Autologous Serum Tears: Historical Overview of Clinical Use for a Broad Range of Ocular Surface Diseases

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HISTORICAL PERSPECTIVE

First described in 1975, autologous serum tears (ASTs) are derived from the patient's own blood serum. Their composition mimics one's natural tears, with components like growth factors and cytokines that are recognized in the literature for promoting healing of the ocular surface epithelium and restoring tear film homeostasis.[1,2] In the first report of the use of AST eyedrops by Fox et al. in 1984,[3] researchers sought a preservative-free alternative to artificial tears. A total of 15 patients with keratoconjunctivitis sicca treated with ASTs had an improvement in both subjective and objective symptom scores (based on rose bengal staining). In the mid-to-late 1990s Tsubota and colleagues published a number of reports describing successful AST treatment for a range of ocular surface disorders.[4,5,6,7] To date, 133 unique studies, 23 of which were randomized controlled trials, have been published on the use of ASTs in a variety of conditions, with the majority of papers focusing on physicians' use of ASTs for dry eye disease (DED), Sjögren's syndrome, and epithelial defects.

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In 2017, as part of its quest to achieve global consensus concerning multiple aspects of DED, the Tear Film & Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS II) initiative adopted the use of autologous serum eye drops (ASEDs) (also referred to as ASTs) as a treatment for DED. The initiative updated the definition of dry eye disease, stating: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[8] This work along with other important research has led to earlier and more comprehensive treatment strategies for this ubiquitous disease with its associated detrimental effects on vision, quality of life, and work productivity.

Algorithms such as those from TFOS DEWS II,[9] the American Society of Cataract and Refractive Surgeons Cornea Clinical Committee,[10] and the Cornea, External Disease and Refractive Society (CEDARS) group[11] have provided much needed direction with regard to streamlining the categorization and staging of DED and recommending treatments. These range from treatment level 1 or stage 1 with recommendations such as patient education, dietary and environmental modification, lid hygiene and over-the-counter ocular lubricating drops to

The TFOS/DEWS II recommendations include ASEDs and ASTs as an important therapeutic option for patients with stage 3 or moderate to severe DED. Beyond DED, physicians have included ASTs in treatment regimens for a broad spectrum of hard to-treat ocular surface conditions.

level 4 with approaches including amniotic membrane grafts and surgery. These recommendations include ASEDs and ASTs as an important therapeutic option for patients with stage 3 or moderate to severe DED. Beyond DED, physicians have included ASTs in treatment regimens for a broad spectrum of hard to-treat ocular surface conditions.[12]

Originally, ASTs were produced on a case-by-case basis by individual physicians, and until recently, production occurred on a small scale and protocols varied by facility. It was not until 2015 that preparation of ASTs was standardized with consistent, validated safety protocols. Today, Vital Tears in Kansas City, Missouri, is the only nationwide source for ASTs, collaborating with a network of facilities that help streamline local blood collection and coordinate standardized quality production, delivery, and billing. Drops are made to clinicians' specifications and available to patients on a short-term or ongoing subscription basis.

SUMMARY OF CLINICAL STUDIES USING ASEDS/ASTS

Beyond DED, physicians have included ASTs in treatment regimens for a broad spectrum of ocular surface conditions.[12] In clinical practice, ASEDs have been used in inflammatory conditions, trauma, and postsurgical recovery. According to the literature, they are associated with positive clinical signs and patient-reported outcomes for a range of ocular surface conditions.

A number of randomized, controlled studies have evaluated the effectiveness of ASTs in DED. A 2014 prospective, double-blind, randomized crossover study compared the use of ASTs to preservative-free artificial tears (PFATs) in 20 patients with severe DED. After 1 month of treatment, the AST group had a significantly higher tear breakup time (TBUT) and a greater decrease in Ocular Surface Disease Index (OSDI) scores than the PFAT group, indicating that ASTs were more effective than conventional eye drops for improving tear film stability and subjective comfort in patients with severe DED.[13] Another prospective, crossover, double blind study compared the effectiveness of ASTs and PFATs in 24 patients with DED. At the end of treatment, TBUT was found to be significantly higher in the AST group compared to the PFAT group, and there was a significant OSDI score decrease in both groups compared to baseline with a more significant decrease in the AST group compared to the PFAT group.[14] In 2019, researchers conducted a prospective, observational case series study to assess patient satisfaction with ASTs for the treatment of DED. The study included 100 patients with severe DED who used ASTs for as little as 1 month and as long as 3 years. They found that

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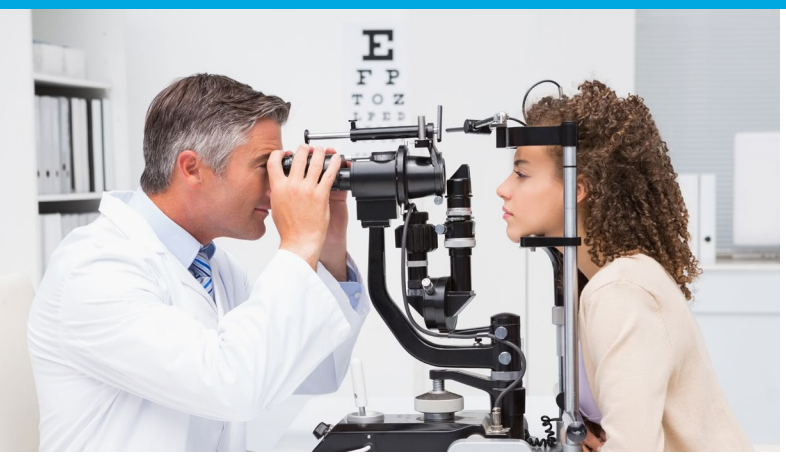


ASTs significantly reduced DED symptoms, with high patients satisfaction scores.[15]

The use of ASTs has also been well-documented in patients with Sjögren's syndrome. In 2022, researchers conducted a prospective randomized controlled trial to compare treatment with 20% ASTs to combination treatment with PFAT and 0.05% cyclosporine in 65 patients with DED due to Sjögren's syndrome. Thirty-three patients received ASTs and 32 patients received combination therapy. After 3 months of treatment, both groups showed improvements in TBUT and Schirmer values with the AST group having significantly lower OSDI scores.[16] A 2016 prospective randomized controlled study used confocal microscopy to compare in vivo changes after AST and AT therapy in two groups of 12 patients with Sjögren's syndrome-related dry eye. They found that patients treated with ASTs had significantly improved symptoms and confocal microscopy findings compared to the AT group.[17] In 1999, Japanese researchers conducted a primary clinical trial to assess the efficacy of ASTs for the treatment of dry eye in 12 patients with Sjögren's syndrome. They found that rose bengal and fluorescein scores improved significantly after 4 weeks of treatment. In addition to the improvement in objective scores, many patients reported the relief of discomfort and pain.[18]

Studies have been conducted in patients suffering from neuropathic corneal pain (NCP) or neurotrophic keratitis (NK).[19,20] A 2019 study looked retrospectively at the efficacy of ASTs in the treatment of 16 NCP patients reporting severe pain. After 3.8 months of AST treatment, pain severity had decreased from a rating of 9.1 to 3.1 and in vivo confocal microscopy of the cornea demonstrated a significant improvement in total nerve length and number as well as a significant decrease in reflectivity and tortuosity.[19] A 2004 retrospective case series reviewed 11 NK patients who were treated with ASTs to evaluate changes in corneal disease state, corneal sensitivity, and BCVA. At follow-up, the changes in corneal disease state, corneal sensitivity, and BCVA were evaluated, and the researchers concluded that the epithelial disorders had healed in all eyes within an average of 17 days. In addition, corneal sensitivity had increased and BCVA had improved by an average of at least two lines.[20]

Studies show that ASTs are also used by physicians for persistent corneal epithelial defects PCEDs). In 2009, researchers reviewed the medical records of 25 patients with PCEDs nonresponsive to conventional medical treatment that were treated with 50% ASTs. At follow up, fluorescein staining revealed that 23 of the 25 eyes studied had healed after AST treatment.[21] A 2022 study retrospectively evaluated 34 eyes of 26 patients treated with ASTs for PCEDs. Post-treatment fluorescein staining indicated that ASTs were effective in 73.5% of eyes and partially effective in 14.7% of eyes. None of the patients displayed complications related to the treatment.[22]

A 2004 prospective case series investigated the efficacy and safety of ASTs in 14 patients with severe DED associated with chronic graft vs. host disease (cGVHD). The patients, who had not previously responded to conventional treatment, were given 20% concentration ASTs 10 times per day. After 4 weeks of treatment, significant improvement was observed in complaint scores, fluorescein scores, rose bengal staining and TBUT.[23] In 2017, a group of German researchers retrospectively analyzed

In a study of Kaiser Permanente patients treated with ASTs, 90% reported an improvement of symptoms, and improved corneal staining was noted in 83% of patients. In addition, topical lubrication use decreased in 40% of patients and steroid use decreased in 50% of patients who were prescribed ASTs.

Forty-one percent of Vital Tears users surveyed reported ordering ASTs for DED patients who have not found relief with over-the-counter eye drops, cyclosporine or liftegrast. Thirty-eight percent use ASTs as first-line therapy for cGVHD patients and 26% choose ASTs as the first treatment option for patients with Sjögren's related DED.

17 cGVHD patients who were treated with ASTs for 6 months. At the follow-up visit, all of the patients showed a significant increase in visual acuity as well as considerable improvement in corneal staining and ocular symptoms.[24]

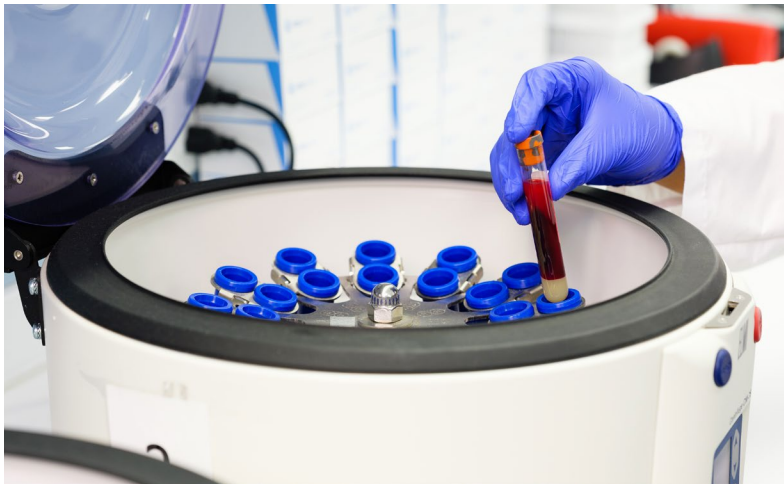
PRACTICAL CONSIDERATIONS FOR USE

The use of ASTs has been largely physician dependent given the challenges around accessibility, cost and insurance coverage. However, the Kaiser Permanente health system has been an exception, having offered ASTs as a covered benefit since 2018. Adoption of ASTs within Kaiser has been much more widespread, and to date Vital Tears has provided ASTs for more than 7,000 patients. Kaiser conducted a retrospective record review of 73 patients who had been treated with ASTs over a 1-year period by 11 cornea specialists. The most common indication was recalcitrant DED, and many of these patients had concurrent conditions. The researchers identified 30 DED patients who had a follow-up visit within 90 days of treatment and found that 90% reported an improvement of symptoms, and improved corneal staining was noted in 83% of patients. In addition, topical lubrication use decreased in 40% of patients and steroid use decreased in 50% of patients who were prescribed ASTs. Of the 10 patients who were being treated with ASTs for persistent epithelial defects, seven healed within an average of 42 days. Of the 3 patients whose conditions did not resolve, 2 had perforation during the study period and 1 was lost to follow-up.[25]

Vital Tears recently surveyed its current users and received responses from 101 eye care providers. Forty-one percent of respondents reported ordering ASTs for DED patients who have not found relief with over-the-counter eye drops, cyclosporine or liftegrast. Thirty-eight percent use ASTs as first-line therapy for cGVHD patients and 26% choose ASTs as the first treatment option for patients with Sjögren's related DED. (Data on file.)

HOW SERUM TEARS ARE MADE

Historically, ASTs were prepared by individual physicians for individual patients without a consistent approach for quality control. Today, Vital Tears is preparing ASTs in a standardized setting using rigorous quality-controlled processing procedures performed by trained and experienced technicians to ensure consistency, quality, and prevent contamination. The first step in developing ASTs is drawing the patients' blood. The blood is drawn at one of Vital Tears' contracted blood collection facilities or by a mobile phlebotomist at the patient's home and shipped overnight to the company's laboratory for processing. Centrifugation is performed to separate the serum from the solid components of the blood, thereby isolating the serum. The serum is diluted with preservative-free balanced salt solution according to the patient's needs and the eye care provider's order. Typically, serum concentration orders range from 20% to 100%. ASTs must be prepared in a sterile manner and properly stored to avoid microbial growth, so the product is kept frozen until ready for use and then refrigerated while in use. Patients are provided uniform instructions with regard to proper care and use to minimize the chance of contamination.[26]



CONCLUSION

ASTs are a well-accepted treatment for a host of ocular surface conditions with a positive safety profile and a growing body of evidence supporting their therapeutic benefits in a variety of patient types, particularly when previous therapies have failed. With a national manufacturer that has standardized the service of preparing ASTs while improving access through a network of blood draw facilities, eye care providers can conveniently and reliably order ASTs that consistently meet the highest quality standards. They can also have peace-of-mind knowing that Vital Tears will work closely with their patients through the entire process to ensure a seamless and positive experience. ■

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