

Autologous serum eye drops for the treatment of severe dry eye in patients with chronic graft-versus-host disease

Y Ogawa^{1,3}, S Okamoto², T Mori², M Yamada¹, Y Mashima¹, R Watanabe², M Kuwana³, K Tsubota^{1,4}, Y Ikeda² and Y Oguchi¹

¹Department of Ophthalmology, School of Medicine, Keio University, Tokyo, Japan; ²KEIO BMT Program, Division of Haematology, Department of Medicine, School of Medicine, Keio University, Tokyo, Japan; ³Institute for Advanced Medical Research, School of Medicine, Keio University, Tokyo, Japan; and ⁴Department of Ophthalmology, Tokyo Dental College, Chiba, Japan

Summary:

We investigated the efficacy and safety of autologous serum eye drops for the treatment of severe dry eye after allogeneic haematopoietic stem cell transplantation (SCT). A total of 14 patients (four males and 10 females; median age, 31.0 years) with severe dry eye associated with chronic graft-versus-host disease (cGVHD) were enrolled in this study. All patients were refractory to treatment with conventional artificial tears. Autologous serum eye drops, a solution made of 20% autologous serum in sterile saline, were applied 10 times per eye per day. The patients were evaluated every 4 weeks according to visual acuity, corneal sensitivity, vital staining of the ocular surface, tear dynamics, and subjective assessments of symptoms (complaints scores). The median follow-up period was 19.4 months (range: 4–41 months). After 4 weeks of treatment, significant improvement was observed in both complaint scores (from 33.7 ± 12.3 to 23.6 ± 10.6 points; $P < 0.01$) and fluorescein scores (from 5.8 ± 2.0 to 2.4 ± 0.9 points; $P < 0.005$). Significant improvements were observed also in rose-bengal staining and tear break-up time. In seven of the 14 patients, the responses were maintained for 6–41 months (median: 19.4 ± 8.3 months), while six of the other seven patients required treatment with punctal plugs in addition to autologous serum eye drops. One of these other seven patients developed eczema around the eyelids, after which the treatment was discontinued. No serious adverse events were observed. We conclude that autologous serum eye drops are safe and effective for treating severe dry eye associated with cGVHD and that more efficient control of dry eye may be achieved by the combined use of autologous serum eye drops with punctal plugs.

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Allogeneic haematopoietic stem cell transplantation (SCT) is now considered a curative treatment for various haematological malignancies. However, chronic graft-versus-host disease (cGVHD) remains a major complication after SCT, and is the largest factor in impairing the quality of life of transplant recipients. Dry eye is one of the major symptoms of cGVHD.^{1,2} Although several therapies have been used to minimize the symptoms of dry eyes associated with cGVHD,^{3–5} an effective treatment has not been established.

Autologous serum eye drops have been indicated for the treatment of severe dry eye in patients with Sjögren's syndrome.^{6–8} This treatment was also effective for advanced cicatricial pemphigoid syndrome, the Stevens–Johnson syndrome, and superior limbic keratitis.^{9,10,11} Autologous serum has been used as eye drops for dry eyes because it contains the vitamins, several growth factors and fibronectin that are important for corneal and conjunctival integrity.^{9,12,13}

To confirm the encouraging results of a previous case report,⁵ we evaluated the safety and efficacy of autologous serum eye drops for the treatment of dry eyes in patients with cGVHD, in a study using more patients and a longer follow-up time.

Patients and methods

A total of 14 patients with severe dry eye associated with cGVHD, and who were refractory to treatment with conventional artificial tears, were enrolled in this study at the dry eye clinic at Keio University Hospital. Written informed consent was obtained before the study was commenced. Severe dry eye was defined as described previously.^{2,14} In brief, patients are considered to have severe dry eye if the Schirmer test with nasal stimulation (reflex tearing) was less than 10 mm and the fluorescein and rose-bengal scores were ≥ 3 points.

The eligibility criteria for treatment with the autologous serum eye drops were as follows: (1) dry eye refractory to treatment with conventional artificial tears, (2) no active systemic infections at the time of autologous serum preparation and treatment, and (3) no active ophthalmic infections, or ophthalmic diseases other than dry eye, at the time of treatment.

Preparation and evaluation of autologous serum eye drops

A volume of 20 ml of peripheral blood was obtained from each patient using a sterile technique, which were then centrifuged at 1500 rpm for 10 min to obtain autologous serum. Serum was then diluted with sterile normal saline at a final concentration of 20% (v/v). A measure of 20 μ l of 0.3% ofloxacin eye drops was also added to the autologous serum/saline solution. The completed solution was aliquotted into 10-ml plastic tubes and stored in a freezer (-20°C) until use. The maximum storage time was 3 months. Once thawed, the autologous serum eye drops^{6,9} were stored in a refrigerator (4°C) and were used within 10 days. At the time the serum was prepared, it was cultured for bacteria and fungi.

Treatment and ophthalmologic evaluation of ocular findings

Patients were instructed to instill the autologous serum eye drops 10 times (2–3 drops per time) per eye per day and were evaluated every 4 weeks. The treatment schedule was the same as that of conventional artificial tears. At the time of follow-up, patients were asked to grade their symptoms relating to dry eye by using a complaint sheet. Evaluations included the best-corrected visual acuity for distance, an assessment of precorneal tear film, and the extent of conjunctival and corneal staining with rose-bengal and fluorescein. Corneal sensitivity was also measured using a

Cochet–Bonnet esthesiometer.

The degree of the rose-bengal staining was recorded at each of the temporal and nasal conjunctiva and the cornea, and was quantified on a scale of 0–3 points; thus, the total score of rose-bengal staining was rated from 0 to 9. Fluorescein staining was also rated from 0 to 9, but only in the cornea.¹⁵ Tear break-up time was measured, and three readings were taken. The Schirmer test was performed with nasal stimulation. For cases in which both scores worsened or were not improved at least 1 month after starting the treatment with autologous serum eye drops, punctal occlusion was performed using silicone plugs (Eagle Vision Inc, Memphis USA and FCI Co. Ltd, Issy les Moulineaux, France). The ocular surface and tear dynamics were also evaluated before and after punctal occlusion.

Statistical analysis

Statistical analysis was performed using the Wilcoxon signed rank test.

Results

Patient description

At the time the autologous serum eye drops were prepared, seven patients were receiving systemic immunosuppressants, the dosages of which were not changed during the experimental treatment. None of the other patients were receiving systemic immunosuppressants.

Clinical characteristics of the patients enrolled in this study and their responses to the treatment are shown in Table 1. There were four males and 10 females. The median age was 31.0 years (range 22–43 years). The pretransplant diagnoses included: chronic myelogenous leukemia (CML)

Table 1 Patient characteristics

Case no.	Age	Gender	Diagnosis	Treatment	cGVHD other than the eyes	Time (Mo)		Systemic immunosuppressant (IS) at the time of treatment		
						SCT to dry eye	Dry eye to AS	PSL	CysA	FK506
1	22	F	AML	AS/ plug	Liver, mouth	12	6	—	65 mg/100 mg every other day	—
2	37	M	CML	AS/ plug	Lung	12	4	—	—	—
3	25	F	ALL	AS/ plug	Skin, liver, mouth, lung	12	12	—	200 mg/ day	—
4	42	F	MDS	AS/ plug	Skin, intestine	5	9	35 mg every other day	—	3 mg every other day
5	27	F	MDS	AS/ plug	(—)	6	12	—	—	—
6	32	F	MDS	AS/ plug	Skin	3	12	—	—	—
7	28	M	CML	AS/ plug	Lung	9	11	5 mg every other day	—	4 mg/2 mg every other day
8	43	F	CML	AS*	(—)	33	2	—	—	—
9	33	M	CML	AS	Skin	—	12	—	—	—
10	30	F	AML	AS	Liver	18	14	—	—	—
11	35	F	CML	AS	Liver, mouth, skin, lung	7	15	35 mg every other day	—	—
12	24	F	MDS	AS	Mouth	5	24	—	—	—
13	43	F	MDS	AS	Mouth	3	2	—	150 mg/day	—
14	28	M	CML	AS	(—)	18	28	10 mg/day	—	—

AS, autologous serum eye drops; F, female; M, male; AML, acute myelogenous leukaemia; CML, chronic myelogenous leukaemia, MDS, myelodysplastic syndrome; Mo, month; SCT, haematopoietic stem cell transplantation; AS*, AS was stopped because of eyelid eczema.

Table 2 Evaluation of ocular surface and tear dynamics before and 4 weeks after the treatment with autologous serum eye drops

	Before treatment	Four weeks after treatment	P-value
Complaints scores	33.7 ± 12.3	23.6 ± 10.6	<0.01
Corneal sensitivity scores	3.8 ± 1.3	4.8 ± 1.2	NS
Fluorescein scores	5.6 ± 2.0	2.2 ± 0.9	<0.005
Rose-bengal scores	5.2 ± 2.1	3.1 ± 1.9	<0.05
Tear break-up time	2.8 ± 1.4	5.8 ± 2.1	<0.05
Value of Shirmer's test	1.4 ± 1.3	3.6 ± 4.7	NS

Mean value ± s.d. of all cases (N = 14).

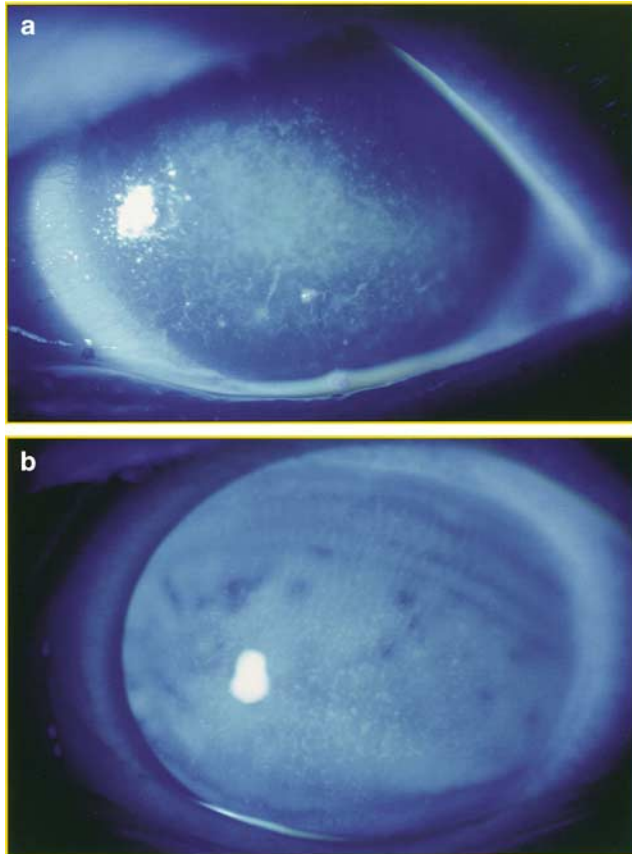


Figure 1 (a) Fluorescein staining of right eye of case 12 showing diffuse punctate keratoconjunctivitis with filamentosa. (b) Fluorescein staining of right eye of the same case at 4 weeks after the treatment with autologous serum eye drops. Superficial punctate keratitis was markedly improved.

(n = 6), myelodysplastic syndrome (MDS) (n = 5), acute myelogenous leukaemia (AML) (n = 2), and acute lymphoblastic leukaemia (ALL) (n = 1). The median time from the diagnosis of dry eye to the beginning of treatment with autologous serum eye drops was 11.6 months (range 2–28 months). The median follow-up period after the treatment with autologous serum eye drops was 19.4 months (range 4–41 months).

Ophthalmologic examination and side effects

At 4 weeks into the treatment, marked improvements in both subjective and objective findings of the ocular surface

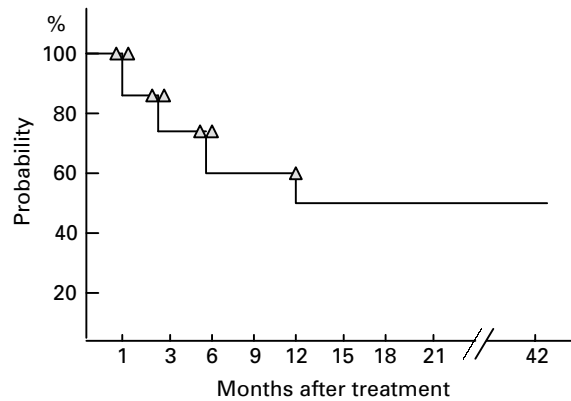


Figure 2 Kaplan-Meier product estimate for probability of time to treatment failure with autologous serum eye drops alone. The closed triangles indicate the times when punctal occlusions were performed.

were observed (Table 2). The mean values of complaint scores fell significantly, from 33.7 to 23.6 points ($P < 0.01$). Mean fluorescein scores and the scores of rose-bengal staining also decreased from 5.6 to 2.2 points ($P < 0.005$) and from 5.2 to 3.1 points ($P < 0.05$), respectively. The improvement was also observed in tear dynamics (Table 2). Tear break-up time was improved from 2.8 to 5.8 s ($P < 0.05$). Corneal sensitivity decreased in seven of 12 patients whose sensitivity was measured before the treatment. There was a trend towards improvement in corneal sensitivity.

Figure 1 shows representative changes in an ocular surface before and after treatment. During the further follow-up, six patients required additional treatment with punctal plugs. The median time from the commencement of the eye drop regimen to the additional treatment with punctal plugs was 5.5 months (range 1–18 months) (Table 1). Seven patients maintained a good response, up to 42 months with autologous serum eye drops alone (Figure 2). One patient developed mild eczema on the eyelids, which was successfully treated with steroid eye ointment and the cessation of autologous serum eye drops. No serious complications related to the treatment with the autologous serum eye drops were observed.

Discussion

The treatment of severe dry eye associated with cGVHD has been unsatisfactory, and therapeutic options remain

limited. This study is the first to assess the efficacy and safety of artificial tears made from autologous serum for severe dry eye after SCT with a sufficient number of patients and a sufficiently long follow-up. Although the mechanisms through which autologous serum eye drops improve dry eye after allogeneic SCT remain to be elucidated, there are a couple of plausible explanations.

Tear components, such as epidermal growth factor (EGF) and vitamin A, are important for the proliferation, differentiation, and maturation of ocular surface epithelium.^{12,16} Cultures of human corneal stromal fibroblasts and endothelial cells were reported to express EGF receptors and to increase their DNA synthesis in the presence of EGF.¹⁷ Artificial tears made from autologous serum could supply these factors and improve the condition of the ocular surface after commercially available artificial tears have failed. Corneal sensitivity tends to recover after treatment with the autologous serum eye drops. The presence of nerve growth factors in serum may explain this tendency.¹⁸

We have previously reported two transplant recipients, in whom systemic treatment with FK506 and corticosteroids for cGVHD in organs other than the eyes was also effective for dry eye associated with cGVHD.⁴ This observation led us to consider using topical immunosuppressants as a preferable therapy for severe dry eye after SCT. To avoid systemic side effects, topical treatment with cyclosporin A eye drops has been investigated for dry eye, but its efficacy for dry eye associated with cGVHD remains to be clarified.^{5,19} It is possible that autologous serum eye drops may have functioned as a topical treatment with immunosuppressants in patients who received systemic immunosuppressants. However, this possibility is difficult to confirm, because patients on systemic immunosuppressants tend to have more severe dry eye. The responses of those who were not on systemic immunosuppressants did not strongly support this possibility.

Punctal occlusion has been used extensively for the treatment of dry eye in patients with Sjögren's syndrome.^{20,21} In the present study, six patients required additional treatment with punctal plugs, and in all of these cases complete or nearly complete resolution of all symptoms and objective findings was achieved. The addition of eye drops to autologous serum with punctal plugs could prolong the retention time of autologous serum over the ocular surface, and supply missing tear components more efficiently. Although several complications have been reported, such as the migration of a plug into the lacrimal drainage system, local irritation, and epiphora,^{20–22} autologous serum eye drops combined with punctal plugs may be the better option, compared with the eye drops alone, to maintain ocular surface integrity and prevent serious ocular surface complications of dry eye associated with cGVHD.

To confirm the efficacy and safety of autologous serum eye drops in patients with dry eyes because of cGVHD, a prospective randomized study comparing autologous serum eye drops with conventional artificial eye drops would be ideal.⁸ However, because the condition of the ocular surface can deteriorate rapidly in patients with cGVHD,^{2,23} it may be difficult to select control subjects to be treated

with conventional artificial eye drops. Thus, we are now considering a randomized study comparing punctal plug plus conventional artificial tears vs punctal plug combined with autologous serum eye drops.

We conclude that autologous serum eye drops are safe and effective for the treatment of severe dry eye associated with cGVHD to replenish essential tear film components of the ocular surface. The results of our longer-term follow-up also suggest that the combination of autologous serum eye drops with punctal occlusion may achieve better control.

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