Use of Autologous Serum Tears for the Treatment of Ocular Surface Disease From Patients With Systemic Autoimmune Diseases

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PURPOSE: To describe the safety and efficacy of autologous serum tears (AST) in managing ocular surface disease resistant to conventional therapy in patients with systemic autoimmune disease(s).

DESIGN: Retrospective, interventional case series.

METHODS: Records of patients from 2009 to 2015 with systemic autoimmune disease treated with AST (20%–50%) for chronic surface disease were analyzed. Standardized measures of subjective dry eye symptoms, objective dry eye staining of the cornea, and slit-lamp findings including punctate epithelial erosion (PEE), filamentary keratopathy (FK), and corneal epithelial defects (KED) were compared during first and last visit. We attempted to standardize outcomes by creating a scale from 1 to 4 for subjective and objective components: worsening (1), no improvement (2), partial improvement (3), and complete resolution (4).

RESULTS: Fifty-one patients (101 eyes) were included. The mean age was 59.8 ± 13.2 years (72.5% female). Average use of AST was 14.3 ± 11.7 months. Complete objective improvement of initial slit-lamp findings was achieved in 30% and partial improvement in 55% of eyes. Presence of PEE, FK, and KED decreased from 92.1% to 52.5% (P < .001), from 22.8% to 9.9% (P = .02), and from 5% to 2% (P = .44) of the eyes, respectively. Full subjective improvement of symptoms was achieved in 34.6%, partial in 50.5%, and none in 14.9% of patients. No adverse side effects were noted during follow-up.

CONCLUSIONS: AST are a safe and effective adjunct therapy in improving both objective signs and subjective symptoms of ocular surface disorders associated with systemic autoimmune disease(s). (Am J Ophthalmol 2018;189:65–70. © 2018 Published by Elsevier Inc.)

METHODS

• PATIENT DATA: This study was approved by the Institutional Review Board of the University of Miami, Miller School of Medicine, Miami, Florida.

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School of Medicine (Medical Science IRB A University of Miami, No: 20130743). The protocol conformed to the requirements of the United States Health Insurance Portability and Accountability Act and the tenets of the Declaration of Helsinki. Informed consent was obtained from the subjects for AST treatment after explanation of the nature and possible consequences of its use.

The study consisted of a retrospective noncomparative case series. A chart review was performed on all patients receiving AST (20%-50%) who had the underlying diagnosis of a systemic autoimmune disease. We excluded patients with incomplete medical records, those lost to follow-up, those who had received less than 2 months of AST treatment, and those receiving other blood derivatives such as platelet-rich plasma (PRP) or plasma rich in growth factors (PRGF).

All patients were seen at the Bascom Palmer Eye Institute (BPEI). Patients were examined prior to the start of AST treatment, where demographic information was collected and a complete ophthalmologic history and examination were performed. At the initial visit, all patients completed a validated symptom questionnaire and underwent a complete ophthalmologic examination. The subjective questionnaire was the Ocular Surface Disease Index (OSDI), which consists of 12 questions aimed to standardize outcomes by creating a scale from 1 to 4, which was assessed at each visit for subjective and objective components: worsening of basal condition (1), no improvement (2), partial improvement (3), and complete resolution of signs or symptoms (4). The objective and subjective responses were analyzed independently.

The ocular surface staining was performed as follows: 3 minutes after instillation of 5 μL of 2% fluorescein with an Eppendorf pipette, a score of 0 (nothing) to 3 (severe) was given to each of the 5 regions of the cornea according to a standardized grading system (National Eye Institute criteria). The total score was then summed, giving the composite score for that cornea.

The patients were then followed at month 1, month 3, and month 6 and biannually thereafter. Only information while on the treatment with the AST was included for efficacy data. However, those on whom AST was stopped were still monitored and their charts were reviewed to ensure no delayed complications were reported.

All patients had failed previous DED therapy with high- and low-viscosity agents as well as other conservative measures. The concomitant topical or systemic treatment after starting the serum drops was maintained, so as not to confuse the potential effect of the AST. Patients were started on 20%-50% concentration of AST according to the treating physician’s criteria and instructed to instill 1 drop in both eyes 4–6 times daily. The only change in management was to increase the concentration of serum tears in a progressive fashion (by 10% every 2 months) if the patient showed no or only partial response. Patients were allowed to instill nonpreserved artificial tears in between AST applications.

### RESULTS

**PATIENT DEMOGRAPHICS:** This study included 101 eyes of 51 patients (both eyes of each subject were included except for 1 patient). Seventy-three percent of the sample were female. The mean age was 59.8 ± 13.2 years (range 28–89 years). The most common systemic autoimmune disease was Sjögren syndrome (n = 27; 52.9%), and 7 patients (13.7%) had secondary Sjögren syndrome. Sixty-three
percent of patients used systemic immunosuppressive medication. Table 1 summarizes the characteristics of the study population at presentation to the BPEI. The baseline treatment, which was continued as an adjunct throughout the therapy with AST, can be seen in Table 2. Of note, 55.4% of the sample had long-term punctual occlusion therapy, either by plugs or cautery, before entering the study.

The mean follow-up of the group was $23 \pm 16$ months (range 2–59 months), with an average AST use of $14.3 \pm 11.7$ months (range 2–50 months). The initial mean best-corrected visual acuity (logMAR) was $0.249 \pm 0.5$ and $0.245 \pm 0.4$ at the last follow-up ($P = .7$).

As seen in Figure 1, the initial concentration of AST prescribed in most patients was 20%. As the follow-up extended, some patients, owing to partial response and changing practice patterns, were increased to higher concentrations of AST. Only 13.9% of patients increased their concentration to $>40\%$.

No complications with phlebotomy, infections, immune deposits, AST intolerance, or other adverse reaction to drops were reported.

- **RESPONSE TO AUTOLOGOUS SERUM TEARS:** The objective improvement in the sample is presented in Figure 2, where we compare the visit prior to the start of AST to the final visit still on treatment. The mean corneal staining in the initial visit was $9.4 \pm 4.9$ and in the final visit $6.8 \pm 3.9$ ($P = .02$). There was a significant decrease in the number of eyes that had any amount of PEE, which decreased from 92.1% to 52.5% (Fisher exact test; $P < .001$). The number of eyes with FK decreased from 22.8% at presentation to 9.9% (Fisher exact test; $P = .02$). The reduction in the number of eyes with a KED was reduced from 5% to 2% (Fisher exact test; $P = .44$). Overall, a significant reduction in the slit-lamp findings (positive objective response) was seen in 80.2% of patients, with 45.5% of them achieving complete resolution of their initial corneal findings. The outcome of patients grouped by autoimmune diagnosis is summarized in Table 3.

The subjective improvement, as reported at each follow-up, is presented in Figure 3. The mean OSDI at the initial visit was $62 \pm 24.2$ and at the final visit $47 \pm 22.3$ ($P = .03$). As a group, 85.1% of the sample reported a significant decrease in ocular symptoms. In fact, a third of the patients (34.6%) considered that their ocular discomfort was completely resolved. On the other hand, 14.9% of the sample did not notice any beneficial effect of the AST treatment. Of note, no patients reported a worsening of symptoms with AST treatment.

### DISCUSSION

AST ARE SAFE AND EFFECTIVE AS AN ADJUNCT TREATMENT in the stepwise approach to the treatment of aqueous-

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**TABLE 1. Characteristics of the Study Population (N = 51)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>59.8 (13.2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37 (72.5)</td>
</tr>
<tr>
<td>Male</td>
<td>14 (27.5)</td>
</tr>
<tr>
<td>Systemic autoimmune disease</td>
<td></td>
</tr>
<tr>
<td>GVHD</td>
<td>21 (41.2)</td>
</tr>
<tr>
<td>SS</td>
<td>27 (52.9)</td>
</tr>
<tr>
<td>MMP</td>
<td>4 (7.8)</td>
</tr>
<tr>
<td>RA</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>SLE</td>
<td>5 (9.8)</td>
</tr>
<tr>
<td>Systemic immunosuppressive medication</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>10 (19.6)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>6 (11.8)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>3 (5.9)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>9 (17.6)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>10 (19.6)</td>
</tr>
</tbody>
</table>

GVHD = graft-vs-host disease; MMP = mucous membrane pemphigoid; RA = rheumatoid arthritis; SLE = systemic lupus erythematosis (SLE); SS = Sjögren syndrome.

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**TABLE 2. Topical Medication Used by Patients With Systemic Autoimmune Diseases That Were Started on Autologous Serum Tears**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubricants</td>
<td>48 (94.1)</td>
</tr>
<tr>
<td>Steroids</td>
<td>31 (60.8)</td>
</tr>
<tr>
<td>Cyclosporine 0.05%</td>
<td>30 (58.8)</td>
</tr>
<tr>
<td>IOP-lowering medication</td>
<td>8 (15.7)</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure.

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**FIGURE 1. Distribution of autologous serum tears concentration prescription from the initial and last visit.**

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deficient DED in the context of autoimmune disease. We included patients with a confirmed diagnosis of a systemic autoimmune disease who had failed previous conservative therapy of DED.

In this series, AST were effective approximately 80% of the time in both subjective and objective components of DED. As in other studies, the positive response rate was high, and complication rate was zero.23 We decided to use a real-world approach to this study, in the sense that patient response was graded in a way that would be easy to understand for patients inquiring about the potential success of treatment with AST. For example, saying “you have an 80% chance of feeling better, and even a 30% chance of resolving all symptoms” is more likely to allow for a better-informed consent process of this therapy rather than saying “your OSDI score is likely to decline by 27%” or “your corneal staining score on average is expected to decrease by 65%.”

With regard to SS, Hussain and associates reported on 11 patients, making no distinction between its primary and secondary forms; they concluded that even though staining scores decrease after treatment, both Schirmer test and symptoms remained the same.16 We show that of 54 eyes (of 27 patients) with SS, 79.6% had a positive objective response, with 55.6% of this group having a complete resolution of their slit-lamp findings. The subjective response in this group was excellent, with 79.6% having a positive response, and 37% of this sample had complete resolution of their symptoms.

Hwang and associates reported using 50% AST diluted in sodium hyaluronate to treat patients with primary and secondary SS. They suggested that owing to increased proinflammatory serum cytokine levels, AST might not be effective for the treatment of secondary SS.14 Although some evidence suggests a theoretical advantage of the slow release of growth factors and better tolerability when hyaluronate is used as a diluent, other reports have suggested normal saline might be a superior diluting agent in this specific patient population (SS).3 In this study, we had 7 patients with secondary SS vs 20 patients with primary SS and did not find any difference in response rates. Of course, this is a retrospective study, not powered to prove a difference, and the treatment type and regimen used varied significantly from those who have previously reported failure.14,16

Interestingly, Hussain and associates report the long-term use of 50% AST drops diluted with 0.9% sodium chloride. In the sub-analysis of patients with GVHD (11 out of 63 patients), they concluded that 48% of these patients have a significant increase of Schirmer scores, a trend for improvement in corneal staining scores, but no significant difference in the OSDI scores. Our results support the conclusion of improvement in slit-lamp findings, as we show that out of 41 eyes (of 21 patients) with GVHD, 78% had a positive objective response with 34.1% of this group having a complete resolution of their slit-lamp findings.

### TABLE 3. Objective Outcome According to Diagnosis (Eyes)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>First Visit, N (%)</th>
<th>Last Visit, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PEE</td>
<td>FK</td>
</tr>
<tr>
<td>GVHD</td>
<td>37 (90.2)</td>
<td>9 (22)</td>
</tr>
<tr>
<td>SS</td>
<td>52 (96)</td>
<td>14 (26)</td>
</tr>
<tr>
<td>RA</td>
<td>8 (80)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>MMP</td>
<td>6 (75)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>SLE</td>
<td>8 (80)</td>
<td>6 (60)</td>
</tr>
</tbody>
</table>

**FK** = filamentary keratopathy; **GVHD** = graft-vs-host disease; **KED** = corneal epithelial defect; **MMP** = mucous membrane pemphigoid; **PEE** = punctate epithelial erosions; **RA** = rheumatoid arthritis; **SLE** = systemic lupus erythematosus; **SS** = Sjögren syndrome.

### FIGURE 2. Objective improvement as evidenced by the presence or absence of punctate epithelial erosions (PEE), filamentary keratopathy (FK), and persistent epithelial defects (PED) initially and at last visit while using autologous serum tears.

### FIGURE 3. Subjective improvement as evidenced by the subjectively reported change in symptoms from baseline. Patients reported complete resolution of symptoms, partial improvement, no change, or worsening at last follow-up.
findings. In contrast to the study described above, the positive subjective response in our subgroup was excellent, with 90.2% showing some amount of improvement and 31.7% of this sample having complete resolution. Similar results have been recently reported by Tahmaz and associates.24

In the group of patients presenting with a KED, we noted the improvement was not significant. Although it did trend in the same direction as the other 2 groups, the number of patients presenting with this condition was small.

Our study is limited by the fact that it is a retrospective analysis of a case series and the sample size could be larger. However, our follow-up duration of AST use was longer than in most reported series. A larger study comparing different sources of blood (autologous, heterologous, or cord), different dilutions, dilutors (hyaluronate, balanced salt solution, or saline), and application strategies would be interesting in this patient population. The differences reported in the other studies discussed likely reflect a difference in these. Ideally, we would isolate the specific compound or compounds that have the most impact on the ocular surface and in this way, produce and distribute a therapeutic eye drop that would not require refrigeration, continuous phlebotomies, or heterogenous preparation methods.

In short, we found that AST diluted in saline solution at concentrations between 20% and 50% are safe and effective in the treatment of DED in patients with autoimmune disorders, especially of SS- and GVHD-associated OSD. Even though biochemical differences found in serum composition of patients with systemic diseases have been described, our clinical practice suggests that their serum does not have a negative effect on the ocular surface and, in fact, can be used as a powerful adjunct in these patients who are often difficult to manage.

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