug delivery technologies, including nanoparticle-loaded eye drops, enhance bioavailability and therapeutic efficacy. Conclusion: Recent developments in comprehending SS-related corneal changes have transformed the management approach to precision medicine. The combination of improved diagnostics and innovative therapy approaches offers potential for reducing disease progression, maintaining corneal health, and enhancing patient outcomes. Subsequent investigations ought to concentrate on enhancing these tactics and examining their long-term safety and effectiveness. Clinicians and researchers must adopt these developments to successfully tackle the difficulties of

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SS-related corneal illness, providing hope for improved care and higher quality of life for those affected.

Keywords: Sjögren's syndrome; autoimmune eye diseases; dry eye disease; keratoconjunctivitis sicca; ocular surface; cornea; corneal pathologies; corneal medical and surgical therapies

1. Introduction

Sjögren's syndrome (SS) is a complex chronic progressive multisystem inflammatory autoimmune disorder of unknown pathogenesis for which a curative therapy does not exist [1]. It is characterized by an autoimmune attack and destruction of the exocrine glands of the body, especially salivary and lacrimal glands, so xerostomia and dry eye represent its hallmark clinical signs [1]. Furthermore, SS may affect several other extraglandular organs, causing heterogeneous clinical manifestations and multiple organ damage, and it is associated with increased risk of malignancies [1–3]. SS may be present alone as primary SS (pSS) (30% of cases), or it can coexist with other systemic autoimmune (AI) disorders, a condition called secondary SS (sSS) or Sjögren's syndrome with overlap [1,4]. Furthermore, SS is classified as one of the AI connective tissue diseases (CTDs), i.e., severe multisystem AI disorders of still uncertain origin that affect the connective tissue proteins, also including rheumatoid arthritis (RA), systemic sclerosis, systemic lupus erythematosus (SLE), and inflammatory myopathies [5].

The cornea is an ocular structure of fundamental importance, with an essential role in refracting light and protecting the internal ocular structures. For still unclear reasons, the cornea is frequently affected in SS [6–10] and in other systemic AI diseases [5,11], with clinical manifestations ranging from benign conditions, like mild eye dryness, to sight-threatening corneal complications, such as sterile corneal melting and peripheral ulcerative keratitis (PUK), that require intensive monitoring and treatments in order to prevent severe loss of visual acuity and eye globe integrity [8–13].

The present manuscript aims to summarize the most recent developments in comprehending SS-related corneal changes, including new, improved diagnostics and innovative therapy approaches that may offer the potential to maintain corneal health, reduce disease progression, and enhance patient outcomes.

2. Sjögren's Syndrome Clinical Manifestations and Ocular Involvement

Primary SS has an estimated worldwide prevalence ranging between 0.01 and 4.8% [14] and a strong female predominance [15], and although it may affect individuals across the age spectrum, it shows a peak of incidence between 50 and 60 years [14,15].

The pSS clinical manifestations may be classified into glandular and extraglandular forms [1–3]. Glandular forms represent the original disease targeting the exocrine glands. Their clinical features include dry eye and/or xerostomia, noted by more than 90% of pSS patients and considered to be the clinical hallmarks of the disease; bilateral salivary glands swelling, present in one-third of cases; and dryness of skin and/or various mucosal surfaces, caused by the involvement of other exocrine glands (20% of cases) [1–3]. Extraglandular forms, present in 30–90% of pSS patients, are thought to be related to a more complex systemic immunological dysregulation, and although any organ of the body may be virtually affected, the most frequent targets include the musculoskeletal apparatus (75% of cases), visual system (25–60% of cases), hematological system (33% of cases), nervous system (15–55% of cases), and respiratory tract (10–25% of cases) [1–3]. The most severe

pSS extraglandular systemic complications are represented by interstitial lung disease (15–20% of cases) and non-Hodgkin lymphoma (5% of cases) [1–3]. Extraglandular systemic manifestations are associated with a worse prognosis and a higher risk of mortality [1–3].

Moreover, 70–80% of pSS patients complain of systemic non-organ-specific symptoms, including persistent fatigue, anxiety, depression, sleep disorders, mild cognitive impairment, Raynaud phenomenon, chronic diffuse and migrant musculoskeletal pain, etc. [1–3]. Eye and oral dryness, musculoskeletal pain, and fatigue indeed represent the classic symptomatologic triad of pSS [1–3].

Considering that eye and mouth dryness are experienced by 30–35% and 20–30% of the general population, respectively, mainly by females older than 50 years [16], a differential diagnosis between SS-related and non-SS dry eye and/or xerostomia is mandatory. The most frequent causes of eye and mouth dryness are represented by aging and drug assumptions, especially anti-cholinergic and/or sympathomimetic medications, although several other variables can be involved [16]. Additionally, it has been estimated that nearly 50% of patients requiring an ophthalmological examination for symptoms related to eye dryness are affected by an occult AI disease, mainly AI thyroiditis or SS, and that approximately 10% of patients affected by clinically significant dry eye have an underlying undiagnosed pSS [17].

SS diagnosis requires the identification of an autoimmune process targeting the salivary or lacrimal glands [1]. The latest proposed pSS diagnostic criteria are the revised 2016 classification criteria of the American College of Rheumatology (ACR)-European League Against Rheumatism (EULAR) [18], which define the Sjögren's syndrome with a weighted score of at least of 4 points, and it assigns 3 points each for salivary gland biopsy positive for the presence of lymphocytic infiltration ($\geq$50 lymphocytes/4mm^2) [19] and the presence of serum SSA/Ro autoantibodies (titers $\geq$ 1:320) [20] and 1 point each for unstimulated whole salivary flow $\leq$ 0.1 mL/min [1], with Schirmer's test results $\leq$ 5 mm/5 min indicating a pathologically reduced aqueous tear production rate [21] and ocular staining score $\geq$ 5 indicating a severe ocular surface damage [22].

The SS ocular involvement may also be divided into glandular and extraglandular forms. Ocular glandular forms are caused by the destruction of the lacrimal glands, which represent the first and principal target of the SS and are characterized by eye dryness [6,7]. Dry eye is a disturbance of the lacrimal functional unit, composed of the lacrimal glands, ocular surface (cornea, conjunctiva, and Meibomian glands), lids, and nerves [23]. The damage of any component may disrupt the homeostasis of the whole unit, leading to a clinical entity known as dry eye disease (DED) or keratoconjunctivitis sicca (KCS) [17]. According to the Tear Film and Ocular Surface Society Dry Eye Workshops (FTOS DEWS) II, DED is defined as a multifactorial condition of the ocular surface marked by a disruption of tear film homeostasis and associated ocular symptoms, wherein tear film instability, hyperosmolarity, ocular surface inflammation, and damage along with neurosensory abnormalities contribute to its etiology [23]. DED may be classified into two forms: the aqueous deficient dry eye (ADDE), caused by reduced tear production and representing 5 to 50% of the DED forms, and the evaporative dry eye, related to excessive tear evaporation [23]. ADDE can be subdivided into SS-related and non-SS-related forms [23], and SS represents one of the most important causes of severe ADDE [1,23].

Extraglandular ocular manifestations include ocular disorders other than DED, such as papillary, follicular, or cicatrizing conjunctivitis as well as recurrent infectious keratitis, sterile corneal haze, scarring, ulcer, melt, perforation, PUK, uveitis, scleritis, episcleritis, optic neuritis, retinal vasculitis, and orbital inflammation [6–9,12,13]. Extraglandular ocular forms affect a percentage of pSS patients ranging between 25% and 60%. Vision-threatening ocular complications with severe visual impairment, including corneal melting,

PUK, necrotizing scleritis, and retinal vasculitis, occur in approximately 10–15% of pSS cases and 15–20% of sSS patients, especially patients affected by rheumatoid arthritis. Severe extraglandular ocular manifestations have a higher prevalence in men and a strong association with life-threatening systemic complications [6–9,12,13].

3. Glandular Ocular Involvement: Dry Eye Disease (DED) or Keratoconjunctivitis Sicca (KCS)

3.1. Histology, Biochemistry, Anatomy, and Physiology

Several studies performed using different methods have demonstrated that patients affected by SS-related DED or KCS show various abnormalities of all ocular surface components (Table 1). The results of these studies are frequently non-univocal because of the lack of a clear distinction between pSS and sSS patients, the inclusion of patients with different disease severity degrees, and the comparison against different control groups (healthy subjects or other non-SS dry eye patients). However, they may still help in understanding the pathogenesis and clinical manifestations of the SS.

Table 1. Ocular surface histological, anatomical, and physiological features in Sjögren's syndrome-related dry eye disease.

Tissue/Organ	Diagnostic Method	Findings
Salivary and lacrimal glands	**Histology [24–26]**	Infiltration of lymphocytes CD4+ T helper cells (Th1 and Th17), CD8+ T cytotoxic cells, B lymphocytes, plasma cells, macrophages, fibroblasts, and dendritic and mast cells; reduced levels of T regulatory cells
		Destruction of the gland tubuloacinar architecture and atrophy in late stages
		High levels of pro-inflammatory cytokines, especially interferon (IFN)-γ and interleukin (IL)-17
		Presence of autoantibodies, such as anti-SSA/Ro and anti-SSB/La
		Presence of Epstein–Barr virus antigens
		Ectopic lymphoid germinal center-like structures containing autoreactive B lymphocytes
Tear film	**Chemical and biochemical analyses [27]**	Tear film hyperosmolarity
		Enhanced levels of proinflammatory cytokines (e.g., IL-1α, IL-1β, IL-6, IL-8, IL-10, IL-17, IL-33, TNF-α, and IFN-γ), matrix metalloproteinase (MMP-9), and defensins
		Over-expression of HLA-DR antigens
		Decreased levels of lysozyme, lactoferrin, and IgA
		Presence of autoantibodies, including anti-Ro/SSA, anti-La/SSB, ANA, and rheumatoid factor
		Decreased levels of epidermal growth factor secreted by the lacrimal gland
		Decreased levels of nerve growth factor secreted by the ocular surface nerves
		Decreased levels of a mucin and transforming growth factor (TGF)-β produced by the conjunctival goblet cells
		Upregulation of several proteins related to the oxidative stress, such as the APEX1 and S100
	Microbiological analyses [28]	Tear film microbiome alterations, with predominant pro-inflammatory bacteria

Table 1. *Cont.*

Tissue/Organ	Diagnostic Method	Findings
Meibomian glands and eyelids	**Slit lamp, keratography [29]**	Anterior blepharitis
		Meibomian gland dysfunction, with reduced number of Meibomian glands, increased number of gland orifices occlusion, and metaplasia
		Decreased thickness and stability of the tear film lipid layer and increased tears evaporability
Conjunctiva	**In vivo confocal scanning laser microscopy, impression cytology [30,31]**	Conjunctival epithelial cells decreased density and morphological alterations, with microcystic degeneration
		Significant reduction in goblet cell density and decreased tear film mucous layer (xerophthalmia);
		Infiltration of lymphocytes CD4+ T helper cells (Th1 and Th17), CD8+ T cytotoxic cells, B lymphocytes, plasma cells, macrophages, fibroblasts, and dendritic and mast cells; reduced levels of T regulatory cells
		Presence of autoantibodies, including anti-Ro/SSA, anti-La/SSB, ANA, and rheumatoid factor
		Increased levels of proinflammatory cytokine (e.g., IL-1, IL-6, and IFN-γ)
		Over-expression of human leukocytes antigen (HLA)-DR and HLA-DQ and CD40 antigens on both lymphocytes and conjunctival epithelial cells
		Over-expression of antigen intercellular adhesion molecule (ICAM)-1, which may induce apoptosis of the epithelial cells
		Conjunctival epithelial squamous metaplasia or keratinization (rare)
		Cicatrizing conjunctivitis (rare)
Cornea	**In vivo confocal scanning laser microscopy [32–34]**	Morphological alteration of all epithelial layers
		Decreased cell density of superficial epithelium and outer and inner layers of the wing cells
		Reduced or increased basal epithelial cell density
		Squamous metaplasia or keratinization of the superficial epithelium (rare)
		Decreased or increased stromal keratocyte density
		Increased stromal dendritic cell density and activation
		Increased Bowman's and stromal collagen degradation and stromal thinning
		Sub-basal nerve plexus morphological abnormalities (increased nerve reflectivity, width, and tortuosity)
		Sub-basal nerve plexus reduced density and length
	Ocular Response Analyzer [35]	Reduced corneal stiffness

The most important findings include those discussed below.

3.1.1. Salivary and Lachrymal Glands

Histological studies have shown salivary and lacrimal gland infiltration by T and B lymphocytes, which represents the histological hallmark of the pSS [24,25] and one of the most important diagnostic features [18]. Considering this, in pSS patients, lacrimal gland damage has been demonstrated to develop earlier than that of the salivary glands [24], and eye dryness may represent the earlier phase of the disease. Ectopic lymphoid germinal

center-like structures containing recirculating autoreactive B cells are present in the salivary glands of 25% of pSS patients and have been associated with an increased risk of B-cell lymphoma development [26].

3.1.2. Tear Film

Chemical and microbiological analyses of tear film composition in SS patients have shown abnormal levels of several molecules involved in host defense, immune response, inflammation, cellular apoptosis, cell signaling, and adhesion [27]. Features that pSS patients share with other non-SS DED subjects include tear hyperosmolarity, increased levels of several proinflammatory cytokines, decreased levels of mucin [27], and tear film microbiome dysbiosis, with predominance of proinflammatory bacteria [28]. Conversely, possible tear film SS diagnostic biomarkers include the presence of anti-Ro/SSA and anti-La/SSB antibodies; upregulation of proinflammatory molecules such as interleukin (IL)-17 and IL-8; upregulation of the human leukocyte antigen (HLA)-DR antigen, which seems to be involved in the self-antigens presentation to autoreactive T cells; downregulation of molecules with antimicrobial properties, including lysozyme and lactoferrin, secreted by the lacrimal glands, and IgA, produced by the lymphocytes; decreased levels of epidermal growth factor secreted by the lachrymal gland, of nerve growth factor produced by the ocular surface nerves, and of transforming growth factor (TGF)-β produced by the conjunctival goblet cells [27].

3.1.3. Meibomian Glands

Slit lamp evaluation or new non-invasive instruments, such as keratography [29], have shown that approximately 20% of SS patients have associated anterior blepharitis, and 45–60% are affected by a Meibomian gland dysfunction (MGD), i.e., a chronic alteration of the specialized sebaceous glands producing the lipid layer of the tears.

3.1.4. Conjunctiva

In vivo confocal scanning laser microscopy [30] and impression cytology studies [31] conducted in SS patients have shown several conjunctival abnormalities, including decreased density and morphological alterations of epithelial and goblet cells; the infiltration of T and B lymphocytes and several other inflammatory cells; the presence of autoantibodies such as anti-SSA/Ro and anti-SSB/La; and the over-expression of several proinflammatory molecules and specific HLA antigens.

3.1.5. Cornea

In vivo confocal scanning laser microscopy studies have found that, as compared with healthy or non-SS DED subjects, SS patients show many corneal alterations, including epithelial cells' decreased density and morphological abnormalities [32]; superficial epithelium squamous metaplasia or keratinization (rare) [32]; reduced density of the stromal keratocytes and stromal thinning [32]; upregulation of the stromal dendritic cells, whose density and size seem to be linked to systemic disease severity (assessed using salivary gland biopsy and serum autoantibodies) and to the ocular surface damage [33]; and decreased density and morphological abnormalities of the sub-basal nerve plexus [32,34]. In particular, corneal nerve density and length have been demonstrated to be inversely related to systemic SS disease activity and the degree of eye dryness severity [34]. Moreover, studies investigating corneal biomechanics have demonstrated significantly reduced corneal stiffness in SS-related DED patients as compared with healthy subjects [35].

3.2. Clinical Characteristics

Clinical signs of DED or KCS are present in almost all SS patients [6,7,17]. SS-related DED is characterized by moderate-to-severe eye dryness, ocular surface fluorosis and damage of various degrees of severity, neurotrophic features, and increased ocular surface susceptibility to infections [6,7,17]. Eye dryness represents the first and most common sign and symptom of pSS, objectively present in 97–100% of cases and reported by 80–92% of pSS patients [6,7,12,17]. SS-related DED may have a wide clinical spectrum, ranging from mild eye dryness and clear ocular surface to severe dry eye with filamentary keratitis. Typical SS-related DED clinical signs at the slit lamp include lacrimal meniscus height reduction; conjunctival and perihepatic hyperemia; punctate superficial keratopathy, mild in 100% of cases and moderate-to-severe in more than 50% of cases; recurrent epithelial erosions/scarring (20%); nonhealing corneal ulcers (1–2% of cases); xerophthalmia (20–35% of cases); filamentary keratitis characterized by debris of damaged epithelium and mucous filaments, present in 20–35% of cases; corneal or conjunctival keratinization (1–2% of cases) [6,7,12,17]; seborrheic anterior blepharitis (20% of cases); or posterior blepharitis or MGD (45–60% of cases) [12,29]. Real cicatrizing conjunctivitis is infrequently associated with SS [6,7,12] and most frequently found in Graft versus host disease or Stevens–Johnson syndrome, so its presence therefore requires investigations to exclude other causes of severe dry eye [16].

The clinical severity of the KCS, as evaluated using the Schirmer's test and the ocular surface staining score, is significantly linked to visual performance [12] and, in pSS (not in sSS patients), appears associated with the systemic disease activity as evaluated using the serum anti-La/SSB and anti-Ro/SSA antibodies and tear IL-17 levels [36]. Characteristic SS-related DED symptoms include eye dryness, discomfort, irritation or pain, photosensitivity, reduced or increased tearing, itching, burning, soreness, grittiness, scratchiness, foreign body sensation, blurred vision, decreased visual acuity, significant vision fluctuation with transient improvement after blinking or artificial tears instillation, blinking, and eye fatigue [6,7,17]. Clinical symptoms of SS-related DED are generally worsened by heat, wind, dust, smoke, air dryness, and activities related to a low blinking rate, such as reading, using a computer, driving, or watching television [6,7,17]. SS-related DED symptoms typically progressively increase in duration and intensity and, in late stages, may become severe pain and chronic visual impairment that significantly reduce the quality of life of SS patients [6,7,17,37].

Eye dryness has been demonstrated to be the single most disturbing symptom in pSS. Together with chronic fatigue, it has the greatest impact on pSS patients' quality of life. Patients perceive it as more burdensome than other systemic manifestations of the disease, and it is the most complained-about symptom when pSS patients require a medical check-up [37].

As compared to non-SS DED, SS-related DED is characterized by several hallmarks, including the following:

- More severe eye dryness developing at a younger age and progressing more severely and rapidly [38]. It has been estimated that 70–85% of SS patients show a Schirmer's test $\leq$ 5 mm/5 min, indicating a severe eye dryness degree [12];
- More complex eye dryness (aqueous deficient + evaporative): Although SS-related DED is classified as a form of ADDE [23], an associated damage of conjunctival goblet cells and Meibomian glands may be present in 45–60% of cases [12,29]. SS-related DED should thus be regarded as a more complex and severe dry eye involving all tear film components, where the aqueous-deficient DED, considered the hallmark of the disease, is complicated by mucous and lipid layers instability and tears evaporation [39];

- More severe ocular surface inflammation and damage: as compared with other DED forms, the SS-related DED is characterized by significantly higher levels of inflammatory biomarkers on the ocular surface [27] and by more severe ocular surface inflammation and damage and visual difficulties [6,7,12,17,38];
- Neurotrophic component and typical discordance between clinical signs and symptoms: Patients with pSS are frequently affected by functional corneal nerves abnormalities. SS-related DED seems to be associated with less severe symptoms of ocular discomfort than non-SS DED forms or similar symptoms in the presence of significantly worse signs in SS patients [38], probably because of the higher degree of corneal nerves dysfunction found in SS patients, especially in more severe and long-lasting cases [40]. Conversely, other SS patients, especially women, may show corneal hypersensitivity, with neuropathic pain and light sensitivity, which may be caused by neuroinflammation [40]. The structural [32,34] and functional [40] corneal nerves abnormalities found in SS patients suggest that the SS-related dry eye disease may be regarded as a form of neurotrophic keratopathy [40];
- Higher risk of corneal and other vision-threatening complications [8,9];
- Higher infective risk: pSS patients show an increased risk of bacterial and fungal infections of the ocular surface [41]. The incidence of the infectious keratitis in the USA general population ranges between 0.0025% to 0.28%, whereas it is approximately 2% in SS patients, with a recurrence in 17% of cases [41];
- The need for more aggressive therapy in order to improve clinical signs and symptoms [17,42–44].

3.3. Pathogenesis

In general, the etiopathogenesis of the pSS is not yet completely elucidated and is believed to be complex and multifactorial [45,46]. Considering specifically the SS-related DED, many scientific data support the existence of a strong interaction amongst ocular surface components and immune and nervous systems in its onset and development [45–47]. A central factor seems to be the loss of the so-called "immune tolerance" or "immune-privilege" of the ocular surface, i.e., its ability to activate specific immunoregulatory mechanisms that prevent continuous and unnecessary inflammatory/immune responses and consequent tissue damage despite the constant exposure to various environmental stimuli [48].

Possible mechanisms involved in the SS-related KCS pathogenesis include the following:

- Environmental factors-triggered autoimmune attack against the lachrymal glands [49], which represent the first and most important pSS target [24,25], leading to reduced aqueous tear film and epithelial growth factors secretion and tear film hyperosmolarity;
- Autoimmune attack against the ocular surface epithelium, conjunctival goblet cells, and Meibomian glands, with reduction in all tear film components, as well as epithelial cells autoantigens expression and proinflammatory molecules release [50];
- Amplification of the inflammatory response by innate and adaptive immune systems with the release of proinflammatory cytokine and chemokines [33,51];
- Neuroinflammation and neurodegeneration [32,34], with reduced tear reflex and NGFs production [40];
- Decreased levels of growth factors on the ocular surface, including epidermal growth factor secreted by the lachrymal gland, nerve growth factors (NGFs) released by the corneal nerves, and transforming growth factor produced by the conjunctival goblet cells [27], with impairment of the epithelial cell proliferation, differentiation, and migration;
- Dysbiosis of the ocular surface, which may trigger an autoimmune attack via autoantigens-mimicry mechanisms and may increase infection susceptibility [28];

- Damage/apoptosis of epithelial cells, corneal dendritic cells, keratocytes, conjunctival goblet cells, and ocular surface nerves involved in the "immune-tolerance" of the ocular surface [48], which may favor autoantigens' presentation of T and B lymphocytes [45,46];
- Genetic and epigenetic factors may favor a dysregulated inflammatory/immune response in predisposed subjects [52,53].

A vicious circle of autoimmune and inflammatory responses, reduction in tear film production, ocular surface damage, and denervation is thought to lead to a chronic, automaintaining, and progressive disease [45–47]. Furthermore, it is still unclear if the ocular surface inflammation and damage are primary, i.e., related to the direct autoimmune attack of the ocular surface epithelium [50], or secondary, i.e., induced by the lacrimal gland dysfunction and the consequent eye dryness [47,54]. Tear hyperosmolarity has been indeed demonstrated to cause upregulation of the inflammatory and innate immune response and damage and dysfunction of the ocular surface epithelial and goblet cells [47,54].

Moreover, the significantly higher incidence of the infectious keratitis found in SS subjects, prevalently bacterial [41], may be related to several predisposing factors, including decreased tears flux, which reduces the ocular surface wash [6,7]; lower levels of antimicrobial tear molecules, such as lactoferrin, lysozyme, and IgA [27]; corneal and conjunctival epithelial defects [12]; ocular surface microbiome dysbiosis, with decreased microbial diversity that may favor the development of atypical ocular infections [28]; and side effects of various different therapeutic approaches, such as contact lens wear or topical and systemic drugs [6,7].

3.4. Treatment Strategies

In general, the optimal therapeutic approach to SS patients is still unknown, and although some treatments may improve symptoms and prevent complications, there is currently no cure for SS [3,45,46]. Several guidelines for the management of SS-related dry eye disease have been released in recent years [42–44,55,56]. The aim of the SS-related DED treatment should be to conserve, stimulate, and replace the tear secretion; to prevent or treat ocular surface inflammation and damage; to reduce eye symptoms; and to identify and grade the presence of an underlying systemic disease activity [42–44,55,56]. Furthermore, the paucity of RCTs supporting therapy recommendations in SS patients [57,58] leads to an extremely heterogeneous approach. Treatments are chosen on an individual basis, depending on the presence and severity of the different clinical manifestations.

SS-related DED therapeutic approach should be based on three cornerstones:

- Comprehensive ophthalmological examination by a corneal specialist: it should be focused on the determination of the relative contribution of aqueous-deficient and evaporative dry eye and the severity level of the ocular surface damage and visual disturbance [55,56];
- Multidisciplinary care team: The involvement of other specialists, such as odontostomatologists, rheumatologists, and immunologists, is of fundamental importance in order to establish glandular and extraglandular systemic involvement and disease activity. The presence of severe vision-threatening ocular complications or systemic manifestation requires a prompt multidisciplinary approach and systemic immunosuppressive therapy prescribed by a rheumatologist/immunologist [42–44,55,56];
- Stepwise approach: the treatment should start with the patient's education about useful lifestyle modifications (Table 2) and with the prescription of artificial tear substitutes (eyedrops, gels, or ointments), which remain the first-line therapy in patients with DED of any cause [59] (Table 3). Other topical (Table 3), mechanical (Table 3), systemic, or surgical therapies should be recommended as second-line approaches depending

on the ocular and systemic associated complications [42–44,55,56]. The treatment of the SS-related KCS is generally limited to topical or mechanical approaches (Table 3). In a subset of SS patients, DED is unresponsive to common treatment, resulting in severe clinical manifestations, including recurrent corneal infections and persistent corneal abrasion or scarring, which may require more complex treatments.

Table 2. Lifestyle habits modifications effective in reducing signs and symptoms of dry eye disease [42–44,55,56].

Maintaining good ocular hygiene
Wearing protective glasses
Avoiding smoking
Avoiding dry or windy environments
Limiting activities associated with reduced blink rate, such as reading or using computer
Limiting medications that may decrease tears production, including anti-cholinergic drugs (antidepressant, anxiolytics, and anti-psychotics), muscarinic antagonists (e.g., tamsulosin and ipratropium), anti-histamines, opiates, anti-hypertensives (e.g., beta-blockers and ACE inhibitors), proton pump inhibitors (e.g., omeprazole), etc.

Table 3. Topical and mechanical approaches to the Sjögren's syndrome-related corneal manifestations.

Therapeutic Option	Active Components	Therapeutic Effects	Drawbacks and Side Effects	Efficacy in DED Patients (Level of Evidence)	Efficacy in SS Patients (Level of Evidence)	Guidelines Recommendation in SS-Related DED [42–44,55,56]
Artificial tear eye drops, lubricating gels, and ointments [59]	Hyaluronic acid, hydroxypropyl methylcellulose, carboxy methylcellulose, polyvinyl alcohol, carbopol, polyvinylpyrrolidone, polyethylene glycol, dextran, and polyacrylic acid liquid polyols	Reduction in friction between ocular surface and lids and increase in ocular surface regularity	Lack of tear components essential for ocular surface homeostasis (e.g., growth factors, vitamins, and immunoglobulins) and preservative-related toxicity [60]	Moderate to high [59,61]	Low [62]	First-line therapy in preservative-free formulations
Autologous or homologous serum prepared as eyedrops [63]	Blood serum containing anti-infective agents (lysozyme, lactoferrin, and IgA), anti-inflammatory molecules (cytokines, interleukin receptor antagonists, and matrix metalloproteinase inhibitors), epitheliotrophic substances (fibronectin, vitamin A, epidermal growth factor, and transforming growth factor-β) [63].	Ocular surface hydration and nutrition, stimulation of epithelial cells and nerves regeneration, and anti-inflammatory and anti-infective actions [63]	Risk of infections, input of proinflammatory cytokines in cases of severe SS systemic disease (prefer allogenic serum), and high preparation costs [63]	Low [64]	Low to moderate [65,66]	Suggested in cases of severe DED

Table 3. *Cont.*

Therapeutic Option	Active Components	Therapeutic Effects	Drawbacks and Side Effects	Efficacy in DED Patients (Level of Evidence)	Efficacy in SS Patients (Level of Evidence)	Guidelines Recommendation in SS-Related DED [42–44,55,56]
Non-steroidal anti-inflammatory drugs (NSAIDs) eyedrops [67]	Diclofenac, bromfenac, flurbiprofen, indomethacin, ketorolac, and nepafenac	Anti-inflammatory and analgesic effects	Corneal sensitivity decrease, epithelium healing delay [68], and association with corneal melting/perforations in general population [68] and SS patients [69,70]	Low to moderate in reducing ocular discomfort and some dry eye signs [67]	Low to moderate in reducing ocular discomfort and some dry eye signs [67]	Better to avoid
Corticosteroids eyedrops [71]	Dexamethasone, methylprednisolone, fluorometholone, and hydrocortisone	Anti-inflammatory effects	Glaucoma, cataract, herpes simplex virus reactivation, epithelial healing delay, stromal collagen production inhibition, and increased risk of corneal/scleral perforation [71]	Low to moderate in improving DED symptoms; low in improving DED signs [71]	High in reducing ocular surface inflammation and improving DED symptoms; moderate in improving DED signs [72–74]	Suggested for short-term or pulse therapy (2–4 weeks) in patients who do not respond to other therapies
Immunosuppressant agents eyedrops	Cyclosporine A [75]	Downregulation of proinflammatory cytokines, T-cells recruitment, and apoptosis	Burning sensation after instillation (60% of cases)	Controversial: high [76] or poor [77]; moderate in treatment of MGD [75]	Controversial evidence: high [76] or moderate [78]	Suggested in cases of moderate-to-severe DED and MGD
Biologic agent eyedrops	Lifitegrast [79,80]	Integrin antagonist inhibiting antigen-presenting cells, CD4+ T cells activation and migration, and intracellular adhesion molecule-1 (ICAM-1)		High in improving signs and symptoms in non-SS DED patients [79] and in improving clinical DED signs in pSS animal models [80]	None	Approved by the FDA to reduce ocular surface inflammation in DED patients [79].

Table 3. *Cont.*

Therapeutic Option	Active Components	Therapeutic Effects	Drawbacks and Side Effects	Efficacy in DED Patients (Level of Evidence)	Efficacy in SS Patients (Level of Evidence)	Guidelines Recommendation in SS-Related DED [42–44,55,56]
Temporary or permanent punctal plugs [81]		Tear deflux reduction, tear meniscus increase	Increased risk of infections and accumulation of pro-inflammatory cytokines on the ocular surface	Controversial: high [62] or poor [81]	High [62] or moderate [82]	Suggested in cases of moderate-to-severe DED
Therapeutic contact lenses [83]		Ocular surface protection from eyelids and environment, increased permanence of artificial tears or drugs on the ocular surface, desiccation reduction, corneal healing promotion, and discomfort relieve	Mechanical damage of the surface, epithelial swelling, hypoxic, and infective and inflammatory complications	Moderate to high [83]	Limited [84]	Suggested in cases of moderate-to-severe DED or in presence of eyelids abnormalities

Artificial tear drops, lubricating gels, and ointments [59] have traditionally been considered the first-line therapy in patients with DED of any cause [55,56]. General rules for their use in DED patients include preferring viscous preparations that last longer and should be instilled less frequently, using artificial tears with lipid components in the presence of the MGD, and preferring preservative-free preparations to avoid local toxicity, which is of crucial importance in SS-related KCS patients that are more prone to developing ocular surface damage [55,56,59]. The most common preservative, benzalkonium chloride, has been indeed demonstrated to be toxic for the epithelium and the goblet cells and to cause tear film instability, ocular surface damage, epithelial apoptosis, conjunctival flogosis, and subconjunctival fibrosis [60]. Although several studies have demonstrated that tear substitutes may improve ocular symptoms and some ocular tests in DED patients [59], only a few studies have specifically included pSS patients [62]. Tear substitutes have varied formulations that differ in composition, viscosity, lipid content, and level of hydration. Moreover, the comparison of efficacy and safety of different artificial tear types has provided poor and inconclusive results, so none of the tear substitutes has been shown to be clearly superior in treating DED, specifically SS-related DED [61].

Autologous or homologous serum can be prepared as eyedrops. Guidelines suggest its use in cases of severe DED [63], although a Cochrane review investigating the use of autologous serum in the dry eye found inconsistency in the benefits for both symptoms and objective measures [64]. Several small studies [65,66] have demonstrated its efficacy in helping the management of glandular and extraglandular corneal manifestations in SS patients.

Non-steroidal anti-inflammatory drugs (NSAIDs) eyedrops have been demonstrated to reduce ocular discomfort and dry eye signs in SS patients [67] but may also decrease corneal sensitivity and delay epithelium healing [68]. Moreover, some cases of corneal melting/perforations have been associated with the use of topical NSAIDs [68] and also in SS patients [69,70]. For these reasons, NSAID eye drops should be used with caution or are better avoided in SS patients [42–44,55,56];

Although a 2022 Cochrane review of the outcomes of topical corticosteroids in DED patients showed small to moderate degrees of DED symptom relief and poor evidence of DED signs reduction [71], CS eyedrops have demonstrated their efficacy in reducing ocular surface inflammation and improving symptoms and some objective parameters in SS-related DED in two RCTs [72,73]. They may have many side effects, including glaucoma, cataracts, herpes simplex virus reactivation [74], epithelial healing delay, and collagen production downregulation, with increased risk of corneal and scleral perforation [69]. Topical CSs should be considered with caution, and guidelines suggest CSs short-term or pulse topical therapy (two to four weeks) in patients who do not respond to other therapies [42–44,55,56].

Cyclosporine A is an immunosuppressive agent [75]. Its topical use has been approved for the treatment of moderate-to-severe DED and also in SS patients [55,56,75] based on RCTs [76]. However, a Cochrane systematic review published in 2019 reported that its efficacy in DED patients may not be better than placebo or artificial tears [77]. Small studies have demonstrated that its use in SS patients may increase the total tear production, the number of conjunctival goblet cells, and the corneal sub-basal nerve density [78]. Lifitegrast is an integrin antagonist that inhibits activation and migration of the antigen-presenting cells and the CD4+ T cells and downregulates the intracellular adhesion molecule-1 (ICAM-1) [79]. It has been shown to improve both signs and symptoms of DED in large RCTs [79], and its ophthalmic formulation was approved in 2016 for the treatment of DED-related ocular surface inflammation by the U.S. Food and Drug Administration (FDA) [79]. Although no specific data about pSS patients are currently available, topical lifitegrast has been shown to improve clinical signs of KCS in pSS animal models [80].

The presence of persistent anterior blepharitis or Meibomian gland dysfunction requires appropriate therapy with eyelid cleaning, warm compresses, and topical and oral antibiotics. More specifically, doxycycline 50 mg per os/daily for 3 months or topical azithromycin ophthalmic solution 1% twice daily for 2 days and once daily thereafter for 28 days have been demonstrated to be effective in treating anterior blepharitis and MGD [55,56].

RCTs [62] have demonstrated the efficacy of punctal plugs in reducing the signs and symptoms of SS-related DED. Punctal plug inserts can be loaded with different therapeutic agents. A recent Cochrane review, however, found very limited and inconclusive evidence of their efficacy in DED patients [81]. Their use in SS patients has shown clinical efficacy similar to or higher than that of artificial tears [62,82].

Therapeutic contact lenses, especially soft scleral lenses, and rigid gas-permeable scleral contact lenses have been shown to reduce dry eye signs and symptoms in DED patients [83]. However, studies investigating their specific efficacy and safety in SS patients are still limited [84]. In severe cases, drug-loaded contact lenses or other inserts can be a viable option [83,84].

4. Extraglandular Corneal Complications

4.1. Clinical Manifestations

The cornea is the ocular structure most frequently and severely involved in extraglandular ocular manifestations. Corneal extra glandular complications are the most

commonly described vision-threatening SS-related disorders. They have a global prevalence of 2.5–4% among SS patients, are present in 2.5% of cases at disease presentation, are more frequently found in men (90% of cases) and in sSS-RA patients (up to 75% of cases), and are typically associated with other extraglandular ocular complications, especially necrotizing scleritis [2,6–9,12,13].

Moreover, severe extraglandular corneal complications are linked to higher levels of systemic inflammatory markers (ESR erythrocyte sedimentation rate and CRP C-reactive protein) and to other extraglandular severe systemic manifestations, especially peripheral neuropathy, interstitial nephritis, and vasculitis as well as greater risk of mortality as compared to the other SS patients [8].

These data suggest that extraglandular corneal complications may have a more complex polyautoimmunitary pathogenesis [45,46] and that they may represent a barometer of systemic disease activity, especially in pSS patients [8].

Corneal extraglandular manifestations include the following:

***A. Sterile central or paracentral corneal scarring/ulcer/melting or keratolysis*:** This is a rare, potentially blinding condition that is occasionally recurrent and may lead to corneal perforation. It can be associated with SS (2.5–3.6% of cases) [8–10,12,13,85,86] and with other systemic AI diseases [11]. It is characterized by the development of epithelial defects and progressive reduction in the stromal components in a non-inflamed eye, and it may evolve into descemetocele formation and corneal perforation [10,13]. The sterile ulcer is typically painless, but in 40% of cases, it may involve the visual axis, inducing blurred vision and reduced visual acuity. The incidence of perforation in sterile ulcers of SS patients is high, reaching 40% of cases, because these ulcers are often painless and have a delayed diagnosis [10,13]. Several instances of sterile corneal ulcers/melting/impeding corneal perforation or frank perforation associated with SS have been described in the literature, especially in sSS-Ra patients [13,85], but also as the initial presentation of an undiagnosed pSS [13,86].

Moreover, several case reports of sterile central/paracentral corneal ulceration/melting/perforation have been described in both pSS and sSS patients typically 2–8 weeks after cataract extraction and associated with a post-operative topical therapy with corticosteroids (CSs) or non-steroidal anti-inflammatory drugs (NSAIDs) [69,70] and also as the first presentation of an undiagnosed pSS [69,70]. Topical NSAID- and CS-induced corneal melt/perforations were previously reported [68]. Topical corticosteroids are thought to impair corneal wound healing processes by decreasing new corneal collagen synthesis [68]. On the other hand, topical NSAIDs have been demonstrated to reduce corneal re-epithelization and corneal ulcer healing with several mechanisms by stimulating the release of the neutrophil collagenases, i.e., the matrix metalloproteinases-8, which seem to play an important role in keratolyisis; by decreasing corneal epithelium migration and keratocytes proliferation; and by reducing corneal sensitivity, with consequent neurotrophic epitheliopathy and corneal re-epithelization impairment [68]. The combination of DED, AI disease, SS-related corneal hyposensitivity with decreased blinking and tear reflex, cataract surgery-inducing inflammation and corneal nerve fiber interruption, and therapy with CSs and NSAIDs seems to be very dangerous for the cornea. It should be considered with extreme caution in SS patients [69,70]. CSs and NSAIDs should thus be avoided in patients prone to corneal epithelial breakdown, such as SS patients.

***B. PUK (peripheral ulcerative keratitis)*:** This is a rare disease, with an incidence of 0.2–3 cases/million subjects [87], but it represents the third most common ocular complication found in systemic AI diseases, following KCS and anterior uveitis [88], and is the most severe ocular manifestation of systemic AI diseases, including SS [88]. It is characterized by acute progressive peripheral epithelial defect and stromal thinning in an actively and

severely inflamed eye that frequently evolves into a corneal perforation [87]. PUK may be idiopathic (Mooren ulcer); it may be associated with several local and systemic infectious (20% of cases); or it may be linked with several non-infectious conditions, including dermatologic and neurologic diseases, systemic malignancy, ocular surgery, and AI diseases [87]. AI diseases represent almost 50% of the non-infectious causes of PUK, and RA is associated with approximately 33–40% of PUK cases, with bilateral involvement in 50% of cases [88]. Several cases of PUK have been described in SS patients, almost exclusively sSS-RA cases [8,85], where PUK presentation frequently occurs before the diagnosis of the underlying AI disease or when the AI disease was in remission by immunosuppressive agents [88].

PUK is associated with systemic vasculitis in more than 50% of cases and has a poor visual and life prognosis [87]. Even if the ulceration may also occur in the central and paracentral regions, the presence of the capillary network at the limbus makes the corneal periphery the characteristic position of the ulcerative process. The clinical manifestations of PUK include ocular pain, redness, photophobia, and the presence of a peripheric corneal ulcer, often present adjacent scleritis, episcleritis, iritis, or conjunctivitis [87]. The presence of an associated scleritis increases the likelihood of the presence of a systemic disorder [87]. A possible serious complication is a corneal perforation with vision loss [87], found in a recent series of PUK patients with underlying SS and RA in more than 80% of cases [88]. Several conditions may mimic PUK and should be excluded, especially marginal keratitis and Terrien marginal degeneration. Because of its association with severe systemic diseases, PUK is not only a possible sight-threatening condition but also carries a high risk of systemic morbidity and mortality when it is associated with other collagen vascular diseases [87].

When PUK is associated with non-infectious necrotizing scleritis, the term necrotizing corneoscleritis is used. Necrotizing scleritis is considered a vasculitis involving the limbal vessels and represents the most severe and vision-threatening form of scleritis [89]. The characteristic manifestations are a limbal corneoscleral melting in a deeply inflamed eye that frequently rapidly evolves into a perforation, with pain, tearing, and decreased vision. Several systemic AI diseases and systemic vasculitis are associated with necrotizing scleritis/sclerokeratitis, the most common being RA, followed by Wegener's granulomatosis, SLE, polyarteritis nodosa, and inflammatory bowel diseases [89], so this pathology is more frequently present in sSS patients, especially sSS-RA patients [85]. Necrotizing keratoscleritis [90] and scleritis [91] have also been described in pSS.

4.2. Pathophysiological Mechanisms

A. A sterile corneal ulcer/melting or keratolysis typically develops in inflamed corneas in the absence of limbal vessel fluorosis [8–10,12,13]. Possible mechanisms involved in their pathogenesis include the following:

- High levels of proinflammatory cytokines, reduced levels of lacrimal gland-derived factors such as the epidermal growth factor, and neurodegeneration with decreased NGFs levels may impair the integrity, proliferation, differentiation, and migration of the ocular surface epithelium, leading to punctata keratoconjunctivitis, corneal erosion, and ulceration [45–47];
- Neuroinflammation, neurodegeneration, and consequently decreased levels of nerve growth factors (NGFs) may lead to a neurotrophic keratopathy-like syndrome characterized by corneal hypo-aesthesia and reduced lachrymal reflex with decreased aqueous tear production, blinking impairment, and reduced trophism, apoptosis, and impaired regeneration of epithelial cells and stromal keratocytes, which may lead to corneal erosion/ulcer [45–47];

The analysis of melted corneas from pSS patients has indeed shown the upregulation of a wide range of proinflammatory molecules, such as IL-1, IL-17, and TNF-α, which may increase epithelial and keratocyte apoptosis, and of the matrix metalloproteinase (MMP)-9, which is related to increased proteolytic activity and may lead to corneal stroma thinning, melting, and perforation [85,92].

B. PUK and necrotizing keratoscleritis develop in severely inflamed corneas, and possible etiopathogenetic mechanisms include the following:

- autoimmune attack against connective tissue proteins: As part of the AI connective tissue diseases (CTDs), SS represents a multisystem AI disorder affecting the connective tissue proteins [5]. Both connective and sclera-corneal tissues contain collagen and proteoglycans that may become the target of a cell-mediated and antibody-mediated autoimmune attack inducing the destruction of the peripheral corneal stroma via matrix metalloproteinases activation [88].

The limbal vessels' deposition of the autoimmune complex may result in an inflammatory cascade involving several proinflammatory cytokines and the recruitment of neutrophils and macrophages, which release collagenases and other proteases, causing rapid keratolysis [88].

4.3. Therapeutic Interventions

***A. General considerations*:** Severe ocular extraglandular manifestations, including persistent sterile corneal abrasion/scarring/ulceration/melting, PUK, necrotizing sclerokeratitis, and corneal/scleral perforation [2,6–9], require a complex approach integrating local treatments, prompt and aggressive systemic immunomodulatory therapies managed by the rheumatologist/immunologist, and sometimes surgical strategies [42–44]. Systemic medications include oral or intravenous corticosteroids [74], oral pilocarpine [93,94], hydroxychloroquine [95,96], and immunosuppressant agents [97–103] (Table 4).

Table 4. Systemic approaches to the Sjögren's syndrome-related corneal manifestations.

Drug Class (Administration Route)	Active Component	Therapeutic Effects	Drawbacks and Side Effects	Efficacy in SS Patients (Level of Evidence)	Guidelines Recommendations [42–44,55,56]
Systemic corticosteroids (oral/intravenous) [74]	Oral prednisolone; intravenous methylprednisolone	Anti-inflammatory and immunosuppressant effects	Hypertension, hyperglycemia, weight gain, lipid profile alteration, osteoporosis and Cushingoid features, and increased risk of infections	Poor [57,58]	First-line systemic approach in cases of pSS patients with severe ocular sight-threatening conditions, such as corneal melting, PUK, necrotizing scleritis, or vasculitis
Parasympathomimetic agonists (oral)	Pilocarpine (Cevimeline, not commercially available in Europe)	Parasympathomimetic muscarinic receptor agonist stimulating exocrine gland secretion	Nausea, excessive sweating, flushing, increased salivation, and urinary frequency	High improvement of mouth dryness; low to moderate in DED [93,94]	FDA-approved for managing moderate to severe; not recommended for dry eye
Disease-modifying anti-rheumatic drugs (DMARDs)(oral)	**Hydroxychloroquine**	T-cell inhibition	Nausea, diarrhea, rash, hair changes, muscle weakness, anemia, and maculopathy	None in cases of non-SS DED [95] and SS-related DED [96]	First choice to treat fatigue and joint pain in SS patients

Table 4. *Cont.*

Drug Class (Administration Route)	Active Component	Therapeutic Effects	Drawbacks and Side Effects	Efficacy in SS Patients (Level of Evidence)	Guidelines Recommendations [42–44,55,56]
Systemic immunosuppressive agents: Antimetabolites [103]	**Methotrexate**	Nucleic acid synthesis/cell proliferation inhibition	Gastrointestinal intolerance, elevated liver enzymes, stomatitis, dry eye, etc.	Some evidence in preventing ocular complications and treating PUK in RA patients	First choice to treat joint disease in SS patients; second choice (after systemic CSs) in sterile corneal ulcer/melt and PUK
	Azathioprine	Nucleic acid synthesis/cell proliferation inhibition	Gastrointestinal intolerance, bone marrow suppression, hepatotoxicity, etc.	None	Second choice (after systemic CSs) in PUK treatment
	Mycophenolic acid	Nucleic acid synthesis/cell proliferation inhibition	Gastrointestinal intolerance and hepatotoxicity	Some evidence in reducing symptoms (not signs) of DED in pSS patients	None
Systemic immunosuppressive agents: T-cell inhibitors (oral) [103]	**Cyclosporine A**	T-cell inhibition	High blood pressure, inflamed gums, tremors, nausea, diarrhea, headache, etc.	None/very poor [57,58]	None/possible use in refractory SS-related DED
Systemic immunosuppressive agents: Biologic agents (intravenous) [103,104]	**Belimumab**	Monoclonal antibody against the B-cell activating factor (BAFF)	Infusion reactions, increased risk of infections, etc.	Moderate in cases of systemic extraglandular manifestation [100]	High systemic disease activity, parotid enlargement, lymphadenopathies, and articular manifestation
	Infliximab	Tumor necrosis factor (TNF)-α inhibitor	Infusion reactions, increased risk of infections, etc.	None in SS-related DED [97]; moderate as adjuvant therapy in SS-related sterile corneal melting [102] and in PUK, scleritis, and vasculitis in RA patients [103]	Possible role in extraglandular ocular manifestation in SS and RA patients
	Adalimumab	TNF-α inhibitor	Infusion reactions, increased risk of infections, etc.	Moderate in PUK, scleritis, and vasculitis in RA patients [103]	Possible role in case of extraglandular ocular manifestation in sSS patients

Table 4. *Cont.*

Drug Class (Administration Route)	Active Component	Therapeutic Effects	Drawbacks and Side Effects	Efficacy in SS Patients (Level of Evidence)	Guidelines Recommendations [42–44,55,56]
Systemic immunosuppressive agents: Biologic agents (intravenous) [103,104]	**Abatacept**	Selective inhibitor of T cells	Infusion reactions, increased risk of infections, etc.	None in pSS patients [101]; moderate in glandular and extraglandular ocular manifestations in sSS-RA patients [103].	Possible role in case of DED and extraglandular ocular manifestation in sSS patients
	Rituximab	Monoclonal antibody directed against the protein CD20 expressed on B cells	Infusion reactions, increased risk of infections, etc.	Poor to moderate in pSS-related DED [98]; none in pSS systemic disease activity and extraglandular systemic manifestation [99]; moderate for PUK and scleritis in RA patients [103]	Possible role in pSS-related DED and PUK and scleritis in RA patients
	Tocilizumab	Interleukin(IL)-6 inhibitor	Infusion reactions, increased risk of infections, etc.	Promising results in PUK and necrotizing scleritis in systemic lupus erythematosus (SLE) and RA patients [103]	Possible role in PUK and scleritis in SLE and RA patients
	Anakinra, tocilizumab, efalizumab, etanercept, and baminercept	Anti-IL-1 (anakinra), anti-IL6 (tocilizumab), anti-CD11 (efalizumab), anti-TNF-α (etanercept), and anti-lymphotoxin B receptor (baminercept)	Infusion reactions, increased risk of infections, etc.	None [99]	None
Antibiotics (oral)	**Doxycycline**	Antibiotic effect and MMPs inhibition with anti-collagenolytic effect	Headache, vomiting, diarrhea, etc.	None in pSS patients [57]; high to moderate in MGD [57]	Anterior blepharitis or MGD

SS = Sjögren's syndrome; pSS = primary Sjögren's syndrome; sSS = secondary Sjögren's syndrome; PUK = peripheral ulcerative keratitis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; MGD = Meibomian gland disease; TNF = tumor necrosis factor; IL = interleukin; MMP = matrix metalloproteinase.

Although not supported by strong scientific evidence [57,58], the clinical guidelines suggest the systemic administration of CSs in pSS patients as a first-line systemic approach in cases of severe ocular sight-threatening conditions such as corneal melting, PUK, necrotizing scleritis, or vasculitis [42–44]. Systemic CSs can be administered orally (prednisolone 1 mg/kg/day till disease control, followed by tapering in steps of 10 mg every week, with a maintenance dose of 5–10 mg/day) or intravenously (methylprednisolone 1 gr/day for three consecutive days, followed by oral CSs). Systemic CSs have several side effects, including hypertension, hyperglycemia, weight gain, lipid profile alteration, osteoporosis,

Cushingoid features, and increased risk of infections [74]. An incomplete or no response after 2–4 weeks of systemic CSs therapy suggests the use of systemic immunosuppressant agents [42–44].

The oral administration of pilocarpine, a parasympathomimetic muscarinic receptor agonist, has been approved by the FDA for managing oral dryness [55,56]. Its off-label use in DED patients has shown to be effective in reducing dry eye symptoms and, less frequently, in improving objective signs, although it is often poorly tolerated [93,94].

Oral hydroxychloroquine is the first choice to treat fatigue and joint pain in SS patients, but it did not show any efficacy in treating both non-SS-related DED [95] and SS-related DED patients [96].

Although supported by several case reports and poor systematic scientific evidence [57,58], methotrexate and azathioprine are considered second-choice therapies in the case of several ocular extraglandular manifestations in order to spare or stop systemic CSs [103].

Although a suggested topical formulation, the systemic use of cyclosporine A is not included in the EULAR recommendations [42] because of the lack of efficacy in SS patients [57,58]; although several biologic agents have shown promising results in the management of various AI diseases [103], their use in SS patients, especially in pSS, has given conflicting results and is still under investigation [58,103,104]. Some agents have been used successfully in the treatment of refractory PUK associated with RA, including TNF inhibitors (etanercept, infliximab, adalimumab, golimumab, and certolizumab), B-cell inhibitors (rituximab), T-cell inhibitors (abatacept), IL-1 receptor antagonist (anakinra), and IL-6 receptor antagonist (tocilizumab) [58,88,103,104]. Infliximab and abatacept have already shown some promising results in the treatment of severe extraglandular ocular complications in SS patients, especially sSS [97,101]. Surgical approaches are generally reserved for patients with stromal thinning, descemetocele, and impending or frank corneal/scleral perforation [42–44]. Cyclosporine A 0.05% eyedrops are administered bi-daily, and corticosteroids, including dexamethasone 0.1%, are advised in pulse regimens lasting 2–4 weeks. Lifitegrast 5% ophthalmic solution is administered bi-daily as sanctioned by the FDA for the management of dry eye disease (DED).

The existence of chronic anterior blepharitis or Meibomian gland dysfunction necessitates suitable treatment, including eyelid hygiene, warm compresses, and both topical and systemic antibiotics. Doxycycline can be given orally at a dosage of 50 mg per day for a duration of 3 months, while topical azithromycin 1% ophthalmic solution can be given twice daily for 2 days, followed by once daily for 28 days.

B. Central and paracentral sterile corneal ulceration/melts require both local and systemic treatments [8–10,12,13,42–44]. The local approach includes preservative-free lubricants, CSs and cyclosporine A eyedrops, punctual occlusion, therapeutic contact lenses, and tarsorraphy. The systemic immunosuppressive medications typically involve the use of systemic CSs followed by antimetabolites, with methotrexate being the first-line option [103]. Since upregulation of the MMPs of the corneal epithelium and stroma has been demonstrated in these cases [92], the use of drugs with anti-MMP activity, such as infliximab, tetracyclines, medroxyprogesterone, cysteine, is also recommended [92].

C. PUK and necrotizing keratoscleritis are typically associated with severe systemic AI vasculitis and CTDs and require the prompt identification of possible underlying AI diseases to start an appropriate aggressive systemic immunosuppressant therapy that has proven to reduce patients' ocular morbidity and potential mortality [42–44,87,88]. Immunosuppression is mandatory in all cases associated with a detectable systemic disease; when no systemic disease is detectable, immunosuppressant agents are used for one-eyed patients in cases with bilateral involvement or with impending or frank perforations [103].

In cases of PUK, local therapy typically includes local lubricants, antibiotics, cyclosporine A, and collagenase inhibitors such as topical 20% acetylcysteine and 1% medroxyprogesterone and CSs [87,88]. Topical CSs should be considered with caution because they may delay epithelial healing and inhibit collagen production, increasing the risk of perforation [74]. Conjunctival resection of the inflamed area plus tissue adhesives can be an option [87,88].

Systemic steroids, especially prednisolone ± antimetabolites (Methotrexate or Azathioprine), are the mainstay PUK systemic treatment and may be associated with collagenase inhibitors (acetylcysteine) and matrix metalloproteinase inhibitors (oral tetracycline) [87,88,103]. In the presence of necrotizing scleritis, topical therapies are generally ineffective, and systemic therapy with NSAIDs (flurbiprofen or indomethacin) is considered the first-line therapy [89]. In severe (impending corneal or scleral perforation) or refractory cases, systemic CSs, antimetabolites (methotrexate or azathioprine), and some biological agents (i.e., infliximab, rituximab, or adalimumab) are currently recommended [89,103].

D. Severe corneal thinning and impending or frank corneal/scleral perforation require prompt surgical interventions (Table 5) to maintain globe integrity. The intervention choice depends on the extent of the disease and the size of the perforation [13,85,87,88]. Available surgical options include the following:

- Human amniotic membrane (AM) transplantation: AM implantation has shown several therapeutic properties, including analgesic, re-epithelizing, anti-fibrotic, antimicrobial, anti-inflammatory, anti-angiogenic, and anti-adhesive effects, and it has been successfully used as temporary biologic bandage in a wide range of the ocular surface disorders [105], such as severe SS-related KCS refractory to standard therapies or to promote healing of corneal ulceration/melting/perforations and PUKs [106,107];
- Cyanoacrylate tissue adhesive (CTA) application represents a routine approach to corneal melts and small uncomplicated perforations (<2–3 mm in diameter) of different causes and also in pSS and sSS patients [108]. Although CTA application is generally used as a temporizing measure to delay penetrating keratoplasty, in 20–45% of cases, it provides satisfactory corneal healing, avoiding more invasive surgical interventions [108];
- Conjunctival flap graft may be used to restore ocular surface integrity in different diseases [109];
- Tarsorrhaphy is indicated in cases of severe ocular surface damage in order to retain tears on the ocular surface for a longer time and to reduce surface exposure [110]. Some cases of tarsorrhaphy have been described in SS patients [110];
- Full-thickness or lamellar corneal/scleral patch grafting is indicated in cases of corneal descemetocele, melting, perforation that cannot be closed with tissue adhesives or AM transplantation, or in eyes with acute inflammation, in which a traditional PK may be at high risk of rejection, aiming to postpone a larger refractive PK until systemic therapy with immunosuppressive and anti-collagenolytic treatments is effective [111]. Several case reports of tectonic corneal/scleral patch grafting performed in SS patients with descemetocele, melting, PUK, or perforation have been published [111,112];
- Tectonic lamellar or penetrating tectonic keratoplasty is generally required in SS extraglandular ocular complications with large corneal perforations (>3 mm in diameter, 10% of cases) [113]. Tectonic lamellar or penetrating keratoplasty has been described in SS patients [5,114,115];
- Keratoprosthesis implantation involves the implant of a synthetic structure that replaces the central portion of a diseased cornea, which is indicated in cases with end-stage corneal blindness and where a routine keratoplasty ± limbal stem cells transplantation and systemic immunosuppressant therapy may have a high risk of

failure [116]. A total of 18 eyes affected by corneal melting/perforation in SS patients have been described in the literature [116].

Table 5. Surgical approaches to the Sjögren's syndrome-related corneal manifestations.

Human amniotic membrane (AM) transplantation	AM is a semi-transparent structure representing the deepest layer of the fetal membranes, and it has shown several therapeutic properties, including analgesic, re-epithelizing, anti-fibrotic, anti-microbial, anti-inflammatory, anti-angiogenic, and anti-adhesive effects. AM transplantation has been successfully used as temporary biologic bandage in a wide range of the ocular surface disorders, including chemical burns, persistent epithelial defects, ocular pemphigoid, bullous keratopathy, corneal ulcer, melting, impeding or full-thickness perforation, etc. [105]. The lack of immunogenicity avoids the need for immunosuppressive therapy. AM can be transplanted with or without sutures, using cyanoacrylate or fibrin glue and a therapeutic contact lens [105]. The benefits of its transplantation are temporary, with a median transplant duration of 3–4 weeks, and most patients complain of foreign body sensation and blurred vision during the AM implant [105]. Single or multilayer AM transplantation has shown to be beneficial in SS patients with severe KCS refractory to standard therapies and to promote healing of corneal ulceration/melting/perforations and peripheral ulcerative keratitis (PUK) [106,107].
Cyanoacrylate tissue adhesive (CTA) application	This represents a routinely approach to severe corneal/scleral thinning, melts, and impending or small uncomplicated corneal/scleral perforation (<2–3 mm in diameter) of different causes, such as infectious keratitis, trauma, neurotrophic or exposure keratopathy, and autoimmune diseases, including SS patients [108]. CTA application aims to re-establish the globe integrity (90% of success rate), to inhibit inflammatory cells blocking keratolysis worsening, and to contain infection due to its additional bacteriostatic effects [108]. Although generally used as a temporizing measure to delay the PK, CTA application can provide satisfactory corneal healing avoiding more invasive surgical interventions in 20–45% of cases [108].
Conjunctival flap graft	This may be used to restore ocular surface integrity in different chronic diseases, including severe DED and neurotrophic or neuroparalytic or bullous keratopathy [109].
Tarsorrhaphy	This involves the temporary or permanent joining of part or all of the upper and lower eyelids in order to partially or completely close the eye. It is indicated in cases of severe ocular surface damage in order to retain tears for a longer time and to reduce surface exposure [110]. Some cases of tarsorrhaphy have been described in SS patients [110].
Full-thickness or lamellar corneal/scleral patch grafting	This involves the placement of a donor corneal/scleral patch to reinforce weakened areas, with the aim to restore globe integrity (tectonic use) [111]. It is indicated in cases of corneal thinning, descemetocele, melting, and perforation that cannot be closed with tissue adhesives or AM transplantation or in eyes with acute inflammation, in which a traditional penetrating keratoplasty may be at high risk of rejection, aiming to postpone a larger refractive PK until systemic immunosuppressive therapy is effective [111]. Advantages over penetrating keratoplasty include lower risk of rejection, addition of tissue to the cornea/sclera that reduce the risk of recurrent perforation, and removal of necrotic epithelium and stroma that are sources of pro-inflammatory molecules that maintain the keratolysis/sclerolysis [111]. The most common indications for the corneal/scleral patch grafting are PUK, infectious keratitis, trauma, and limbal stem cell deficiency, with a reported rate of success, defined as globe integrity achievement, of 60–90% [111]. Several case reports of tectonic corneal/scleral patch grafting performed in SS patients with descemetocele, melting, PUK, or perforation have been published [111,112].
Tectonic lamellar or penetrating keratoplasty (PK)	This is indicated in cases of large central corneal perforations (>3 mm in diameter) of different causes (tectonic keratoplasty). Large-diameter grafts (9–9.5 mm) may be indicated to remove inflamed tissue but have a high risk of rejection due to the adjacent limbal vasculature [113]. Small-diameter tectonic grafts, ranging from 3 to 5.5 mm in diameter, are associate with poor visual outcome [113]. Keratoplasty requires a therapy with CSs, cyclosporine, and other systemic immunosuppressives [113]. Tectonic lamellar or penetrating keratoplasty have been described in SS patients [5,114,115].

Table 5. *Cont.*

Keratoprosthesis implantation	This involves the implant of a synthetic structure that replaces the central portion of a diseased cornea. It is indicated in cases with end-stage corneal blindness and where a routine keratoplasty ± limbal stem cells transplantation and systemic immunosuppressant therapy may have a high risk of failure [116]. Typical indications are severe dry eye with coexisting chronic cicatrizing conjunctivitis, adnexal disorders, and limbal stem cell deficiency such as chemical and thermal ocular burns, Stevens–Johnson syndrome, ocular mucous membrane pemphigoid, and SS [116]. Keratoprosthesis has the advantages of a relatively rapid visual recovery without requiring systemic immunosuppression [116]. A total of 18 eyes affected by corneal melting/perforation in SS patients have been described in the literature [116]

AM = amniotic membrane; PUK = peripheral ulcerative keratitis; CTA = cyanoacrylate tissue adhesive; PK = penetrating keratoplasty.

Descemetocele or perforations smaller than 2–3 mm may be managed with conjunctival flap graft, multilayer AM implantation, and/or the use of tissue adhesives, such as cyanoacrylate, followed by the application of a contact lens, with a reported rate of success, defined as achievement of the tectonic integrity, of 50–60% [13,85,87,88]. Melt areas measuring more than 7 mm or perforations larger than 3 mm may require conjunctival, corneal, or scleral patch graft; penetrating or lamellar keratoplasty; or keratoprosthesis [13,85,87,88].

E. New and promising therapeutic options

Several new and promising therapeutic approaches aiming to manage glandular and extraglandular SS manifestations are actually under investigation in pSS animal models and clinical trials [3,45,46,117–135] (Table 6). Topical therapies that have shown encouraging results in improving signs and symptoms of SS-related DED include umbilical cord serum eyedrops [65]; platelet-rich plasma eyedrops [66]; acetylcysteine 5–10% ophthalmic solution, which has shown efficacy in treating keratitis filamentosa for its mucolytic action and in cases of sterile corneal melt for its collagenase inhibition effect [121]; and 0.1% tacrolimus, a new T-cell immunosuppressor that has shown efficacy comparable to that of 1% cyclosporine eyedrops [122], although it is frequently poorly tolerated [123].

Table 6. New and promising therapeutic approaches to the Sjögren's syndrome-related corneal manifestations.

Therapeutic Agent/Approach	Therapeutic Effects	Scientific Evidences
Umbilical cord serum eyedrops	Serum components intake	Promising results in reducing sign and symptoms of SS-related DED [65]
Platelet-rich plasma eyedrops	Plasma components intake	Superior to autologous serum in improving dry eye symptoms in pSS patients [66]
Acetylcysteine 5–10% eyedrops	Mucolytic effect and collagenase inhibition	Possible use in cases of keratitis filamentosa and corneal melt [121]
Tacrolimus 0.1% eyedrops	T-cell immunosuppression	Effective in improving signs and symptoms of DED in SS patients [123], with efficacy comparable to topical cyclosporine A [122]; burning after instillation (80% of cases) [123]
Diquafosol (3% eyedrops)	Antagonist of the P2Y2 purinergic receptor increasing tear and mucin production	Controversial results: no differences against placebo in a large RCT of DED patients including a small percentage of SS patients [124]; more effective than artificial tears in DED patients in a recent meta-analysis [125]; effective and safe to treat SS-related DED in small cohort [126]

Table 6. *Cont.*

Therapeutic Agent/Approach	Therapeutic Effects	Scientific Evidences
Regenerating agents (RGTA) eye drops: Poly-carboxymethyl glucose sulphate eyedrops	Drugs bioengineered to replace the heparin sulphate molecules of the corneal/scleral stroma, with reparative and regenerative effects	Effective as adjuvant therapy of corneal melting in pSS patients [86].
Lacripep eyedrops	Amino acid fragment of lacritin, a regulator of the ocular surface homeostasis	Encouraging results in improving signs and symptoms of DED in pSS [127]
Rapamycin eyedrops (pSS animal models)	Immunosuppression	Improves tear secretion and reduces ocular surface damage in pSS animal model [128]
Remibrutinib	Selective Bruton's tyrosine kinase and B-cell inhibition	Effective in reducing systemic disease activity in SS patients (ocular manifestations not evaluated) [45,118–120]
Dazodalibep	CD40 ligand antagonist suppressing stimulatory signals amongst T and B cells and antigen-presenting cells	Effective in reducing systemic disease activity in SS patients [45,118–120]
Epratuzumab	Humanizedanti-CD22 monoclonal antibody	Effective in reducing systemic disease activity in pSS patients [45,118–120]
Iguratimod	Anti-rheumatic agent	Effective in reducing systemic disease activity in SS patients [45,118–120]
Ianalumab	Human monoclonal antibody able to deplete B cells	Effective in reducing systemic disease activity in pSS patients [45,118–120]
Leflunomide combined with hydroxychloroquine	Type I IFN-associated proteins downregulation	Effective in reducing systemic disease activity in pSS patients [45,118–120]
Iscalimab (CFZ533)	Anti-CD40 monoclonal antibody	Effective in reducing systemic disease activity in pSS patients [45,118–120]
Sequential administration of Belimumab and Rituximab	Monoclonal antibody against B-cell activating factor (Belimumab); monoclonal antibody against CD20 protein of the B cells (Rituximab)	Effective in reducing systemic disease activity in pSS patients [45,118–120]
Baricitinib	Janus kinase (JAK) inhibitor	Promising results in improving signs and symptoms of DED in pSS; effective in reducing systemic disease activity in pSS patients [45,118–120]
Interleukin 2	T-cell suppression when administered in low doses	Effective in reducing systemic diseases activity in SS patients [45,118–120]
Interferon α-2b	Immunomodulation	Effective in improving signs and symptoms of xerostomia in SS patients at low dose; at high doses, used to treat hepatitis C or multiple myeloma, it has been associated with the development of dry eye and SS [45,118–120]
RO5459072	Cysteine protease cathepsin/T-cell inhibitor	Promising results in reducing systemic diseases activity in pSS patients [45,118–120]
Diet supplements (omega-3 and omega-6 fatty acids, oral hyaluronic acid, astaxanthin, maquiberry extract, 1and bilberry extract)	Anti-oxidant, anti-inflammatory, anti-apoptotic, and immunomodulatory effects	Poor-to-moderate efficacy in reducing DED signs and/or symptoms [57,58,129,130]; no data on SS patients are available so far
Microbiota transfer (pSS animal models)	Microbiota dysbiosis treatment	Germ-free mice colonized with human intestinal microbiota derived from pSS patients showed reduced CD4+T-regulatory cells and greater tendency of corneal barrier disruption when compared with germ-free mice colonized with intestinal microbiota of healthy subjects [131]

Table 6. *Cont.*

Therapeutic Agent/Approach	Therapeutic Effects	Scientific Evidences
Stem cells transplantation (pSS animal models)	Trophic, regenerative, and immunomodulatory effects (possible graft rejection)	Mesenchymal stem cells or allogenic multipotent hematopoietic stem cells transplantation on the ocular surface has shown promising results in increasing tear secretion, tear film stability, and epithelial and goblet cells regeneration and in reducing ocular surface flogosis [132]. The administration of mesenchymal stem cells by intra-lacrimal gland and subconjunctival injections has proven to inhibit epithelial cells autophagy, to reduce lymphocytic infiltration, and to decrease the objective signs of dry eye [133].
Gene transfer (animal models and human clinical trials)	Genetic integrity restitution	Adenoviral-mediated gene transfer or ultrasound assisted non-viral gene transfer of the AQP1 gene into damaged salivary glands are under investigation in several animal models [134] and in few clinical trials [135] and have shown promising preliminary results in increasing the parotid salivary flow.

SS = Sjögren's syndrome; pSS = primary Sjögren's syndrome; DED = dry eye disease; RCT = randomized controlled trial; INF = interferon; AQP = aquaporin.

Diquafosol is a purinergic receptor antagonist able to stimulate tear and mucin production, whose 3% ophthalmic solution has been tested in DED patients with contradictory results [124,125] and in SS-related DED patients with encouraging outcomes [126]. Polycarboxymethylglucosesulphate is a bioengineered molecule with reparative and regenerative properties, whose administration as eyedrops has shown to improve healing of SS-related corneal melting [86]. Lacripep is a molecule with anti-inflammatory/immunoregulatory effects on the ocular surface [127]; rapamycin is a new immunosuppressor whose topical administration has improved tear secretion and ocular surface damage in a pSS animal model [128].

Experimental therapeutic strategies to manage SS include various biological drugs that target different inflammation signaling pathways related to the activation of B and T cells and the regulation of several proinflammatory cytokine expressions. To date, several biologic drugs have been shown to significantly improve clinical systemic manifestations in pSS patients in randomized placebo-controlled clinical trials, including rem ibrutinib, dazodalibep, epratuzumab, iguratimod, ianalumab, leflunomide associated with hydroxychloroquine, iscalimab, sequential administration of belimumab and rituximab, baricitinib, low doses of interleukin-2, interferon alfa-2b, and RO5459072 [45,118,120]. Unfortunately, data about the efficacy of these drugs on the SS-related glandular and extraglandular ocular manifestation are generally unavailable [118,120].

Diet supplements, including omega-3 and omega-6 fatty acids, oral hyaluronic acid, astaxanthin, maquiberry extract, and bilberry extract, having well-known anti-oxidant, anti-inflammatory, anti-apoptotic, and immunomodulatory effects, have shown poor-to-moderate therapeutic efficacy in improving signs and/or symptoms in DED patients [57,58,129,130]. Their assumption as a supplementary therapy in DED patients is endorsed by recent investigations [130]. Nevertheless, no specific data on SS patients are currently available.

Microbiota transfer therapy has shown promising results in animal models. Germ-free mice colonized with human intestinal microbiota derived from healthy subjects showed higher levels of CD4+T-regulatory cells in the ocular draining cervical lymph nodes and a lower tendency of corneal barrier disruption when compared with germ-free mice colonized with intestinal microbiota of pSS patients [131].

The transplantation of allogenic mesenchymal stem cells or multipotent hematopoietic stem cells, having trophic and immunomodulatory properties, is under examination

because high rates of graft rejection counterbalance their promising results despite local immunosuppression [120]. The implantation of mesenchymal stem cells on the ocular surface and the mesenchymal stem cells extract-based therapy have shown the ability to increase tear secretion, tear film stability, and epithelial and goblet cell regeneration and reduce the ocular surface flogosis in animal models of pSS [132]. Moreover, the administration of mesenchymal stem cells by intra-lacrimal gland and subconjunctival injections in a pSS animal model has proven to inhibit epithelial cell autophagy, reduce lymphocytic infiltration, and decrease the objective signs of dry eye [133].

Finally, gene transfer therapy (with adenoviral-mediated gene transfer or ultrasound-assisted non-viral gene transfer) of the AQP1 gene into the damaged salivary glands is under investigation in several animal models [134]. In a few clinical trials [135], promising preliminary results have been shown in increasing the parotid salivary flow.

5. Conclusions and Future Directions

SS represents one of the systemic disorders that most frequently affects the cornea [10]. Several other systemic diseases, including endocrine, genetic, deposit disorders, virus and bacterial infections, and autoimmune and inflammatory disorders, may have a great impact on corneal health, although they often remain under-evaluated [10,11]. Corneal manifestations may precede the onset of other extraocular features, therefore representing the first sign of an undiagnosed systemic condition. In these cases, the identification of the corneal involvement may provide insight into the pathogenesis of the underlying systemic condition. It may help facilitate early diagnosis and prompt treatment, thus limiting systemic disease progression [10,11].

Several studies in the literature have enhanced our comprehension of SS and its intricate relationship with DED and corneal pathology. The TFOS DEWS II Definition and Classification Report by Craig et al. (2017) [23] offers a thorough and standardized definition of DED, highlighting its multifactorial characteristics and recognizing tear film instability, hyperosmolarity, inflammation, and neurosensory abnormalities as primary etiological factors. This concept has established the basis for much of the ensuing research and clinical categorization of SS-related ocular involvement.

New insights onto the pathophysiological mechanisms underlying the SS-related corneal involvement may be extremely relevant in understanding clinical disease manifestations, helping in effective patient counseling and suggesting new customized therapeutic strategies. For example, the corneal nerve abnormalities found in Sjögren's syndrome patients, characterized by diminished nerve density, heightened tortuosity, and atypical reflectivity on in vivo confocal scanning laser microscopy [32,34], may elucidate the paradox often observed in SS patients, whereby considerable corneal staining and epithelial injury coexist with low reported discomfort or where, conversely, neuropathic ocular pain, burning, and photophobia are disproportionate to objective findings [38,40]. Since specific corneal nerve abnormalities have been found to precede other SS clinical manifestations, their detection may be useful in order to anticipate disease diagnosis [32,34]. Furthermore, the comprehension of the role of neuro-inflammation and neuronal degeneration in SS-related DED may direct research towards the use of neuroprotective or neuroregenerative agents (e.g., nerve growth factor-based eyedrops).

The upregulation of pro-inflammatory cytokines, including IL-17, IL-8, IFN-γ, and TNF-α, is commonly detected in the tear film and ocular surface tissues of DED patients but appears significantly more pronounced in Sjögren's syndrome patients [27]. These cytokines have been demonstrated to worsen lachrymal gland damage, epithelial barrier disruption, goblet cells loss, and degeneration of corneal nerves, resulting in severe eye dryness, persistent ocular surface staining, corneal and conjunctival scarring, and dimin-

ished corneal sensitivity. The discovery of their upregulation in SS patients has suggested the use of several topical and systemic anti-inflammatory molecules in the SS-related DED, including steroids [71,74], cyclosporine A [75], lifitigrast [79,80], and many systemic immunomodulatory agents [103,104].

Elevated IL-17 tears levels are associated with more severe corneal pathology and reduced efficacy of standard lubricants, prompting doctors to contemplate the earlier use of biologic medicines or serum eye drops in the treatment protocol [27].

The upregulation of the matrix metalloproteinase (MMP)-9 has been linked to the increased proteolytic activity found in cases of sterile central corneal ulcer [85,92] and may suggest the use collagenase inhibitors such as acetylcysteine [123] or doxycycline [57].

The frequent and sometimes severe corneal involvement in SS patients may have several explanations. Chronic eye dryness and tear film hyperosmolarity, caused by the autoimmune attack against the lachrymal gland, may lead to significant corneal epithelium damage, with persistent abrasions, ulcers, and increased risk of corneal infections [10,45–47]; on the other hand, some evidence suggests that the corneal epithelium may be the direct target of the SS autoimmune attack [50]. The dysregulation of the inflammatory/immunitary responses with loss of the ocular surface immune tolerance [33,51] may amplify the corneal epithelial damage. The frequently associated corneal nerve alterations [32,34] may cause a neurotrophic-like keratopathy with impaired tear reflex and decreased NGF secretion [40].

The downregulation of various growth factors released by damaged lachrymal glands, corneal nerves, and conjunctival goblet cells may impair corneal epithelial cell proliferation, differentiation, and migration [45–47]. The dysbiosis of the ocular surface may increase corneal infection susceptibility and trigger an autoimmune attack against the corneal epithelium via mimicry mechanisms [28]. Molecular mimicry denotes the occurrence in which microbial antigens have a structural resemblance to host self-antigens, hence eliciting an autoimmune response. In Sjögren's syndrome, specific gut and ocular surface bacteria produce proteins that resemble autoantigens, including Ro/SSA and La/SSB. This mimicry activates autoreactive T and B cells, resulting in injury to the lacrimal glands and inflammation of the ocular surface [28]. Finally, the histologic similarity between cornea (and sclera) and connective tissue, both containing collagen and proteoglycans, can make the cornea an important target of SS and all connective tissue diseases [5].

The clinical severity of the SS-related corneal involvement may be extremely variable, ranging from mild eye dryness with clear ocular surface [6,7,17] to sight-threatening corneal complications such as sterile cornel melt or PUK that may lead to corneal perforation and vision loss [8,9,13,88]. A recent study [136] has presented a new perspective by establishing a significant association between ocular surface signs and symptoms, systemic pain, and oral dryness in patients with SS. This research substantiates the notion of the eye as a diagnostic and prognostic indicator of systemic autoimmune activity, emphasizing the clinical significance of comprehensive ocular evaluation in Sjögren's syndrome beyond just local illness management.

Severe corneal manifestations, typically found in RA- and systemic lupus erythematosus (SLE)-related sSS patients, are thought to have a complex polyautoimmunitary pathogenesis and are often linked to other severe extraglandular ocular and systemic complications, high levels of systemic inflammatory markers, and great risk of mortality [8,9]. These data suggest that extraglandular corneal complications may represent a barometer of systemic disease activity, especially in pSS patients [8,9]. They may require a complex multidisciplinary approach to control the systemic inflammation and maintain the ocular integrity [42–44].

Moreover, considering the well-known discordance between signs and symptoms in SS patients, where severe DED may be associated with minimal subjective symptoms de-

spite significant ocular surface damage [6,7,40], all patients evaluated by a rheumatologist and suspected or diagnosed to be affected by a systemic rheumatologic, connective, or autoimmune disease must undergo a regular comprehensive ophthalmologic evaluation, even though they are asymptomatic, to ensure an early identification and treatment of a possible ocular involvement [42–44]. The ocular surface assessment is of fundamental importance. It requires objective measures, such as Schirmer's test and ocular surface staining, which are necessary to prevent ocular complications and to give the rheumatologist information about the disease activity in extraarticular organs.

On the other hand, patients evaluated by the ophthalmologist with a suspected or confirmed SS should be promptly referred to a dentist for oral disease prevention/management and to a rheumatologist/immunologist for systemic evaluation and appropriate systemic treatment. SS-related corneal involvement may require lifestyle habits modification (Table 2) and topical (Table 3), mechanical (Table 3), systemic (Table 4), or surgical (Table 5) treatments depending on the degree of severity.

In general, although current evidence supports the efficacy and safety of the main topical therapeutic options, limited data are available from controlled trials on the systemic treatments [57,58]. In particular, the effectiveness of topical preservative-free lubricants, CSs, and cyclosporine and that of mechanical tear-conserving strategies have moderate evidence in treating SS-related corneal manifestations [57,58]. Moreover, while artificial tears have traditionally been regarded as the primary treatment for DED, recent therapeutic innovations have relegated their function to adjunctive support rather than primary intervention in DED patients, suggesting that targeted therapies that focus on the underlying pathophysiology rather than merely alleviating symptoms may be regarded as first-line approaches [130]. On the other hand, oral secretagogues (pilocarpine) have shown greater efficacy for oral than for eye dryness [94]; oral hydroxychloroquine, commonly prescribed in SS to reduce fatigue and joint pain, did not have significant efficacy in SS-related dry eye [96]; the use of systemic corticosteroids, although considered as the first-line therapy in cases of severe corneal complications, is not supported by strong scientific data [57,58]. Oral prednisolone is given at a dosage of 1 mg/kg/day until disease control is achieved, followed by a reduction of 10 mg per week to reach a maintenance dose of 5–10 mg/day. Methylprednisolone is delivered intravenously at a dosage of 1 g per day for three consecutive days. Little evidence suggests the use of antimetabolites [103] and some new biological agents [103,104] in cases of sterile corneal melting, PUK, and necrotizing keratoscleritis.

Both SS-related extraglandular systemic and ocular manifestations need adequate systemic immunosuppressive therapy that is generally managed by the rheumatologist [42–44]. Furthermore, the presence of ocular complications is often underdiagnosed, and the use of systemic immunosuppressive agents in cases of extraglandular ocular complications is poorly recognized and applied [42–44]. Moreover, the efficacy of many new therapeutic agents on the corneal involvement remains uncertain (Table 6).

Several new therapeutic approaches targeting different pathogenetic pathways have recently been proposed [3,45,46,117–120] (Table 6). Some topical medications, including umbilical cord serum [65], platelet-rich plasma [66], 0.1% tacrolimus eye drops [122], diquafosol 3% ophthalmic solution [126], and topical regenerating agents [86], have shown promising results in treating mild-to-moderate corneal involvement (Table 6).

Several new biologic agents, especially those targeting B cells, B–T cell–cell costimulation, and the IFN pathway, have shown efficacy in improving the SS systemic manifestation. However, poor data are available about their effects on corneal involvement [45,118,120] (Table 6).

Diet supplements have shown some efficacy in improving DED clinical signs and/or symptoms [57,58,129,130], although data on SS patients are still lacking.

Microbiota transfer therapy [131], stem cell transplantation [132,133], and gene transfer therapy [134,135] are still under investigation in many animal models and in a few preliminary human studies and may hopefully reshape SS management.

In conclusion, further efforts are needed to improve SS patient management: more systematic diagnostic approaches, stronger collaborations between ophthalmologists and rheumatologists, higher awareness of the importance of the diagnosis and treatment of SS-related ocular/corneal involvement, better comprehension of the SS pathogenesis, identification of biomarkers able to stratify patients and predict disease severity and response to treatments, and investigation of the new specific therapies targeting the different pathogenetic disease pathways with double-masked RCTs, large sample size, and strict selection criteria. The combination of improved diagnostics and innovative therapy approaches may offer the potential for reducing disease progression, maintaining corneal health, and enhancing patient outcomes.

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References

1. Negrini, S.; Emmi, G.; Greco, M.; Borro, M.; Sardanelli, F.; Murdaca, G.; Indiveri, F.; Puppo, F. Sjögren's syndrome: A systemic autoimmune disease. *Clin. Exp. Med.* **2022**, *22*, 9–25. [CrossRef] [PubMed] [PubMed Central]
2. Akpek, E.K.; Bunya, V.Y.; Saldanha, I.J. Sjögren's Syndrome: More Than Just Dry Eye. *Cornea* **2019**, *38*, 658–661. [CrossRef] [PubMed] [PubMed Central]
3. Maleki-Fischbach, M.; Kastsianok, L.; Koslow, M.; Chan, E.D. Manifestations and management of Sjögren's disease. *Arthritis Res. Ther.* **2024**, *26*, 43. [CrossRef] [PubMed] [PubMed Central]
4. Kollert, F.; Fisher, B.A. Equal rights in autoimmunity: Is Sjögren's syndrome ever 'secondary'? *Rheumatology* **2020**, *59*, 1218–1225. [CrossRef] [PubMed]
5. Asif, M.I.; Kalra, N.; Sharma, N.; Jain, N.; Sharma, M.; Sinha, R. Connective tissue disorders and eye: A review and recent updates. *Indian. J. Ophthalmol.* **2023**, *71*, 2385–2398. [CrossRef] [PubMed] [PubMed Central]
6. Bjordal, O.; Norheim, K.B.; Rødahl, E.; Jonsson, R.; Omdal, R. Primary Sjögren's syndrome and the eye. *Surv. Ophthalmol.* **2020**, *65*, 119–132. [CrossRef] [PubMed]
7. Roszkowska, A.M.; Oliverio, G.W.; Aragona, E.; Inferrera, L.; Severo, A.A.; Alessandrello, F.; Spinella, R.; Postorino, E.I.; Aragona, P. Ophthalmologic Manifestations of Primary Sjögren's Syndrome. *Genes* **2021**, *12*, 365. [CrossRef] [PubMed] [PubMed Central]
8. Mathews, P.M.; Robinson, S.A.; Gire, A.; Baer, A.N.; Akpek, E.K. Extraglandular ocular involvement and morbidity and mortality in primary Sjögren's Syndrome. *PLoS ONE* **2020**, *15*, e0239769. [CrossRef] [PubMed] [PubMed Central]
9. Singh, S.; Das, A.V.; Basu, S. Ocular Involvement in Sjögren Syndrome: Risk Factors for Severe Visual Impairment and Vision-Threatening Corneal Complications. *Am. J. Ophthalmol.* **2021**, *225*, 11–17. [CrossRef] [PubMed]
10. Iyer, G.; Srinivasan, B. Sjogren's disease and the cornea: Bridging disciplines for enhanced ocular health. *Kerala J. Ophthalmol.* **2024**, *36*, 220–223. [CrossRef]
11. Shah, R.; Amador, C.; Tormanen, K.; Ghiam, S.; Saghizadeh, M.; Arumugaswami, V.; Kumar, A.; Kramerov, A.A.; Ljubimov, A.V. Systemic diseases and the cornea. *Exp. Eye Res.* **2021**, *204*, 108455. [CrossRef] [PubMed] [PubMed Central]

12. Villarreal-Gonzalez, A.J.; Jocelyn Rivera-Alvarado, I.; Rodriguez-Gutierrez, L.A.; Rodriguez-Garcia, A. Analysis of ocular surface damage and visual impact in patients with primary and secondary Sjögren syndrome. *Rheumatol. Int.* **2020**, *40*, 1249–1257. [CrossRef] [PubMed]
13. Singh, S.; Chaudhary, S.; Das, A.V.; Basu, S. Presentation, aetiology and outcomes of corneal ulceration in Sjogren's Syndrome. *Eye* **2023**, *37*, 3217–3220. [CrossRef] [PubMed] [PubMed Central]
14. Beydon, M.; McCoy, S.; Nguyen, Y.; Sumida, T.; Mariette, X.; Seror, R. Epidemiology of Sjögren syndrome. *Nat. Rev. Rheumatol.* **2024**, *20*, 158–169. [CrossRef] [PubMed]
15. Xuan, Y.; Zhang, X.; Wu, H. Impact of sex differences on the clinical presentation, pathogenesis, treatment and prognosis of Sjögren's syndrome. *Immunology* **2024**, *171*, 513–524. [CrossRef] [PubMed]
16. Baer, A.N.; Walitt, B. Update on Sjögren Syndrome and Other Causes of Sicca in Older Adults. *Rheum. Dis. Clin. N. Am.* **2018**, *44*, 419–436. [CrossRef] [PubMed] [PubMed Central]
17. Wang, H.; Wang, P.B.; Chen, T.; Zou, J.; Li, Y.J.; Ran, X.F.; Li, Q.X. Analysis of Clinical Characteristics of Immune-Related Dry Eye. *J. Ophthalmol.* **2017**, *2017*, 8532397. [CrossRef] [PubMed] [PubMed Central]
18. Shiboski, C.H.; Shiboski, S.C.; Seror, R.; Criswell, L.A.; Labetoulle, M.; Lietman, T.M.; Rasmussen, A.; Scofield, H.; Vitali, C.; Bowman, S.J.; et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis Rheumatol.* **2017**, *69*, 35–45. [CrossRef] [PubMed] [PubMed Central]
19. Bautista-Vargas, M.; Vivas, A.J.; Tobón, G.J. Minor salivary gland biopsy: Its role in the classification and prognosis of Sjögren's syndrome. *Autoimmun. Rev.* **2020**, *19*, 102690. [CrossRef] [PubMed]
20. Vílchez-Oya, F.; Balastegui Martin, H.; García-Martínez, E.; Corominas, H. Not all autoantibodies are clinically relevant. Classic and novel autoantibodies in Sjögren's syndrome: A critical review. *Front. Immunol.* **2022**, *13*, 1003054. [CrossRef] [PubMed] [PubMed Central]
21. Brott, N.R.; Zeppieri, M.; Ronquillo, Y. Schirmer Test. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2025. [PubMed]
22. Srinivas, S.P.; Rao, S.K. Ocular surface staining: Current concepts and techniques. *Indian. J. Ophthalmol.* **2023**, *71*, 1080–1089. [CrossRef] [PubMed] [PubMed Central]
23. Craig, J.P.; Nichols, K.K.; Akpek, E.K.; Caffery, B.; Dua, H.S.; Joo, C.K.; Liu, Z.; Nelson, J.D.; Nichols, J.J.; Tsubota, K.; et al. TFOS DEWS II Definition and Classification Report. *Ocul. Surf.* **2017**, *15*, 276–283. [CrossRef] [PubMed]
24. Xu, K.P.; Katagiri, S.; Takeuchi, T.; Tsubota, K. Biopsy of labial salivary glands and lacrimal glands in the diagnosis of Sjögren's syndrome. *J. Rheumatol.* **1996**, *23*, 76–82. [PubMed]
25. Kaneko, N.; Chen, H.; Perugino, C.A.; Maehara, T.; Munemura, R.; Yokomizo, S.; Sameshima, J.; Diefenbach, T.J.; Premo, K.R.; Chinju, A.; et al. Cytotoxic $CD8^+$ T cells may be drivers of tissue destruction in Sjögren's syndrome. *Sci. Rep.* **2022**, *12*, 15427. [CrossRef] [PubMed] [PubMed Central]
26. Pringle, S.; Verstappen, G.M.; van Ginkel, M.S.; Nakshbandi, U.; Girigoria, Z.; Bootsma, H.; van der Vegt, B.; Kroese, F.G.M. Lymphoepithelial lesions in the salivary glands of primary Sjögren's syndrome patients: The perfect storm? *Clin. Exp. Rheumatol.* **2022**, *40*, 2434–2442. [CrossRef] [PubMed]
27. Peng, J.; Feinstein, D.; DeSimone, S.; Gentile, P. A Review of the Tear Film Biomarkers Used to Diagnose Sjogren's Syndrome. *Int. J. Mol. Sci.* **2024**, *25*, 10380. [CrossRef] [PubMed] [PubMed Central]
28. Pal, S.; Vani, G.; Donthineni, P.R.; Basu, S.; Arunasri, K. Tear film microbiome in Sjogren's and non-Sjogren's aqueous deficiency dry eye. *Indian. J. Ophthalmol.* **2023**, *71*, 1566–1573. [CrossRef] [PubMed] [PubMed Central]
29. Sullivan, D.A.; Dana, R.; Sullivan, R.M.; Krenzer, K.L.; Sahin, A.; Arica, B.; Liu, Y.; Kam, W.R.; Papas, A.S.; Cermak, J.M. Meibomian Gland Dysfunction in Primary and Secondary Sjögren Syndrome. *Ophthalmic Res.* **2018**, *59*, 193–205. [CrossRef] [PubMed]
30. Wakamatsu, T.H.; Sato, E.A.; Matsumoto, Y.; Ibrahim, O.M.; Dogru, M.; Kaido, M.; Ishida, R.; Tsubota, K. Conjunctival in vivo confocal scanning laser microscopy in patients with Sjögren syndrome. *Investig. Ophthalmol. Vis. Sci.* **2010**, *51*, 144–150. [CrossRef] [PubMed]
31. de Paiva, C.S.; Trujillo-Vargas, C.M.; Schaefer, L.; Yu, Z.; Britton, R.A.; Pflugfelder, S.C. Differentially Expressed Gene Pathways in the Conjunctiva of Sjögren Syndrome Keratoconjunctivitis Sicca. *Front. Immunol.* **2021**, *12*, 702755. [CrossRef] [PubMed] [PubMed Central]
32. Matsumoto, Y.; Ibrahim, O.M.A.; Kojima, T.; Dogru, M.; Shimazaki, J.; Tsubota, K. Corneal In Vivo Laser-Scanning Confocal Microscopy Findings in Dry Eye Patients with Sjögren's Syndrome. *Diagnostics* **2020**, *10*, 497. [CrossRef] [PubMed] [PubMed Central]
33. Hao, R.; Ding, Y.; Li, X. Alterations in corneal epithelial dendritic cell in Sjogren's syndrome dry eye and clinical correlations. *Sci. Rep.* **2022**, *12*, 11167. [CrossRef] [PubMed] [PubMed Central]

34. Hao, R.; Chou, Y.; Ding, Y.; Liu, Z.; Wang, Y.; Ren, X.; Li, X. Corneal subbasal nerve analysis in patients with primary Sjogren's syndrome: A novel objective grading method and clinical correlations. *Int. Ophthalmol.* **2023**, *43*, 779–793. [CrossRef] [PubMed]
35. Borrego-Sanz, L.; Sáenz-Francés San Baldomero, F.; Díaz Valle, D.; Santos Bueso, E.; Sánchez Jean, R.; Martínez de la Casa, J.M.; Benítez Del Castillo, J.M.; García Feijóo, J.; Rodríguez Rodríguez, L. Comparison of corneal biomechanical properties of patients with dry eye secondary to Sjögren's syndrome and healthy subjects. *J. Fr. Ophtalmol.* **2018**, *41*, 802–808. [CrossRef] [PubMed]
36. Chung, J.K.; Kim, M.K.; Wee, W.R. Prognostic factors for the clinical severity of keratoconjunctivitis sicca in patients with Sjogren's syndrome. *Br. J. Ophthalmol.* **2012**, *96*, 240–245. [CrossRef] [PubMed]
37. Miyamoto, S.T.; Valim, V.; Fisher, B.A. Health-related quality of life and costs in Sjögren's syndrome. *Rheumatology* **2021**, *60*, 2588–2601. [CrossRef] [PubMed]
38. Xiong, F.; Pula, D.; Akpek, E.K.; Bunya, V.Y.; Shiboski, C.H.; Lietman, T.L.; Gonzales, J.A. Sjögren's Versus Non-Sjögren's Ocular Features: Similar Symptoms, But Significantly Worse Signs. *Invest. Ophthalmol. Vis. Sci.* **2024**, *65*, 23. [CrossRef] [PubMed] [PubMed Central]
39. Wang, Y.; Qin, Q.; Liu, B.; Fu, Y.; Lin, L.; Huang, X.; Jin, X. Clinical Analysis: Aqueous-Deficient and Meibomian Gland Dysfunction in Patients With Primary Sjogren's Syndrome. *Front. Med.* **2019**, *6*, 291. [CrossRef] [PubMed] [PubMed Central]
40. Sanchez, V.; Dobzinski, N.; Fox, R.; Galor, A. Rethinking Sjögren Beyond Inflammation: Considering the Role of Nerves in Driving Disease Manifestations. *Eye Contact Lens* **2024**, *50*, 200–207. [CrossRef] [PubMed] [PubMed Central]
41. Kim, S.Y.; Kim, S.H.; Yoon, C.H.; Kim, M.K.; Oh, J.Y. Infectious Keratitis in Patients with Ocular Sjögren's Syndrome. *Korean J. Ophthalmol.* **2022**, *36*, 407–412. [CrossRef] [PubMed] [PubMed Central]
42. Ramos-Casals, M.; Brito-Zerón, P.; Bombardieri, S.; Bootsma, H.; De Vita, S.; Dörner, T.; Fisher, B.A.; Gottenberg, J.E.; Hernandez-Molina, G.; Kocher, A.; et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann. Rheum. Dis.* **2020**, *79*, 3–18. [CrossRef] [PubMed]
43. Price, E.J.; Baer, A.N. How to treat Sjögren's syndrome. *Rheumatology* **2021**, *60*, 2574–2587. [CrossRef] [PubMed]
44. Price, E.J.; Benjamin, S.; Bombardieri, M.; Bowman, S.; Carty, S.; Ciurtin, C.; Crampton, B.; Dawson, A.; Fisher, B.A.; Giles, I.; et al. British Society for Rheumatology guideline on management of adult and juvenile onset Sjögren disease. *Rheumatology* **2025**, *64*, 409–439. [CrossRef] [PubMed]
45. Zhan, Q.; Zhang, J.; Lin, Y.; Chen, W.; Fan, X.; Zhang, D. Pathogenesis and treatment of Sjogren's syndrome: Review and update. *Front. Immunol.* **2023**, *14*, 1127417. [CrossRef] [PubMed] [PubMed Central]
46. Baldini, C.; Fulvio, G.; La Rocca, G.; Ferro, F. Update on the pathophysiology and treatment of primary Sjögren syndrome. *Nat. Rev. Rheumatol.* **2024**, *20*, 473–491. [CrossRef] [PubMed]
47. Bron, A.J.; de Paiva, C.S.; Chauhan, S.K.; Bonini, S.; Gabison, E.E.; Jain, S.; Knop, E.; Markoulli, M.; Ogawa, Y.; Perez, V.; et al. TFOS DEWS II pathophysiology report. *Ocul. Surf.* **2017**, *15*, 438–510, Erratum in *Ocul. Surf.* **2019**, *17*, 842. [CrossRef] [PubMed]
48. Chen, Y.; Wang, S.; Alemi, H.; Dohlman, T.; Dana, R. Immune regulation of the ocular surface. *Exp. Eye Res.* **2022**, *218*, 109007. [CrossRef] [PubMed] [PubMed Central]
49. Utomo, S.W.; Putri, J.F. Infections as Risk Factor of Sjögren's Syndrome. *Open Access Rheumatol.* **2020**, *12*, 257–266. [CrossRef] [PubMed] [PubMed Central]
50. Ogawa, Y.; Takeuchi, T.; Tsubota, K. Autoimmune Epithelitis and Chronic Inflammation in Sjögren's Syndrome-Related Dry Eye Disease. *Int. J. Mol. Sci.* **2021**, *22*, 11820. [CrossRef] [PubMed] [PubMed Central]
51. Chivasso, C.; Sarrand, J.; Perret, J.; Delporte, C.; Soyfoo, M.S. The Involvement of Innate and Adaptive Immunity in the Initiation and Perpetuation of Sjögren's Syndrome. *Int. J. Mol. Sci.* **2021**, *22*, 658. [CrossRef] [PubMed] [PubMed Central]
52. Khatri, B.; Tessneer, K.L.; Rasmussen, A.; Aghakhanian, F.; Reksten, T.R.; Adler, A.; Alevizos, I.; Anaya, J.-M.; Aqrawi, L.A.; Baecklund, E.; et al. Genome-wide association study identifies Sjögren's risk loci with functional implications in immune and glandular cells. *Nat. Commun.* **2022**, *13*, 4287, Erratum in *Nat. Commun.* **2022**, *13*, 6519. https://doi.org/10.1038/s41467-022-34311-8; Erratum in *Nat. Commun.* **2023**, *14*, 598. [CrossRef] [PubMed] [PubMed Central]
53. Thorlacius, G.E.; Björk, A.; Wahren-Herlenius, M. Genetics and epigenetics of primary Sjögren syndrome: Implications for future therapies. *Nat. Rev. Rheumatol.* **2023**, *19*, 288–306. [CrossRef] [PubMed] [PubMed Central]
54. Alam, J.; de Paiva, C.S.; Pflugfelder, S.C. Desiccation Induced Conjunctival Monocyte Recruitment and Activation—Implications for Keratoconjunctivitis. *Front. Immunol.* **2021**, *12*, 701415. [CrossRef] [PubMed] [PubMed Central]
55. Jones, L.; Downie, L.E.; Korb, D.; Benitez-Del-Castillo, J.M.; Dana, R.; Deng, S.X.; Dong, P.N.; Geerling, G.; Hida, R.Y.; Liu, Y.; et al. TFOS DEWS II Management and Therapy Report. *Ocul. Surf.* **2017**, *15*, 575–628. [CrossRef] [PubMed]
56. Amescua, G.; Ahmad, S.; Cheung, A.Y.; Choi, D.S.; Jhanji, V.; Lin, A.; Mian, S.I.; Rhee, M.K.; Viriya, E.T.; Mah, F.S.; et al. Dry Eye Syndrome Preferred Practice Pattern®. *Ophthalmology* **2024**, *131*, P1–P49. [CrossRef] [PubMed]
57. Shih, K.C.; Lun, C.N.; Jhanji, V.; Thong, B.Y.; Tong, L. Systematic review of randomized controlled trials in the treatment of dry eye disease in Sjogren syndrome. *J. Inflamm.* **2017**, *14*, 26. [CrossRef] [PubMed] [PubMed Central]

58. Brito-Zerón, P.; Retamozo, S.; Kostov, B.; Baldini, C.; Bootsma, H.; De Vita, S.; Dörner, T.; Gottenberg, J.E.; Kruize, A.A.; Mandl, T.; 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**, *5*, e001064. [CrossRef] [PubMed] [PubMed Central]
59. Barabino, S.; Benitez-Del-Castillo, J.M.; Fuchsluger, T.; Labetoulle, M.; Malachkova, N.; Meloni, M.; Utheim, T.P.; Rolando, M. Dry eye disease treatment: The role of tear substitutes, their future, and an updated classification. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 8642–8652. [CrossRef] [PubMed]
60. Goldstein, M.H.; Silva, F.Q.; Blender, N.; Tran, T.; Vantipalli, S. Ocular benzalkonium chloride exposure: Problems and solutions. *Eye* **2022**, *36*, 361–368. [CrossRef] [PubMed] [PubMed Central]
61. Pucker, A.D.; Ng, S.M.; Nichols, J.J. Over the counter (OTC) artificial tear drops for dry eye syndrome. *Cochrane Database Syst. Rev.* **2016**, *2*, CD009729. [CrossRef] [PubMed] [PubMed Central]
62. Qiu, W.; Liu, Z.; Ao, M.; Li, X.; Wang, W. Punctal plugs versus artificial tears for treating primary Sjögren's syndrome with keratoconjunctivitis SICCA: A comparative observation of their effects on visual function. *Rheumatol. Int.* **2013**, *33*, 2543–2548. [CrossRef] [PubMed]
63. Vazirani, J.; Sridhar, U.; Gokhale, N.; Doddigarla, V.R.; Sharma, S.; Basu, S. Autologous serum eye drops in dry eye disease: Preferred practice pattern guidelines. *Indian J. Ophthalmol.* **2023**, *71*, 1357–1363. [CrossRef] [PubMed] [PubMed Central]
64. Pan, Q.; Angelina, A.; Marrone, M.; Stark, W.J.; Akpek, E.K. Autologous serum eye drops for dry eye. *Cochrane Database Syst. Rev.* **2017**, *2*, CD009327. [CrossRef] [PubMed] [PubMed Central]
65. Rodríguez Calvo-de-Mora, M.; Domínguez-Ruiz, C.; Barrero-Sojo, F.; Rodríguez-Moreno, G.; Antúnez Rodríguez, C.; Ponce Verdugo, L.; Hernández Lamas, M.D.C.; Hernández-Guijarro, L.; Villalvilla Castillo, J.; Fernández-Baca Casares, I.; et al. Autologous versus allogeneic versus umbilical cord sera for the treatment of severe dry eye disease: A double-blind randomized clinical trial. *Acta Ophthalmol.* **2022**, *100*, e396–e408. [CrossRef] [PubMed]
66. Wróbel-Dudzińska, D.; Przekora, A.; Kazimierczak, P.; Ćwiklińska-Haszcz, A.; Kosior-Jarecka, E.; Żarnowski, T. The Comparison between the Composition of 100% Autologous Serum and 100% Platelet-Rich Plasma Eye Drops and Their Impact on the Treatment Effectiveness of Dry Eye Disease in Primary Sjogren Syndrome. *J. Clin. Med.* **2023**, *12*, 3126. [CrossRef] [PubMed] [PubMed Central]
67. Aragona, P.; Stilo, A.; Ferreri, F.; Mobrici, M. Effects of the topical treatment with NSAIDs on corneal sensitivity and ocular surface of Sjögren's syndrome patients. *Eye* **2005**, *19*, 535–539. [CrossRef] [PubMed]
68. Rigas, B.; Huang, W.; Honkanen, R. NSAID-induced corneal melt: Clinical importance, pathogenesis, and risk mitigation. *Surv. Ophthalmol.* **2020**, *65*, 1–11. [CrossRef] [PubMed]
69. Murtagh, P.; Comer, R.; Fahy, G. Corneal perforation in undiagnosed Sjögren's syndrome following topical NSAID and steroid drops post routine cataract extraction. *BMJ Case Rep.* **2018**, *2018*, bcr2018225428. [CrossRef] [PubMed] [PubMed Central]
70. Hammad, M.; Ahmed, L.; Seifelnasr, M. NSAID-induced corneal melt as the first presentation of Sjögren's syndrome. *BMJ Case Rep.* **2024**, *17*, e258829. [CrossRef] [PubMed]
71. Liu, S.H.; Saldanha, I.J.; Abraham, A.G.; Rittiphairoj, T.; Hauswirth, S.; Gregory, D.; Ifantides, C.; Li, T. Topical corticosteroids for dry eye. *Cochrane Database Syst. Rev.* **2022**, *10*, CD015070. [CrossRef] [PubMed] [PubMed Central]
72. Aragona, P.; Spinella, R.; Rania, L.; Postorino, E.; Sommario, M.S.; Roszkowska, A.M.; Puzzolo, D. Safety and efficacy of 0.1% clobetasone butyrate eyedrops in the treatment of dry eye in Sjögren syndrome. *Eur. J. Ophthalmol.* **2013**, *23*, 368–376. [CrossRef] [PubMed]
73. Lin, T.; Gong, L. Topical fluorometholone treatment for ocular dryness in patients with Sjögren syndrome: A randomized clinical trial in China. *Medicine* **2015**, *94*, e551. [CrossRef] [PubMed] [PubMed Central]
74. Kapugi, M.; Cunningham, K. Corticosteroids. *Orthop. Nurs.* **2019**, *38*, 336–339. [CrossRef] [PubMed]
75. Flts, A.; Medina, R.; Akpek, E.K. The evolution of cyclosporine treatments for treatment of ocular surface diseases. *Curr. Opin. Allergy Clin. Immunol.* **2024**, *24*, 360–367. [CrossRef] [PubMed]
76. Sall, K.; Stevenson, O.D.; Mundorf, T.K.; Reis, B.L. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. *Ophthalmology* **2000**, *107*, 631–639, Erratum in *Ophthalmology* **2000**, *107*, 1220. [CrossRef] [PubMed]
77. de Paiva, C.S.; Pflugfelder, S.C.; Ng, S.M.; Akpek, E.K. Topical cyclosporine A therapy for dry eye syndrome. *Cochrane Database Syst. Rev.* **2019**, *9*, CD010051. [CrossRef] [PubMed] [PubMed Central]
78. Levy, O.; Labbé, A.; Borderie, V.; Hamiche, T.; Dupas, B.; Laroche, L.; Baudouin, C.; Bouheraoua, N. Increased corneal sub-basal nerve density in patients with Sjögren syndrome treated with topical cyclosporine A. *Clin. Exp. Ophthalmol.* **2017**, *45*, 455–463. [CrossRef] [PubMed]
79. Haber, S.L.; Benson, V.; Buckway, C.J.; Gonzales, J.M.; Romanet, D.; Scholes, B. Lifitegrast: A novel drug for patients with dry eye disease. *Ther. Adv. Ophthalmol.* **2019**, *11*, 2515841419870366. [CrossRef] [PubMed] [PubMed Central]

80. Guimaraes de Souza, R.; Yu, Z.; Stern, M.E.; Pflugfelder, S.C.; de Paiva, C.S. Suppression of Th1-Mediated Keratoconjunctivitis Sicca by Lifitegrast. *J. Ocul. Pharmacol. Ther.* **2018**, *34*, 543–549. [CrossRef] [PubMed] [PubMed Central]
81. Ervin, A.M.; Law, A.; Pucker, A.D. Punctal occlusion for dry eye syndrome. *Cochrane Database Syst. Rev.* **2017**, *6*, CD006775. [CrossRef] [PubMed] [PubMed Central]
82. Ahn, H.; Ji, Y.W.; Jun, I.; Kim, T.I.; Lee, H.K.; Seo, K.Y. Comparison of Treatment Modalities for Dry Eye in Primary Sjögren's Syndrome. *J. Clin. Med.* **2022**, *11*, 463. [CrossRef] [PubMed] [PubMed Central]
83. Lim, L.; Lim, E.W.L. Therapeutic Contact Lenses in the Treatment of Corneal and Ocular Surface Diseases-A Review. *Asia Pac. J. Ophthalmol.* **2020**, *9*, 524–532. [CrossRef] [PubMed]
84. Romano, V.; Romano, D.; Semeraro, P.; Forbice, E.; Iaria, A.; Pizzolante, T.; Frassi, M.; Franceschini, F.; Semeraro, F. Therapeutic Hyper-CL soft contact lens in Sjögren's syndrome. *Am. J. Ophthalmol. Case Rep.* **2022**, *28*, 101685. [CrossRef] [PubMed] [PubMed Central]
85. Acharya, M.; Dave, A. Commentary: Corneal involvement in rheumatoid arthritis. *Indian J. Ophthalmol.* **2021**, *69*, 73–74. [CrossRef] [PubMed] [PubMed Central]
86. Tzamalis, A.; Matsou, A.; Anastasopoulos, E.; Ziakas, N. Treatment of spontaneous corneal perforation secondary to undiagnosed Sjögren's syndrome using regenerating agent and autologous serum eye drops. *Eur. J. Ophthalmol.* **2021**, *31*, NP17–NP21. [CrossRef] [PubMed]
87. Hassanpour, K.; HElSheikh, R.; Arabi, A.; RFrank, C.; MElhusseiny, A.; KEleiwa, T.; Arami, S.; RDjalilian, A.; Kheirkhah, A. Peripheral Ulcerative Keratitis: A Review. *J. Ophthalmic Vis. Res.* **2022**, *17*, 252–275. [CrossRef] [PubMed] [PubMed Central]
88. Cao, Y.; Zhang, W.; Wu, J.; Zhang, H.; Zhou, H. Peripheral Ulcerative Keratitis Associated with Autoimmune Disease: Pathogenesis and Treatment. *J. Ophthalmol.* **2017**, *2017*, 7298026. [CrossRef] [PubMed] [PubMed Central]
89. Dutta Majumder, P.; Agarwal, S.; Shah, M.; Srinivasan, B.; K, P.; Iyer, G.; Sharma, N.; Biswas, J.; McCluskey, P. Necrotizing Scleritis: A Review. *Ocul. Immunol. Inflamm.* **2024**, *32*, 1405–1419. [CrossRef] [PubMed]
90. Bamrolia, N.R.; Arora, R.; Yadava, U. Unusual presentation of a case of Sjogren's syndrome with neurological and ocular manifestation. *Contact Lens Anterior Eye* **2012**, *35*, 85–88. [CrossRef] [PubMed]
91. Narain, S.; Pyare, R.; Rath, P.D. A Rare Presentation: Bilateral Necrotizing Scleritis in Primary Sjögren's Syndrome. *Ocul. Immunol. Inflamm.* **2025**, *33*, 146–148. [CrossRef] [PubMed]
92. Brejchova, K.; Liskova, P.; Hrdlickova, E.; Filipec, M.; Jirsova, K. Matrix metalloproteinases in recurrent corneal melting associated with primary Sjörgen's syndrome. *Mol. Vis.* **2009**, *15*, 2364–2372. [PubMed] [PubMed Central]
93. Papas, A.S.; Sherrer, Y.S.; Charney, M.; Golden, H.E.; Medsger, T.A., Jr.; Walsh, B.T.; Trivedi, M.; Goldlust, B.; Gallagher, S.C. Successful Treatment of Dry Mouth and Dry Eye Symptoms in Sjögren's Syndrome Patients With Oral Pilocarpine: A Randomized, Placebo-Controlled, Dose-Adjustment Study. *J. Clin. Rheumatol.* **2004**, *10*, 169–177. [CrossRef] [PubMed]
94. Felberg, S.; Dantas, P.E.C.; Sato, E.H. Oral pilocarpine for the treatment of dry eye in patients with Sjögren's syndrome. *Arq. Bras. Oftalmol.* **2022**, *85*, 269–276. [CrossRef] [PubMed] [PubMed Central]
95. Yoon, C.H.; Lee, H.J.; Lee, E.Y.; Lee, E.B.; Lee, W.W.; Kim, M.K.; Wee, W.R. Effect of Hydroxychloroquine Treatment on Dry Eyes in Subjects with Primary Sjögren's Syndrome: A Double-Blind Randomized Control Study. *J. Korean Med. Sci.* **2016**, *31*, 1127–1135. [CrossRef] [PubMed] [PubMed Central]
96. Wang, S.Q.; Zhang, L.W.; Wei, P.; Hua, H. Is hydroxychloroquine effective in treating primary Sjogren's syndrome: A systematic review and meta-analysis. *BMC Musculoskelet. Disord.* **2017**, *18*, 186. [CrossRef] [PubMed] [PubMed Central]
97. Betül Türkoğlu, E.; Tuna, S.; Alan, S.; İhsan Arman, M.; Tuna, Y.; Ünal, M. Effect of Systemic Infliximab Therapy in Patients with Sjögren's Syndrome. *Turk. J. Ophthalmol.* **2015**, *45*, 138–141. [CrossRef] [PubMed] [PubMed Central]
98. Souza, F.B.; Porfírio, G.J.; Andriolo, B.N.; Albuquerque, J.V.; Trevisani, V.F. Rituximab Effectiveness and Safety for Treating Primary Sjögren's Syndrome (pSS): Systematic Review and Meta-Analysis. *PLoS ONE* **2016**, *11*, e0150749. [CrossRef] [PubMed] [PubMed Central]
99. Chu, L.L.; Cui, K.; Pope, J.E. Meta-Analysis of Treatment for Primary Sjögren's Syndrome. *Arthritis Care Res.* **2020**, *72*, 1011–1021. [CrossRef] [PubMed]
100. Álvarez-Rivas, N.; Sang-Park, H.; Díaz Del Campo, P.; Fernández-Castro, M.; Corominas, H.; Andreu, J.L.; Navarro-Compán, V. Efficacy of belimumab in Primary Sjögren's syndrome: A systematic review. *Reumatol. Clin.* **2021**, *17*, 170–174. [CrossRef] [PubMed]
101. Baer, A.N.; Gottenberg, J.E.; St Clair, E.W.; Sumida, T.; Takeuchi, T.; Seror, R.; Foulks, G.; Nys, M.; Mukherjee, S.; Wong, R.; 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*, 339–348. [CrossRef] [PubMed] [PubMed Central]
102. Utine, C.A.; Birlik, M.; Özizmirliler, D.; Karakaş, A.; Akbulut, B.; Durak, I. TNF-α Inhibitors for the Management of Intractable Corneal Melt: Report of Three Cases and Review of the Literature. *Eye Contact Lens* **2021**, *47*, 372–377. [CrossRef] [PubMed]
103. Kate, A.; Basu, S. Systemic Immunosuppression in Cornea and Ocular Surface Disorders: A Ready Reckoner for Ophthalmologists. *Semin. Ophthalmol.* **2022**, *37*, 330–344. [CrossRef] [PubMed]

104. Srivastava, A.; Makarenkova, H.P. Innate Immunity and Biological Therapies for the Treatment of Sjögren's Syndrome. *Int. J. Mol. Sci.* **2020**, *21*, 9172. [CrossRef] [PubMed] [PubMed Central]
105. Sanders, F.W.B.; Huang, J.; Alió Del Barrio, J.L.; Hamada, S.; McAlinden, C. Amniotic membrane transplantation: Structural and biological properties, tissue preparation, application and clinical indications. *Eye* **2024**, *38*, 668–679. [CrossRef] [PubMed] [PubMed Central]
106. Shafer, B.; Fuerst, N.M.; Massaro-Giordano, M.; Palladino, V.; Givnish, T.; Macchi, I.; Sulewski, M.E.; Orlin, S.E.; Bunya, V.Y. The use of self-retained, cryopreserved amniotic membrane for the treatment of Sjögren syndrome: A case series. *Digit. J. Ophthalmol.* **2019**, *25*, 21–25. [CrossRef] [PubMed] [PubMed Central]
107. Chen, Z.; Lao, H.Y.; Liang, L. Update on the application of amniotic membrane in immune-related ocular surface diseases. *Taiwan J. Ophthalmol.* **2021**, *11*, 132–140. [CrossRef] [PubMed] [PubMed Central]
108. Anchouche, S.; Harissi-Dagher, M.; Segal, L.; Racine, L.; Darvish-Zargar, M.; Robert, M.C. Cyanoacrylate Tissue Adhesive for the Treatment of Corneal Thinning and Perforations: A Multicenter Study. *Cornea* **2020**, *39*, 1371–1376. [CrossRef] [PubMed]
109. Zemba, M.; Stamate, A.C.; Tataru, C.P.; Branisteanu, D.C.; Balta, F. Conjunctival flap surgery in the management of ocular surface disease (Review). *Exp. Ther. Med.* **2020**, *20*, 3412–3416. [CrossRef] [PubMed] [PubMed Central]
110. Jan, R.L.; Ho, C.H.; Wang, J.J.; Tseng, S.H.; Chang, Y.S. Associations between Sjögren Syndrome, Sociodemographic Factors, Comorbid Conditions, and Scleritis in a Taiwanese Population-Based Study. *J. Pers. Med.* **2022**, *12*, 105. [CrossRef] [PubMed] [PubMed Central]
111. Asfuroğlu, Y.; Karaca, E.E.; Orman, C.; Evren Kemer, Ö. Clinical and surgical outcomes of tectonic corneal patch grafts: Insights from a tertiary referral hospital. *BMC Ophthalmol.* **2024**, *24*, 516. [CrossRef] [PubMed] [PubMed Central]
112. Choi, W.; Lee, S.S.; Park, Y.G.; Yoon, K.C. A case of necrotizing keratoscleritis in primary Sjogren's syndrome. *Korean J. Ophthalmol.* **2011**, *25*, 275–277. [CrossRef] [PubMed] [PubMed Central]
113. Gurnani, B.; Kaur, K. Therapeutic Keratoplasty. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2025. [PubMed]
114. Artaechevarria Artieda, J.; Estébanez-Corrales, N.; Sánchez-Pernaute, O.; Alejandre-Alba, N. Peripheral Ulcerative Keratitis in a Patient with Bilateral Scleritis: Medical and Surgical Management. *Case Rep. Ophthalmol.* **2020**, *11*, 500–506. [CrossRef] [PubMed] [PubMed Central]
115. Elhaddad, O.; Achiron, A.; Yahalomi, T.; Avadhanam, V.; Tole, D.; Darcy, K. Modified "Top-up sandwich" technique for the management of corneal perforations: A case report and a literature review. *Am. J. Ophthalmol. Case Rep.* **2022**, *29*, 101765. [CrossRef] [PubMed] [PubMed Central]
116. Sharma, S.; Donthineni, P.R.; Iyer, G.; Chodosh, J.; de la Paz, M.F.; Maskati, Q.; Srinivasan, B.; Agarwal, S.; Basu, S.; Shanbhag, S.S. Keratoprosthesis in dry eye disease. *Indian J. Ophthalmol.* **2023**, *71*, 1154–1166. [CrossRef] [PubMed] [PubMed Central]
117. Wang, B.; Chen, S.; Zheng, Q.; Li, Y.; Zhang, X.; Xuan, J.; Liu, Y.; Shi, G. Early diagnosis and treatment for Sjögren's syndrome: Current challenges, redefined disease stages and future prospects. *J. Autoimmun.* **2021**, *117*, 102590. [CrossRef] [PubMed]
118. Zeng, W.; Zhou, X.; Yu, S.; Liu, R.; Quek, C.W.N.; Yu, H.; Tay, R.Y.K.; Lin, X.; Feng, Y. The Future of Targeted Treatment of Primary Sjögren's Syndrome: A Focus on Extra-Glandular Pathology. *Int. J. Mol. Sci.* **2022**, *23*, 14135. [CrossRef] [PubMed] [PubMed Central]
119. Fox, R.I.; Fox, C.M.; McCoy, S.S. Emerging treatment for Sjögren's disease: A review of recent phase II and III trials. *Expert. Opin. Emerg. Drugs* **2023**, *28*, 107–120. [CrossRef] [PubMed] [PubMed Central]
120. Almulhim, A. Therapeutic Targets in the Management of Dry Eye Disease Associated with Sjögren's Syndrome: An Updated Review of Current Insights and Future Perspectives. *J. Clin. Med.* **2024**, *13*, 1777. [CrossRef] [PubMed] [PubMed Central]
121. Nepp, J.; Knoetzl, W.; Prinz, A.; Hoeller, S.; Prinz, M. Management of moderate-to-severe dry eye disease using chitosan-N-acetylcysteine (Lacrimera®) eye drops: A retrospective case series. *Int. Ophthalmol.* **2020**, *40*, 1547–1552. [CrossRef] [PubMed] [PubMed Central]
122. Moawad, P.; Shamma, R.; Hassanein, D.; Ragab, G.; El Zawahry, O. Evaluation of the effect of topical tacrolimus 0.03% versus cyclosporine 0.05% in the treatment of dry eye secondary to Sjogren syndrome. *Eur. J. Ophthalmol.* **2022**, *32*, 673–679. [CrossRef] [PubMed]
123. Moscovici, B.K.; Holzchuh, R.; Sakassegawa-Naves, F.E.; Hoshino-Ruiz, D.R.; Albers, M.B.; Santo, R.M.; Hida, R.Y. Treatment of Sjögren's syndrome dry eye using 0.03% tacrolimus eye drop: Prospective double-blind randomized study. *Contact Lens Anterior Eye* **2015**, *38*, 373–378. [CrossRef] [PubMed]
124. Tauber, J.; Davitt, W.F.; Bokosky, J.E.; Nichols, K.K.; Yerxa, B.R.; Schaberg, A.E.; LaVange, L.M.; Mills-Wilson, M.C.; Kellerman, D.J. Double-masked, placebo-controlled safety and efficacy trial of diquafosol tetrasodium (INS365) ophthalmic solution for the treatment of dry eye. *Cornea* **2004**, *23*, 784–792, Erratum in *Cornea* **2007**, *26*, 514. [CrossRef] [PubMed]
125. Sun, X.; Liu, L.; Liu, C. Topical diquafosol versus hyaluronic acid for the treatment of dry eye disease: A meta-analysis of randomized controlled trials. *Graefes Arch. Clin. Exp. Ophthalmol.* **2023**, *261*, 3355–3367. [CrossRef] [PubMed]
126. Yokoi, N.; Kato, H.; Kinoshita, S. The increase of aqueous tear volume by diquafosol sodium in dry-eye patients with Sjögren's syndrome: A pilot study. *Eye* **2016**, *30*, 857–864. [CrossRef] [PubMed] [PubMed Central]

127. Tauber, J.; Laurie, G.W.; Parsons, E.C.; Odrich, M.G.; Lacripep Study Group; Lacripep Study Group. Lacripep for the Treatment of Primary Sjögren-Associated Ocular Surface Disease: Results of the First-In-Human Study. *Cornea* **2023**, *42*, 847–857. [CrossRef] [PubMed] [PubMed Central]
128. Wang, S.; Wang, M.; Liu, Y.; Hu, D.; Gu, L.; Fei, X.; Zhang, J. Effect of Rapamycin Microspheres in Sjögren Syndrome Dry Eye: Preparation and Outcomes. *Ocul. Immunol. Inflamm.* **2019**, *27*, 1357–1364. [CrossRef] [PubMed]
129. Castrejón-Morales, C.Y.; Granados-Portillo, O.; Cruz-Bautista, I.; Ruiz-Quintero, N.; Manjarrez, I.; Lima, G.; Hernández-Ramírez, D.F.; Astudillo-Angel, M.; Llorente, L.; Hernández-Molina, G. Omega-3 and omega-6 fatty acids in primary Sjögren's syndrome: Clinical meaning and association with inflammation. *Clin. Exp. Rheumatol.* **2020**, *38* (Suppl. 126), 34–39. [PubMed]
130. Kawahara, A. Treatment of Dry Eye Disease (DED) in Asia: Strategies for Short Tear Film Breakup Time-Type DED. *Pharmaceutics* **2023**, *15*, 2591. [CrossRef] [PubMed] [PubMed Central]
131. Schaefer, L.; Trujillo-Vargas, C.M.; Midani, F.S.; Pflugfelder, S.C.; Britton, R.A.; de Paiva, C.S. Gut Microbiota From Sjögren syndrome Patients Causes Decreased T Regulatory Cells in the Lymphoid Organs and Desiccation-Induced Corneal Barrier Disruption in Mice. *Front. Med.* **2022**, *9*, 852918. [CrossRef] [PubMed] [PubMed Central]
132. Abughanam, G.; Elkashty, O.A.; Liu, Y.; Bakkar, M.O.; Tran, S.D. Mesenchymal Stem Cells Extract (MSCsE)-Based Therapy Alleviates Xerostomia and Keratoconjunctivitis Sicca in Sjogren's Syndrome-Like Disease. *Int. J. Mol. Sci.* **2019**, *20*, 4750, Erratum in *Int. J. Mol. Sci.* **2021**, *22*, 894. [CrossRef] [PubMed] [PubMed Central]
133. Shin, S.; Yoon, S.G.; Kim, M.; Cheon, E.J.; Jeon, Y.; Lee, H.J.; Chung, S.H. The Effect of Mesenchymal Stem Cells on Dry Eye in Sjogren Syndrome Mouse Model. *Int. J. Mol. Sci.* **2023**, *24*, 1039. [CrossRef] [PubMed] [PubMed Central]
134. Teos, L.Y.; Zheng, C.Y.; Liu, X.; Swaim, W.D.; Goldsmith, C.M.; Cotrim, A.P.; Baum, B.J.; Ambudkar, I.S. Adenovirus-mediated hAQP1 expression in irradiated mouse salivary glands causes recovery of saliva secretion by enhancing acinar cell volume decrease. *Gene Ther.* **2016**, *23*, 572–579. [CrossRef] [PubMed] [PubMed Central]
135. Alevizos, I.; Zheng, C.; Cotrim, A.P.; Liu, S.; McCullagh, L.; Billings, M.E.; Goldsmith, C.M.; Tandon, M.; Helmerhorst, E.J.; Catalán, M.A.; et al. Late responses to adenoviral-mediated transfer of the aquaporin-1 gene for radiation-induced salivary hypofunction. *Gene Ther.* **2017**, *24*, 176–186. [CrossRef] [PubMed] [PubMed Central]
136. Baeza, D.C.; Sanchez, V.; Goldhardt, R.; McCoy, S.S.; Tang, F.; Baer, A.; Fox, R.; Galor, A. The eye as a window to oral and pain symptoms in Sjögren's disease. *Br. J. Ophthalmol.* **2025**, bjo-2024-326748. [CrossRef] [PubMed]

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