Unlocking hope for refractory Sjögren's Syndrome patients

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Sjögren's Syndrome

Sjögren's syndrome (SS) constitutes a chronic, inflammatory autoimmune disorder predominantly affecting women aged between the fourth and sixth decades of life, although it can manifest at any age[1].

The fundamental pathogenesis of SS involves inflammation of exocrine glands leading to eventual dysfunction, and resulting in diminished tear and saliva production. The hallmark clinical manifestations include xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes), collectively referred to as **sicca symptoms, which are prevalent in over 95% of patients**[1].

Approximately 8% of adults over age 50 experience dry eye symptoms. Of these individuals, 1 in 10 have Sjögren's Syndrome, but only one third will receive a correct diagnosis of SS. Consequently, **two-thirds of patients with dry eye associated with Sjögren's syndrome remain undiagnosed**[2].

Sjögren's Syndrome associated dry eye can be one of the most challenging ocular surface conditions encountered in ophthalmology and optometry. **Sjögren's syndrome-related dry eye disease (SS-DED) frequently presents with more severe symptoms** and clinical exam findings compared to non-SS dry eye disease (DED)[3,4]. Ocular irritation, vision disturbances, difficulties in performing visual tasks[5] and disturbed sleep[6] are some of the symptoms that patients with SS live with everyday.

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Impact of **Sjögren's syndrome-related dry eye disease** (SS-DED) on patients

Quality of life

Schiffman RM et al. (2003)[7] and Buchholz P et al. (2006)[8] reported the quality of life scores for patients with severe DED. Their utility assessments **equated the impact of severe DED to that of severe angina** and reported **a worse impact on quality of life than that associated with an immobilizing hip fracture**.

The work by Michaelov E et al. (2022)[9] was the first Canadian study reporting on various aspects of daily living and adherence to therapy among patients with Sjögren's Syndrome-related dry eye disease (SS-DED). Their findings revealed the **significant mental health burden experienced by people living with SS-DED**. **Fifty percent** of study participants reported having a **fear of going blind** and **nearly 80%** reported worrying about **a diminished quality of life related to their dry eye symptoms**.

Significant mental health burden
experienced by people living with SS-DED

Adherence and financial burden of therapy

Michaelov's study[9] also revealed **significant challenges faced by SS patients related to adherence to therapy**. The study found the most commonly reported reason for non-adherence was the **financial burden associated with the cost of therapy.** The impact of economic factors on patient management and adherence to therapy is significant in this patient population:

The most commonly reported **reason for non-adherence** was the **financial burden** associated with the **cost of therapy**

- **83%** of respondents endorsed the practice of **drop rationing to reduce the financial burden of therapy**
- **30%** of respondents reported a **household income of less than CAD 40,000.00**
- Only **3%** of participants reported having **private insurance coverage** for non-prescription dry eye therapeutic agents
- **25%** of respondents reported a **reluctance to disclose their non-adherence to their eye care provider**

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Sjögren's dry eye and workplace challenges

In a systemic review and meta-analysis, Sivakumar K.G et al. (2021)[6] highlighted the impact of DED symptoms in the work environment. This meta-analysis found **an association between SS-DED symptoms and impairment in work-related domains** including:

- **Decreased productivity** and activity engagement
- Increased **presenteeism** and **absenteeism**
- Lower employment rates and **reduced working hours**
- Increased prevalence of **work disability**

The authors suggest that **clinicians who treat patients with SS-DED are well-positioned to assist patients** in **advocating for accommodations in their workplaces** and **advocating for insurance coverage for therapeutic agents**. Such efforts may help keep people living with SS-DED employed and productive.

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Current diagnostic and treatment options for SS-DED

There is no single gold-standard test to diagnose SS-DED. A combination of clinical signs and symptom scores obtained from validated screening questionnaires can **increase diagnostic accuracy**[10] :

- Clinical signs such as **corneal** and **conjunctival staining**, **TBUT** (tear break-up time), **Schirmer's testing**, **tear meniscus height** measurements
- **Review of systems**
- Validated **SS-DED screening** questionnaires such as the **DEQ-5**

Suspected Sjögren's cases warrant specific serologic testing and rheumatologist referral for possible systemic management.

No cure exists for SS or DED. The 2017 TFOS Dry Eye Workshop II (DEWS II) treatment guidelines[11] start with patient education, environmental and lifestyle modification. Lid hygiene, warm compresses, omega-3 supplements, and adequate use of artificial tears are the foundation of the DED management plan. Optimizing both the aqueous and lipid components of the tear film is crucial since fifty percent of patients with SS-DED exhibit meibomian gland dysfunction[12]. In addition, goblet cell apoptosis is a common finding in DED, further aggravating the unstable tear film. Currently available oral secretagogues show suboptimal stimulation of lacrimation. However, inhaled cholinergic agents have the potential to increase natural tear production by activating the trigeminal afferent nerves within the nose. Enhancing tear secretion as well as improving tear quality will promote

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a more stable, healthy tear film. Treatment of DED with autologous serum represents a means to deliver trophic factors, vitamins and other mediators to improve tear quality and restore the health of the ocular surface.

Autologous serum drops in the management of SS-DED should be considered earlier in the management hierarchy. Conventional autologous serum is a growth factor-rich alternative to artificial tears, demonstrating corneal healing and improvement in dry eye signs and symptoms. Many studies support its use, reporting improvement in symptoms, TBUT, staining, and conjunctival morphology and goblet cell density. Although Schirmer's test results may not improve, other dryness markers have demonstrated improvement[11]. Autologous serum is suitable for long-term use. However, the absence of a standardized and reproducible method of autologous serum preparation can adversely impact its consistency in terms of composition, such as the concentration of growth factors.

The DEWS II Therapeutic Report discussed the role of **platelet-rich plasma (PRP)** in treating ocular surface disorders. Because platelets are reservoirs of highly active growth factors, PRP delivers a higher concentration of growth factors to the ocular surface as compared with topical autologous serum. Platelet-rich plasma demonstrates superior *in vitro* effects on epithelial cell proliferation, migration, and differentiation.

Endoret plasma rich in growth factors (PRGF) is a standardized form of PRP. **Endoret is a PRGF eye drop that is prepared via a proprietary, standardized, controlled, and scientifically-proven protocol**. Unlike autologous serum, the blood is not clotted, enabling the platelets to be concentrated and activated to release growth factors into the plasma. **Endoret is used undiluted as an eye drop**[13]. Additionally, Endoret drops **do not contain leukocytes** that can release pro-inflammatory cytokines onto the ocular surface. Endoret PRGF exhibits **20 times higher epithelial growth factor concentrations** than 20% autologous serum, delivering a balanced mixture of growth factors onto the ocular surface[14].

Endoret PRGF has demonstrated favourable clinical effect with a patient-friendly dosing of 4 to 6 drops daily. Various studies demonstrate its safety and efficacy in moderate to severe DED and SS-DED patients, improving signs, symptoms, and vision[15,16,17]. Endoret PRGF has shown effective healing of persistent epithelial defects, yielding an 85% healing rate in 11 weeks[18]. In a recent multicenter, interventional case series[19], 74% of participants showed improvement in corneal staining, with a reduction in punctate erosions from 76% to 47%. Epithelial defects decreased from 23% to ~8%. Additionally, SANDE symptom scores (including visual function), showed significant improvement. These findings **demonstrate the potential advantages of Endoret PRGF in the management of complex ocular surface conditions such as SS-DED**.

There is **no single gold-standard test** to **diagnose SS-DE**

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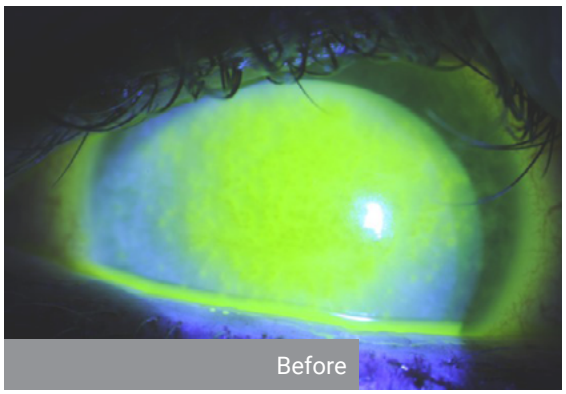
Challenging DED case reports

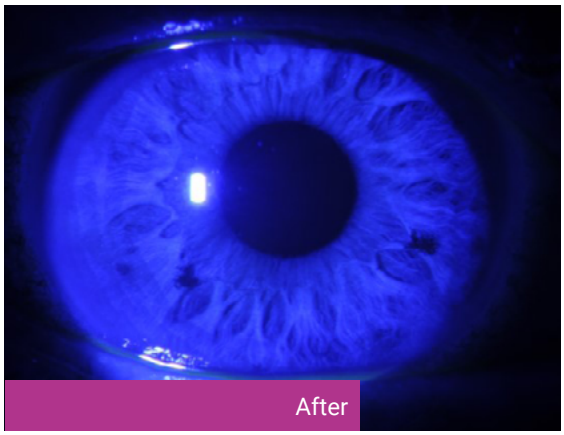
Endoret PRGF has therapeutic advantages over conventional therapy for patients with DED. The following is a summary of **five challenging cases of SS-DED and non-SS-DED patients who were unresponsive to conventional therapy**.

Case 1:

A 67-year-old female with SS-DED and a previous history of a sterile corneal ulcer, previously unresponsive to autologous serum. Despite a regimen including non-preserved artificial tears, non-preserved dexamethasone, Restasis, lubricant ointment, Loteprednol ointment, and sublingual 4% pilocarpine, her baseline symptoms did not improve. **Constant irritation, redness, dryness, excessive mucus production and fluctuating vision impaired her ability to read, drive, and use her computer**. Her score on the **Canadian Dry Eye Assessment (CDEA)** was **24/48**.



Endoret PRGF was initiated in **August 2021**. By **September 2021**, the patient showed a complete absence of staining, reduced mucus accumulation, and more stable vision. **The CDEA score decreased from 24 to 10**. Her reported difficulty level for driving, previously reported to occur "half of the time", was reported as "none of the time" at follow up. With a baseline TBUT of 1 second, almost negligible TMH, and grade 3 diffuse corneal staining at baseline, these parameters significantly improved as well. The patient reported **no adverse effects with Endoret treatment and expressed satisfaction with the results and chose to continue therapy**.



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Case 2:

A 44-year-old female with SS-DED and five years of persistent dry eye symptoms despite previous treatment including artificial tears, dexamethasone, lubricant ointment, punctal plugs, and scleral lenses. D**espite a severe CDEA score of 46/48, a Schirmer's score of 0, and significant staining (grade 3), her visual acuity was 20/25 OU**. This patient experienced great difficulty functioning at work due to her fluctuating vision.

Upon starting Endoret PRGF in August 2021, applying drops three times daily (after removal of her scleral lenses), she reported reduced dependency on her scleral lenses and improved ocular comfort. By **October 2021, she had considerably less staining, her CDEA score dropped to 32, with significant improvement in comfort and computer vision**.

Case 3:

An 83-year-old female diagnosed **with glaucoma and non-Sjögren's dry eye**. Her corneal sensation was absent due to prolonged use of topical glaucoma agents. Following a calcium-chelation procedure, she developed a persistent epithelial defect leading to corneal ulceration. Despite various interventions, including bandage lenses, antibiotics, dexamethasone, punctal occlusion, Botox-induced ptosis, and amniotic membrane, **she failed to re-epithelialize**. **Endoret PRGF was initiated 4 times per day in July, 2021** and the e**pithelium healed 13 days later**. Within a month, her discomfort resolved and in **December 2021, she showed sustained improvement**. **No further epithelial breakdown occurred since**.

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Case 4:

A 74-year-old female with severe dryness persisting for over ten years, characterized by a mixed aqueous tear deficiency and meibomian gland disease. Previous treatments included non-preserved artificial tears, dexamethasone, punctal occlusion, Restasis, and albumin drops. Her preference to wear soft contact lenses was related to her high hyperopia as well for ocular comfort. **Her main concern was fluctuating vision**. On exam, she had poor tear film (TBUT of 5 sec, TMH 0.2 mm) and diffuse corneal staining (grade 2). E**ndoret PRGF was prescribed while her albumin drops were discontinued**. **After a month of using Endoret PRGF, the corneal staining resolved**. Although her DED symptoms remained largely unchanged, her vision improved slightly but remained fluctuating. With an additional month of Endoret treatment, she reported an improvement in symptoms, **stating that her eyes had "never felt better"**. **She opted to continue Endoret treatment and subsequently underwent uneventful cataract surgery with a positive outcome. This case highlights the role of Endoret PRGF in addressing DED prior to cataract surgery**.

Case 5:

A 48-year-old female with **severe dry eye** managed **over 12 years with treatments** including Restasis, Xiidra, autologous serum drops, Insulin drops, Prokera, Lipiflow, Blephex, scleral lenses, amniotic membrane and tarsorrhaphy. Her rheumatology workup was negative. Her symptoms included severe dryness, conjunctival injection, fluctuating vision, but notably no pain. Objective tests revealed a Schirmer's score of 0, TBUT of 1 sec, TMH of 0mm, and poor corneal sensation. Her symptoms of **fluctuating vision ranging from 20/20 to 20/100 were most bothersome to her**. Coarse, diffuse corneal and conjunctival staining (grade 3) was present. **After 10 weeks of Endoret PRGF, this patient showed no improvement**. She declined further cycles, opting to return to her previous regimen. **This case demonstrates the complexity of DED management and highlights the effect of disease chronicity and sensorineural changes that occur in some cases of DED**.

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While **Endoret PRGF has proven beneficial for many patients with DED**, it **may not produce effective outcomes for all patients**. Multiple cycles of Endoret may be required in chronic cases of DED in combination with other interventions that address contributing factors such as neurotrophic keratopathy, exposure keratopathy and other coexisting conditions.

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Final thoughts

Endoret PRGF therapy fits into Step 3 of the DEWS II Treatment Algorithm. Patients with moderate to severe DED may benefit from an "accelerated" step-wise DEWS II approach. Combining the DEWS II Step 1 and Step 2 in this patient population allows the clinician to assess response to therapy and signs of progression earlier and to initiate therapies such as Endoret PRGF, scleral lenses and surgical procedures before the onset of persistent defects and ulceration. Stepping up therapy may also be required periodically for patients experiencing seasonal variations in symptoms or those preparing for ocular surgery.

Advancing therapy in SS-DED patients requires a proactive approach since these patients have a diminished capacity to heal from ocular surfaces stressors such as surgical procedures and changes in weather and humidity. Controlling inflammation, growth factor therapy and tear retention are important measures in preventing severe dryness cycles and decompensation of the ocular surface. Chronic, unresponsive cases of DED likely require multiple therapeutic combinations and cycles of interventions, including Endoret PRGF. Adjunctive therapies such as Endoret PRGF drops in scleral lenses, punctal occlusion or new agents such as inhaled tear stimulants (Tyrvaya) may enhance effectiveness of treatment. **Taking time with patients to discuss next steps in management, provides patients with hope and time for logistical planning such as financial and insurance considerations**.

Collaborating and coordinating our efforts with our rheumatology colleagues is essential[20]. We need to learn more about the effectiveness of systemic therapies on lacrimal gland functioning, so we can employ evidence-based management to control inflammation and restore homeostasis of the ocular surface. **The goal is to optimize patient management, instill hope, and improve the overall quality of life for people living with Sjögren's Syndrome**.

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At the Proctor Foundation, UCSF, Dr. Mather developed her interest in managing the ocular complications of Sjogren's Syndrome, Graft vs Host disease and Mucous Membrane Pemphigoid. She enjoys seeing patients with a variety of complex conditions, including infectious and immune-mediated processes of the ocular surface, and she initiated and currently runs multidisciplinary clinics for patients with Dry Eye Disease and Mucous Membrane Pemphigoid. Dr. Mather performs cataract surgery, cornea transplants and ocular surface surgeries and has performed refractive procedures such as topography-guided excimer treatments with collagen crosslinking for keratoconus and laser vision correction.

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