



# Human albumin eye drops as a therapeutic option for the management of keratoconjunctivitis sicca secondary to chronic graft-versus-host disease after stem-cell allografting

J.T. Seki RPh BSc(Phm) PharmD,<sup>\*†‡</sup> N. Sakurai BSc(Phm) MSc,<sup>\*</sup> S. Moldenhauer PharmD,<sup>\*†</sup> J. Dam RPhT,<sup>\*</sup> E.G. Atenafu MSc,<sup>\*</sup> P.M. Yip PhD,<sup>§</sup> T. Mazzulli MD,<sup>¶||</sup> T. Henderson BSc,<sup>#</sup> J. Pendergrast BA BSc(Med) MD,<sup>§</sup> C. Cserti HBSc MD,<sup>§</sup> J.P. Velazquez MD,<sup>\*</sup> R. Simpson MD,<sup>\*</sup> G. Felluga CPhT,<sup>\*</sup> H.A. Messner MD PhD,<sup>\*</sup> and J.H. Lipton MD PhD<sup>\*</sup>

## ABSTRACT

**Background** Keratoconjunctivitis sicca from chronic graft-versus-host disease (CGVHD) after allogeneic stem cell transplantation is common, leading to severe corneal damage and blindness if not treated. We retrospectively examined the efficacy and safety of pooled human albumin eye drops (HAEDS) for symptom relief in 40 stem-cell transplantation patients after other alternatives had failed.

**Methods** The *Common Terminology Criteria for Adverse Events* (version 4.0) and the CGVHD grading scale were used to compare response in the patients during January 2000 and July 2013. In addition, on days 1 and 30, the HAEDS were subjected to quality assurance testing for sterility, oncotic pressure, albumin measurement, viscosity, pH, and purity by protein electrophoresis.

**Results** Use of HAEDS resulted in symptom relief for 37 patients (92.5%); 3 patients (7.5%) failed to improve with use of HAEDS ( $p \leq 0.0001$ ). Of the 37 patients having symptom relief, 7 (19%) improved from grade 3 to no dry eye symptoms. Proportionately, post-treatment symptom improvement by two grade levels, from 3 to 1 (70%), was significantly higher than improvement by one grade level, from 3 to 2 (11%) or from 2 to 1 (19%,  $p \leq 0.0001$ ). Time to symptom relief ranged from 2 weeks to 28 weeks. Of the 40 patients, 38 (95%) had no adverse reactions. Days 1 and 30 quality assurance testing results were equivalent.

**Conclusions** Complications of keratoconjunctivitis sicca were well managed and well tolerated with HAEDS when other remedies failed. Quality assurance testing confirmed that HAEDS were safe and stable in extreme conditions.

**Key Words** Post-transplant dry eye management

*Curr Oncol.* 2015 Oct;22(5):e357-e363

[www.current-oncology.com](http://www.current-oncology.com)

## INTRODUCTION

The rate of chronic graft-versus-host disease (CGVHD) affecting the eye in patients who undergo allogeneic stem-cell transplantation has been reported to be in the 40%–60% range<sup>1</sup>. The two most common late clinical complications included cataract formation and

keratoconjunctivitis sicca (KCS) or dry eye syndrome (xerophthalmia), which are severely debilitating because of worsening ocular surface disease<sup>2,3</sup>. Usually, KCS is part of a syndrome of extensive CGVHD that is more general and all-encompassing, including dryness of the eye, mouth, vagina, and skin. It has been described to resemble, in the broad sense, Sjögren syndrome<sup>4</sup>. In

part, it results in lacrimal insufficiency and dysfunction of the meibomian gland, causing reduced tear flow and dry eye pathophysiology<sup>3,5-9</sup>. Total body irradiation is another factor contributing to kcs<sup>2</sup>. The pathophysiology of cGVHD, including ocular GVHD, was summarized by Ferrara and Reddy 2006<sup>10</sup>. When untreated, kcs can be damaging to the cornea and can be associated with eye infection, leading, in extreme cases, to blindness<sup>2</sup>. Such events can limit the patient's daily activities, leading to poor quality of life and potentially affecting psychological health, including causing depression<sup>11,12</sup>.

Although kcs and its associated potential complications were described in the 1970s<sup>4</sup>, few definitive therapeutic measures are available. It has been sensible to target dry eye syndrome with the use of tear-like products to replenish and lubricate dry eyes, products that reduce evaporation of moisture and fluid drainage, agents to control inflammatory processes, and agents to preserve integrity of the mucosa<sup>1</sup>, but those approaches have often been inadequate. Treatment recommendations depending on the level of severity have been made.

Patients with kcs were introduced to human albumin eye drops (HAEDS) for their moisture-sequestering quality (initially in theory) and their ability to ameliorate or palliate dry eye symptoms. Optimal maintenance on HAEDS after patients become refractory to the many lines of commercially available products (Table 1) has been described. Human albumin eye drops have been found to offer safety and effectiveness as a therapeutic option for patients who develop dry eye syndrome because of cGVHD.

**METHODS**

Patients from the stem-cell transplantation program at Princess Margaret Cancer Centre between January 2000 and July 2013 were included in this retrospective analysis. Patients could be enrolled in the study if they were more than 18 years of age and had developed cGVHD presenting

(at least in part) as ocular symptoms requiring an ophthalmology consult. Patients who developed ocular GVHD and who were subsequently treated with HAEDS were identified using the outpatient pharmacy system. The institutional research ethics board approved the study.

Patients diagnosed with kcs were initially offered symptomatic care measures for dry eyes (Table 1). When necessary, some patients were managed with concurrent temporary or permanent punctal occlusion to increase tear retention time, improving moisture to the outer eye<sup>13,14</sup>. Human albumin in the form of an eye drop was offered to patients who were refractory to all previous medical and surgical interventions. Patients were prescribed 1-2 HAEDS into each affected eye 4 times daily for dry eye symptoms. The drops being non-toxic and well tolerated, patients were advised to administer them with increased frequency when needed, depending on severity of symptoms and need for better control.

For patient use, 5 mL of 25% HAEDS prepared as 1-in-6 dilutions was transferred into 10-mL bottles and frozen until dispensed. Patients kept the bottles in a freezer, defrosting a new bottle for each day's use. The expiry date of the frozen HAEDS was determined to be 3 months after preparation.

Initial symptoms at presentation, any prior therapy tried, symptoms after use of HAEDS, whether improvement of symptoms occurred with HAEDS, and time to improvement were analyzed. The *Common Terminology Criteria for Adverse Events* [CTCAE (version 4)]<sup>15</sup> was used to compare corneal staining or superficial keratitis with a visual acuity baseline, and treatment scores before and after HAEDS were documented. Adverse effects were also collected. The U.S. National Institutes of Health cGVHD score was also used during the study to assess the severity of symptomatic dry eye<sup>1,11,16</sup>.

Physical and chemical characteristics of the HAEDS were examined as a quality control measure. The stability and integrity of the human albumin products were thus

**TABLE 1** Commonly prescribed interventions for dry eye

Class	Product
Lubricants	Acetylcysteine; artificial tears; BION Tears <sup>a</sup> ; GenTeal eye drops, ointment, or gel <sup>a</sup> ; Lacrinorm <sup>b</sup> ; Liposic <sup>b</sup> ; Puralube <sup>c</sup> ; Refresh Tears, Lacri-lube, Liquigel, or Endura <sup>d</sup> ; Systane or Systane ultra <sup>a</sup> ; Tear-gel <sup>a</sup> ; Tears Naturale <sup>a</sup> ; Visine <sup>e</sup>
Steroids	FML <sup>d</sup> eye drops; Maxidex eye drops or ointment <sup>a</sup> ; Pred Forte <sup>d</sup>
Immunosuppressants	Restasis <sup>d</sup> (equivalent not yet marketed in Canada)
Antibiotics	Tobrex <sup>a</sup> , Fucithalamic <sup>f</sup> , Zymar <sup>d</sup>
Mechanical interventions	SmartPLUG <sup>g</sup> , punctal plugs
Surgical interventions	Bilateral lower tear-duct cauterization
Others	Voltaren <sup>a</sup> , Tobradex <sup>a</sup>

<sup>a</sup> Novartis Canada, Dorval, QC.  
<sup>b</sup> Bausch & Lomb, Rochester, NY, U.S.A.  
<sup>c</sup> Fera Pharmaceuticals, Locust Valley, NY, U.S.A.  
<sup>d</sup> Allergan, Parsippany, NJ, U.S.A.  
<sup>e</sup> Johnson & Johnson, Markham, ON.  
<sup>f</sup> Amdipharm Mercury Company Limited, London, U.K.  
<sup>g</sup> Medennium, Irvine, CA, U.S.A.

validated in extreme conditions. Handling of the HAEDS by patients in conditions of extreme temperature variation, especially during summer months, was a major concern. The transfer of the HAEDS from the hospital freezer ( $-20^{\circ}\text{C}$ ) into the ice-packed Styrofoam container used by patients for transporting the drops (sometimes in a journey of 2 hours or more) to the home freezer created a large temperature gradient.

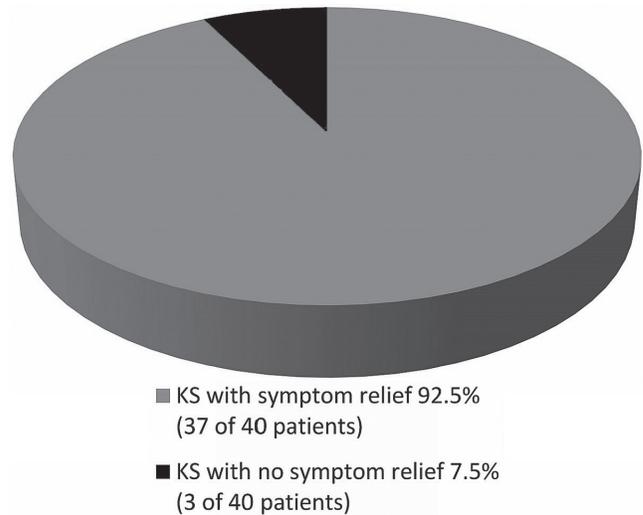
The HAEDS were subjected to quality assurance testing on day 1 for sterility, oncotic pressure, albumin measurement, viscosity, pH, and purity by protein electrophoresis. Albumin concentration was measured by the bromocresol green dye-binding method on the Architect c8000 chemistry analyzer (Abbott Diagnostics, Abbott Park, IL, U.S.A.). Viscosity was measured by torque resistance using the Wells–Brookfield viscometer (Brookfield Engineering Laboratories, Middleboro, MA, U.S.A.). Measurement of pH by ion selective electrode was performed on the Siemens RapidPoint 405 blood gas analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY, U.S.A.). Albumin purity (homogeneity) was assessed by protein electrophoresis on the Sebia Hydrasys 2 instrument using the manufacturer's alkaline-buffered agarose gel kits, followed by densitometric quantitation with the Gelscan system (Sebia, Norcross, GA, U.S.A.). Oncotic pressure was determined using a Wescor Colloid Osmometer (model 4420; Wescor, Logan, UT, U.S.A.), which uses a pressure transducer to measure the oncotic pressure of high molecular weight blood solutes that are non-diffusible through a semipermeable membrane.

Quality assurance testing of the HAEDS was performed at the Laboratory Medicine Program, Toronto General Hospital Division, University Health Network; the Toronto Hospital for Sick Children Laboratory; and the Microbiology lab, Mount Sinai Hospital. Quality controls and maintenance for the devices in use were completed daily for the duration of the study. A random 4% sampling rule applied for all tests. The tests mimicked the freeze–thaw cycle expected during transportation of the HAEDS from hospital to home. Similar tests were performed over a period of 16 hours, mimicking eye applications while awake. The samples were kept in a refrigerator ( $4\text{--}5^{\circ}\text{C}$ ) during the day. Stability tests were repeated on day 30.

## RESULTS

We retrospectively reviewed 40 patients who had developed ocular GVHD during the study period. The initial symptoms reported by all patients consisted of various combinations of descriptors (symptoms: dryness,  $n = 35$ ; irritation, discomfort, burning, or soreness,  $n = 16$ ; redness,  $n = 9$ ; photophobia,  $n = 6$ ; pain,  $n = 5$ ; blurriness,  $n = 4$ ; and foreign body sensation,  $n = 4$ ). Other complaints such as eye discharge, watery eye, and reduced quality of life were documented.

General symptom relief, categorized by various degrees of improvement, occurred in 37 patients (92.5%); 3 patients (7.5%) failed to improve with HAEDS ( $p \leq 0.0001$ , Figure 1). Although 7 of the 37 patients who experienced improvement had stable symptoms, they had to maintain their HAEDS use to control ongoing symptoms. No clear improvement was achieved with other supportive care measures.



**FIGURE 1** The proportion of patients treated with human albumin eye drops for keratoconjunctivitis sicca that did and did not experience symptom relief.

Based on CTCAE grading (grades 1–3), 7 patients (19%) experienced optimal improvement from grade 3 to no dry eye symptoms (Table II). Proportionately, post-treatment symptom improvement by two grade levels, from 3 to 1 (26 of 37, 70%), was significantly greater than was improvement by one grade level, from 3 to 2 (4 of 37, 11%) or from 2 to 1 (9 of 37, 19%,  $p \leq 0.0001$ ). Time to achieve symptom relief ranged from 2 weeks to 28 weeks. In 19 patients (47.5%), symptom relief started between weeks 2 and 4 of treatment. Another 7 patients (17.5%) responded in 5–8 weeks. Time-to-response information was not available for 5 patients (Figure 2).

The National Institutes of Health cGVHD grading scale is divided into 4 levels: grade 0 is described as no dry eye symptoms; grades 1–3 describe some form of dry eye symptoms, with eye drops being used. By this scale, 30 patients experienced symptom improvement (grade 3 to grade 2), and 7 patients had stable symptoms at grade 2 ( $p = 0.0003$ , Table II). Of the 40 patients, 38 (95%) experienced no adverse effects; burning and stinging pain were reported by 1 patient each. The patient experiencing stinging pain kept using the HAEDS, although treatment was suboptimum. The other patient occasionally experienced a burning sensation, but kept on using the HAEDS despite the discomfort. In both patients, HAEDS were eventually discontinued.

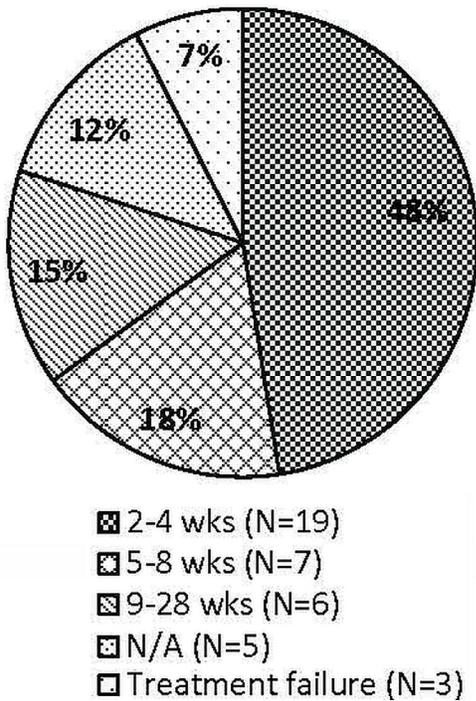
Patients had been using other commercially available therapies (topical lubricating eye drops, gels, and ointments; topical corticosteroids or antibiotics; cyclosporine eye drops; topical nonsteroidal anti-inflammatory agents; lower tear duct cauterization; punctal plugs) before using HAEDS, and they were given the option of using those therapies in combination with the HAEDS. Of the 40 patients, 3 (7.5%) were taking oral cyclosporine while using HAEDS. Of those 3 patients, 2 responded well to the combination, and 1 did not.

Most patients experiencing symptomatic improvement also showed grading changes from a higher to a lower grade.

**TABLE II** Change in grade, by two scoring methods, for 37 responding patients with dry eye syndrome from chronic graft-versus-host disease who used human albumin eye drops

Scoring method	Grade				Response	
	0	1	2	3	Change in grade	Pts (n)
CTCAE	—	Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants	Symptomatic; multiple agents indicated; limits instrumental ADL	Decrease in visual acuity (<20/40); limits self-care ADL	3→2	4
					3→1	26
					2→1	7
cGVHD	No dry eye symptoms	Dry eye symptoms not affecting ADL (eye drops ≤3 daily), or asymptomatic with signs of keratoconjunctivitis sicca	Dry eye symptoms partially affecting ADL (eye drops >3 daily or punctal plugs), without vision impairment	Dry eye symptoms, significantly affecting ADL (special eyewear to relieve pain), or unable to work because of ocular symptoms or loss of vision caused by keratoconjunctivitis sicca	3→2	30
					2→2	7

Pts = patients; CTCAE = *Common Terminology Criteria for Adverse Events*, version 4.0; ADL = activities of daily living; cGVHD = U.S. National Institutes of Health cGVHD score.



**FIGURE 2** Changes in the *Common Terminology Criteria for Adverse Events* (version 4.0) score or grade for dry eyes, by number of weeks of treatment, in 40 evaluable patients who used human albumin eye drops.

Some patients became asymptomatic with continuous application. One patient with keratitis and one with conjunctivitis had stable symptoms. Visual acuity was documented in 22 of the 40 patients, with 14 patients (63.6%) showing improved acuity, 5 (22.7%) showing worsened acuity, and 3 (13.6%) showing unchanged acuity while using HAEDS (Table III).

The study patients continued to benefit from HAEDS after the start of treatment for cGVHD and at post-treatment follow-up. Patients who experienced improvement or stable disease depended on HAEDS for maintenance of quality of life and palliation of dry eye symptoms long after GVHD was resolved. Application of HAEDS has been especially useful for 7 patients who felt it necessary to continue with the drops for as long as symptom control continued.

No relapses were reported, and dry eye symptoms from KCS did not correlate with any other clinical parameter because KCS was the end-result of a post-treatment complication.

Quality assurance tests to ensure the microbiologic, physical, and chemical integrity of the HAEDS (Table IV) were maintained throughout the entire course of patient care. Values obtained in the day 1 and day 30 tests were very similar, indicating that the quality of the HAEDS dispensed to patients (30-day supply at a time) could be maintained with proper handling. The hour 0 and hour 16 values were also similar on each of the testing days.

## DISCUSSION

Our cohort is one of the largest to be evaluated for the efficacy and safety of therapy with pooled HAEDS. The use of HAEDS for dry eye syndrome was initially introduced by one of the coauthors (HAM) more than 30 years ago. He hypothesized that a tear supplement having a protein component such as albumin would, in theory, sequester more moisture because of its inherent ability to regulate tissue fluid distribution, which could initiate a process of symptom relief<sup>17</sup>. Human albumin is commercially produced (Baxter Corporation, Mississauga, ON) and is widely available for supportive care and other indications. Relying on a commercial source for this intervention is thus feasible. Albumin, an essential natural tear component (54 mg/L) for eye well-being<sup>18,19</sup>, should be well tolerated when administered as eye drops.

**TABLE III** Change in grade, by the *Common Terminology Criteria for Adverse Events* (CTCAE, version 4.0), for common ocular symptoms other than dry eyes in 37 responding patients with chronic graft-versus-host disease who used human albumin eye drops

CTCAE symptom	Grade				Response	
	1	2	3	4	Change in grade	Pts (n)
Keratitis (n=17)	—	Symptomatic; medical intervention indicated (for example, topical agents); limits instrumental ADL	Decline in vision (worse than 20/40 but better than 20/200); limits self-care ADL	Perforation or blindness (20/200 or worse) in the affected eye	3→2	2
					3→1	4
					2→2	1
					2→1	10
Conjunctivitis (n=9)	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; topical intervention indicated (for example, antibiotics); limits instrumental ADL	Limits self-care ADL	—	3→1	3
					2→2	1
					2→1	5
Photophobia (n=3)	Symptomatic but not limiting ADL	Limits instrumental ADL	Limits self-care ADL	—	3→asymptomatic	2
					2→asymptomatic	1
Eye pain (n=3)	Mild pain	Moderate pain; limits instrumental ADL	Severe pain; limits self-care ADL	—	3→asymptomatic	3
Blurred vision (n=3)	Intervention not indicated	Symptomatic; limits instrumental ADL	Limits self-care ADL	—	3→asymptomatic	1
					2→asymptomatic	2

Pts = patients; ADL = activities of daily living.

**TABLE IV** Quality assurance testing of human albumin eye drops at days 1 and 30

Parameter	Day 1		Day 30	
	Hour 0	Hour 16	Hour 0	Hour 16
Sterility	Negative	NA	NA	NA
Oncotic pressure (mmHg)	15.6	15.9	17.4	17.4
Albumin (g/L)	45	46	46	46
Viscosity (centipoise)	1.16	1.26	1.59	1.35
pH	6.77	6.74	6.79	6.77
Purity (%)	96	NA	97	NA

NA = not applicable.

Two studies characterized the application of human albumin for severe dry eye: one used a rat model; the other, rabbits and a small number of human subjects with Sjögren syndrome<sup>18,20</sup>. In the rat desiccation eye model, albumin was able to suppress the apoptosis resulting from caspase-3 activation because of serum deprivation when corneal epithelium was scraped off. Shimmura *et al.*<sup>20</sup> described how albumin eye drops in rabbits inhibited caspase activity and increased conjunctival cell viability. Corneal erosions in rabbits healed significantly faster with the use of either 5% or 10% albumin than with the use of saline. All patients in the study experienced a statistically significant improvement in fluorescein, rose bengal score, tear break-up time, and subjective symptomatic face score over the 4-week

study period. In our cohort, 19 patients (47.5%) showed symptomatic relief within 2–4 weeks of treatment with HAEDS, and 26 patients (65%) demonstrated improvement after use of the drops for 5–8 weeks.

Other potential benefits of albumin that could contribute to its clinical efficacy have been described. Albumin has been documented to have antioxidant activity<sup>21,22</sup> and anti-inflammatory properties<sup>23</sup>. In 2003, Shimmura and colleagues postulated that, during concomitant administration of albumin and other topical medications, conjugations might potentially occur, allowing for a longer medication retention time on the eye surface<sup>20</sup>. The binding of drugs to albumin could have positive clinical implications in terms of adjunctive healing<sup>17</sup>. Another possible attribute of commercially prepared albumin for infusion is that the small proportions of human serum transport proteins—such as transferrin, ceruloplasmin, prealbumin, and other micronutrients—present in the preparation might exert a therapeutic effect on the eye surface<sup>24</sup>. Transferrin has been known to be bacteriostatic because of its high affinity for iron. Like the patient cohort treated by Unterlauff<sup>24</sup>, our patients treated with HAEDS either continued or concurrently started other treatments, including commercially available artificial tear products, topical steroids, antimicrobials, immunosuppressants, and punctal plugs in various combinations.

Historically, application of autologous serum to the eyes began in 1975 with the use of an intermittently administered mobile profusion pump for 12 patients suffering from severe dry eye<sup>25</sup>. Patients could carry the pump with them wherever they went, giving them mobility. Since the late 1990s, autologous serum for ophthalmic treatment has

been more widely used<sup>25</sup>. Common indications for its use are ocular surface disorders such as Sjögren syndrome<sup>27</sup>. Autologous serum has also been offered as a therapeutic option to cGVHD patients with varying degrees of success<sup>28–30</sup>. The disadvantages of autologous serum have been well publicized, making its use a challenge to operationalize. One of the most commonly discussed deterrents is the potential risk for transmission of viral infectious diseases as a result of unintended sample swapping by a third party. The lack of appropriate regulatory measures and screening for viruses in sera further accentuated the risk<sup>31,32</sup>, and called for stricter enforcement of screening for HIV, hepatitis B, and hepatitis C in blood products. Other potential roadblocks, such as the needs for good manufacturing practices, licenses for serum preparation, protocol optimization and standardization, and cost and inconvenience to patients were discussed by Ralph and colleagues<sup>25</sup>. One case report<sup>33</sup> detailed the use of allogeneic serum albumin donated from close relatives as an option for KCS treatment. The treatment proved successful, but generated the inevitable ethics considerations. In contrast, the rigorous screening and regulation of commercial pooled human albumin results in the lowest possible risk of viral transmission. The standardized concentrations available would result in a consistent positive effect on eye healing rates, and patients would not be required to face the inconvenience of regular hospital visits to make serum donations.

At study start, we used CTCAE scores for analyzing and evaluating patient response to treatment. Later, however, we decided also to use the cGVHD criteria, given that the scores in the two systems seem to differ. Whichever system was used, most patients experienced a significant improvement in symptoms (Tables II and III). Positive clinical outcomes and changes to asymptomatic status were both documented. It was interesting to note that, although asymptomatic, some patients continued to use 3 eye drops or more daily. Based on the cGVHD criteria, most patients who did well improved by only 1 grade (that is, grade 3 to grade 2); however, in the CTCAE scoring system, similar symptomatology would qualify as an improvement by 2 grades (grade 3 to grade 1). More than 50% of the patients experienced a time to response that was relatively short (about 2–4 weeks, Figure 2), but we were unable to quantify any effectiveness at all for 3 patients.

In addition to KCS, most patients had additional eye complications such as bacterial keratoconjunctivitis, cataracts, corneal ulcers, or worsening of visual acuity. Various other eye drops were used for those complications. When patients did not respond well to their multiple eye drops, gels, and ointments, HAEDS were applied as an adjunct concurrent therapy. The HAEDS were usually discontinued after the patient's eye condition had improved, but some patients continued to use HAEDS for symptom stability.

Compared with previously published results, our data represent a large cohort of patients with KCS who experienced positive outcomes after using HAEDS produced from pooled albumin. In addition to optimal symptom relief in most patients, adverse effects were very limited, and the drops were extremely well tolerated by most patients. Although cost comparison is not within the scope of the

present work, autologous serum acquisition seems quite labour-intensive and would seemingly be more costly than obtaining a supply of government-regulated pooled albumin. No incidents of infection transmission from HAEDS have been reported.

Adherence to HAEDS therapy is critical, and subtherapeutic dosing can negatively affect treatment outcome. Third-party insurance does not cover HAEDS. All our patients who were prescribed HAEDS were compliant and paid for the HAEDS, except for 1 patient.

The primary limitation to our study is its retrospective nature. Because the clinical response to HAEDS was not prospectively graded by an examining physician (whether using CTCAE criteria or the cGVHD guidelines), but rather by a research team at the time of data extraction, biases in terms of the degree of severity of eye symptoms, the quality of the response, and the duration of therapy might have been introduced.

The oncotic pressure and viscosity tests performed on day 30 resulted in slightly higher readings than those obtained on day 1, which might be attributable to moisture evaporation from the HAEDS given the extreme freezer temperature during storage. Similar evaporation could have occurred during freezer storage in the patient's own home, but no ill effect for the patients was observed.

## CONCLUSIONS

Our data are unique compared with those published to date, because the HAEDS used to effectively palliate KCS symptoms in our study were produced from regulated pooled albumin deemed to be safe. This retrospective chart review provides a degree of insight about the safety and benefit of HAEDS when used either in a combination regimen (with conventional eye drops) or alone as a rescue agent for KCS in cGVHD patients. Most HAEDS recipients experienced significant symptom relief for their dry eye syndrome over the course of therapy. The results of the HAEDS quality assurance tests showed that the albumin concentration, pH, and purity of the drops were not significantly changed during 30 days in the storage environment (a freezer kept at  $-20^{\circ}\text{C}$ ). Oncotic pressure and viscosity were slightly increased, which might be a result of moisture evaporation in the freezer. Overall, those minor changes did not affect response by patients to the HAEDS, which were physically and chemically stable over the study period.

## ACKNOWLEDGMENTS

We are grateful to Wallace Lam of the inpatient sterile-product operations and to outpatient pharmacy staff for tracking and recording HAEDS recipients throughout the study period.

## CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

## AUTHOR AFFILIATIONS

\*Princess Margaret Cancer Centre, Toronto, ON; †College of Pharmacy and Health Sciences, Drake University, IA, U.S.A.; ‡Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON; §Toronto General Hospital, Toronto, ON; ¶Mount Sinai Hospital, Toronto, ON; #The Hospital for Sick Children, Toronto, ON.

## REFERENCES

- Nassiri N, Eslani M, Panahi N, Mehravaran S, Ziaei A, Djalilian AR. Ocular graft versus host disease following allogeneic stem cell transplantation: a review of current knowledge and recommendations. *J Ophthalmic Vis Res* 2013;8:351–8.
- Carpenter PA. Late effects of chronic graft-versus-host disease. *Best Pract Res Clin Haematol* 2008;21:309–31.
- Socié G, Salooja N, Cohen A, *et al.* on behalf of the Late Effects Working Party of the European Study Group for Blood and Marrow Transplantation. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood* 2003;101:3373–85.
- Gratwohl AA, Moutsopoulos HM, Chused TM, *et al.* Sjögren-type syndrome after allogeneic bone-marrow transplantation. *Ann Intern Med* 1977;87:703–6.
- Hirst LW, Jabs DA, Tutschka PJ, Green WR, Santos GW. The eye in bone marrow transplantation. I. Clinical study. *Arch Ophthalmol* 1983;101:580–4.
- Fraunfelder FT, Meyer SM. Ocular toxicity of antineoplastic agents. *Ophthalmology* 1983;90:1–3.
- Tichelli A, Duell T, Weiss M, *et al.* Late-onset keratoconjunctivitis sicca syndrome after bone marrow transplantation: incidence and risk factors. European Group or Blood and Marrow Transplantation (EBMT) Working Party on Late Effects. *Bone Marrow Transplant* 1996;17:1105–11.
- Ogawa Y, Yamazaki K, Kuwana M, *et al.* A significant role of stromal fibroblasts in rapidly progressive dry eye in patients with chronic GVHD. *Invest Ophthalmol Vis Sci* 2001;42:111–19.
- Tabbara KF, Al-Ghamdi A, Al-Mohareb F, *et al.* Ocular findings after allogeneic hematopoietic stem cell transplantation. *Ophthalmology* 2009;116:1624–9.
- Ferrara JL, Reddy P. Pathophysiology of graft-versus-host disease. *Semin Hematol* 2006;43:3–10.
- Riemens A, Te Boome LC, Kalinina Ayuso V, *et al.* Impact of ocular graft-versus-host disease on visual quality of life in patients after allogeneic stem cell transplantation: questionnaire study. *Acta Ophthalmol* 2014;92:82–7.
- Li M, Gong L, Chapin WJ, Zhu M. Assessment of vision-related quality of life in dry eye patients. *Invest Ophthalmol Vis Sci* 2012;53:5722–7.
- Sabti S, Halter JP, Braun Fränkl BC, Goldblum D. Punctal occlusion is safe and efficient for the treatment of keratoconjunctivitis sicca in patients with ocular GVHD. *Bone Marrow Transplant* 2012;47:981–4.
- Yaguchi S, Ogawa Y, Kamoi M, *et al.* Surgical management of lacrimal punctal cauterization in chronic GVHD-related dry eye with recurrent punctal plug extrusion. *Bone Marrow Transplant* 2012;47:1465–9.
- United States, Department of Health and Human Services, National Institutes of Health, National Cancer Institute (NCI). *Common Terminology Criteria for Adverse Events*. Ver. 4.0. Washington, DC: NCI; 2009.
- Filipovich AH, Weisdorf D, Pavletic S, *et al.* National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant* 2005;11:945–56.
- Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. *Br J Anaesth* 2000;85:599–610.
- Higuchi A, Ueno R, Shimmura S, Suematsu M, Dogru M, Tsubota K. Albumin rescues ocular epithelial cells from cell death in dry eye. *Curr Eye Res* 2007;32:83–8.
- Tsubota K, Higuchi A. Serum application for the treatment of ocular surface disorders. *Int Ophthalmol Clin* 2000;40:113–22.
- Shimmura S, Ueno R, Matsumoto Y, *et al.* Albumin as a tear supplement in the treatment of severe dry eye. *Br J Ophthalmol* 2003;87:1279–83.
- Cao G, Alessio HM, Cutler RG. Oxygen-radical absorbance capacity assay for antioxidants. *Free Radic Biol Med* 1993;14:303–11.
- Cantin AM, Paquette B, Richter M, Larivée P. Albumin-mediated regulation of cellular glutathione and nuclear factor kappa B activation. *Am J Respir Crit Care Med* 2000;162:1539–46.
- Zhang WJ, Frei B. Albumin selectively inhibits TNF alpha-induced expression of vascular cell adhesion molecule-1 in human aortic endothelial cells. *Cardiovasc Res* 2002;55:820–9.
- Unterlauff JD, Kohlhaas M, Hofbauer I, Kasper K, Geerling G. Albumin eye drops for treatment of ocular surface diseases [German]. *Ophthalmologe* 2009;106:932–7.
- Ralph RA, Doane MG, Dohlman CH. Clinical experience with a mobile ocular perfusion pump. *Arch Ophthalmol* 1975;93:1039–43.
- Jeng BH. Use of autologous serum in the treatment of ocular surface disorders. *Arch Ophthalmol* 2011;129:1610–12.
- Tsubota K, Goto E, Fujita H, *et al.* Treatment of dry eye by autologous serum application in Sjögren's syndrome. *Br J Ophthalmol* 1999;83:390–5.
- Geerling G, MacLennan S, Hartwig D. Autologous serum eye drops for ocular surface disorders. *Br J Ophthalmol* 2004;88:1467–74.
- Rocha EM, Pelegrino FS, de Paiva CS, Vigorito AC, de Souza CA. GVHD dry eyes treated with autologous serum tears. *Bone Marrow Transplantation* 2000;25:1101–3.
- Ogawa Y, Okamoto S, Mori T, *et al.* Autologous serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host-disease. *Bone Marrow Transplant* 2003;31:579–83.
- Eberle J, Habermann J, Gurtler LG. HIV-1 infection transmitted by serum droplets into the eye: a case report. *AIDS* 2000;14:206–7.
- Weisbach V, Dietrich T, Kruse FE, Eckstein R, Cursiefen C. HIV and hepatitis B/C infections in patients donating blood for use as autologous serum eye drops. *Br J Ophthalmol* 2007;91:1724–5.
- Chiang CC, Lin JM, Chen WL, Tsai YY. Allogeneic serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease. *Cornea* 2007;26:861–3.