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ORIGINAL PAPER

Effectiveness of photodynamic therapy with verteporfin combined with intrastromal bevacizumab for corneal neovascularization in Stevens–Johnson syndrome

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Abstract

Purpose To investigate the effectiveness of combined photodynamic therapy with verteporfin and intrastromal injection of bevacizumab for the treatment of corneal neovascularization in patients with Stevens–Johnson syndrome (SJS).

Methods Eight eyes of eight patients with SJS having corneal neovascularization who were refractory to 1% prednisolone instillation received photodynamic therapy with verteporfin (6 mg/m^2) combined with intrastromal bevacizumab injection (2.5 mg/0.1 mL). Best-corrected visual acuity and intraocular pressure were assessed, and slit-lamp biomicroscopic examination was performed before treatment and at 1 week and every month. A chronic ocular manifestation score was assigned based on the involvement area or the severity before treatment. The cumulative length of corneal blood vessels and area of corneal neovascularization were measured by anterior segment photographs before and after treatment.

Results At 3 and 6 months after treatment, all eyes showed regression of corneal neovascularization. Complete regression was achieved in five eyes (62.5%) and partial regression in three eyes (37.5%). Among five patients who were followed up for more than 1 year, two eyes maintained complete regression and one eye maintained partial regression at 1 year. However, two eyes with severe chronic ocular manifestation showed revascularization.

Conclusions Combined photodynamic therapy with intrastromal bevacizumab injection can effectively inhibit corneal neovascularization in patients with SJS. However, patients with severe chronic ocular manifestation may exhibit revascularization.

Keywords Steven–Johnson syndrome · Corneal neovascularization · Photodynamic therapy · Intrastromal injection of bevacizumab

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Introduction

Stevens–Johnson syndrome (SJS) and its more severe form, toxic epidermal necrolysis (TEN), are characterized by an acute febrile illness associated with prodromal target lesions, followed by skin detachment and involvement of at least two mucous membrane sites [1, 2]. SJS is an acute epithelial blistering disease with variable involvement of the eyes that can result in extensive, permanent damage to the ocular surface and eyelids [3, 4]. Ocular manifestations include chronic ocular surface inflammation, dry eye, limbal stem cell deficiency (LSCD), stromal opacification, ocular surface keratinization and corneal/conjunctival neovascularization [5, 6].

Corneal neovascularization is a particularly prominent feature of SJS that results in visual loss due to accompanying scarring and lipid deposition [7]. It results from chronic microtrauma by blinking and abnormal tear dynamics due to goblet cell dysfunction, dry eye, tarsal scarring and trichiasis. The sustained damage causes a slow, persistent worsening of ocular surface conditions over time and may result in corneal blindness due to LSCD and corneal neovascularization [4, 8].

The conventional treatments for corneal neovascularization include medications such as steroids or angiogenesis inhibitors, laser photocoagulation, fine needle diathermy and surgery; all have clinical limitations [9–14]. Photodynamic therapy (PDT) with verteporfin can produce microvascular thrombosis with minimal damage to normal tissues and has been used safely and effectively to treat corneal neovascularization [15, 16]. Injection of vascular endothelial growth factor (VEGF), such as bevacizumab into the corneal stroma reduces angiogenesis and vascular permeability [17, 18]. However, PDT showed a rebound effect associated with enhanced VEGF expression [19]. In addition, anti-VEGF monotherapy may not induce complete occlusion and requires several injections to induce regression of new vessels [20, 21].

Corneal neovascularization in SJS is more difficult to treat compared with other corneal diseases because the process of microtrauma cannot be resolved in the chronic stage of SJS. Our previous study revealed that combined therapy with PDT and anti-VEGF had a synergistic effect on corneal neovascularization [22]. Although several studies reported the short-term efficacy of anti-VEGF therapy in patients with SJS associated corneal neovascularization, no clinical trial has been documented on the effect of combined PDT with anti-VEGF therapy on corneal neovascularization in patients with SJS. The present pilot study investigated the effectiveness of combined PDT with verteporfin and intrastromal injection of bevacizumab for the treatment of corneal neovascularization in patients with SJS.

Materials and methods

Patient selection

This interventional case series evaluated the efficacy of PDT with verteporfin combined with intrastromal injection of bevacizumab in eight SJS patients (eight eyes) with corneal neovascularization. All patients were refractory to treatment with 1% prednisolone acetate eyedrops, instilled four times per day for at least 1 month. Individuals who had active keratitis with vessel proliferation, uncontrolled inflammation, active hepatitis, clinically significant liver disease, porphyria or other porphyrin sensitivity were excluded. Ethics committee approval was obtained from the Chonnam National University Hospital Institutional Review Board (CNUH-2017-228). The study protocol followed the guidelines of the Declaration of Helsinki.

Procedures

PDT with lipid-formulation verteporfin (Visudyne; Novartis Ophthalmics AG, Hettlingen, Switzerland) was performed over a neovascular corneal area as previously described [16]. Briefly, verteporfin solution, prepared at a dose of 6 mg/m^2 of body surface area and diluted with 5% dextrose in water to a volume of 30 mL, was administered intravenously over 10 min. Fifteen minutes after the initiation of administration, a 689 nm nonthermal laser light (Opal Photoactivator; Coherent Inc., Santa Clara, CA, USA) was delivered directly over a neovascular area with a spot size of 4 mm at a power intensity of 600 mW/cm^2. When the neovascular area was larger than the intended spot size, consecutive overlapping laser spots were applied. After PDT, a single dose of bevacizumab (Avastin; Roche, Welwyn Garden City, UK)

at 2.5 mg/0.1 mL was prepared sterilely into a syringe with a 30-G needle. Before injection, 0.5% proparacaine hydrochloride eyedrops (Alcain; Alcon, Forth Worth, TX) were applied. Intrastromal injection of approximately 0.01 mL was administered in the corneal stroma next to pathologic new vessels. Patients were educated to avoid direct sunlight exposure during outdoor activities for 3 days after treatment.

Outcome measurements

Basic patient information (age, sex and medical history) was taken. Best-corrected visual acuity, intraocular pressure and slit-lamp biomicroscopic examinations were assessed before treatment and at 1 week and every month for at least 3 months. Before treatment, a chronic ocular manifestation score (COMS) was assigned based on the involvement area or the severity of the above-mentioned factors, according to the grading system proposed by Sotozono et al. [23] Thirteen clinical signs of ocular complications of three ocular surface structures (cornea, conjunctiva and eyelid) were graded on a scale of 0–3, depending on the severity of ocular involvement. Severe chronic ocular manifestation was defined as having a COMS $\geq$ 13 [24, 25].

Slit-lamp photographs were taken at each visit and analyzed using publicly available Java-based image processing software developed by the National Institutes of Health (Image J version 1.4.1; National Institutes of Health, Rockville, MD, USA) before, 3 and 6 months after treatment. The cumulative length of corneal blood vessels and area of corneal neovascularization were measured in a blinded fashion. The long-term effectiveness of combined treatment was evaluated in patients who were followed up 1 year after treatment.

Statistical analysis

Statistical analysis was performed using SPSS Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean $\pm$ standard deviation (SD). A Wilcoxon signed rank test was used to compare changes of variables before and after treatment. A p value of less than 0.05 was considered to have statistical significance.

Results

Among eight patients, three were men and five were women. The mean age was 61.25 $\pm$ 16.72 years (range 36–78 years). The mean pretreatment visual acuity (logarithm of the minimum angle of resolution) and intraocular pressure were 1.08 $\pm$ 0.80 LogMAR and 15.4 $\pm$ 2.3 mmHg. The mean COMS was 10.4 $\pm$ 3.9 (range 7–18); three patients had severe chronic ocular manifestation. The mean pretreatment length of cumulative vessels was 10.8 $\pm$ 4.0 mm, and the mean pretreatment area of neovascularization was 7.1 $\pm$ 2.4 mm^2. The mean follow-up period after PDT combined with intrastromal injection of bevacizumab was 12.1 $\pm$ 4.0 months (range 6–16 months) (Table 1).

One week after treatment, mild corneal edema was noted in two eyes. Hemorrhage around corneal neovascularization was present in one eye, but improved within 1 month. No other significant systemic or ocular complications associated with the procedures were observed.

At 3 months, the mean post-treatment visual acuity and intraocular pressure were 1.05 $\pm$ 0.83 LogMAR ($p = 0.95$) and 15.6 $\pm$ 1.9 mmHg ($p = 0.82$). No significant differences in visual acuity or intraocular pressure were detected. The mean length of cumulative vessels and area of corneal neovascularization decreased to 3.2 $\pm$ 5.1 mm ($p < 0.01$) and 1.9 $\pm$ 2.8 mm^2 ($p < 0.01$). Complete vascular regression was noted in five eyes (62.5%), and partial vascular regression was observed in three eyes (37.5%) that had severe chronic ocular manifestation with a high COMS. Six months after treatment, the mean visual acuity and intraocular pressure were 1.05 $\pm$ 0.78 LogMAR ($p = 0.94$) and 15.1 $\pm$ 1.9 mmHg ($p = 0.82$). The mean length of cumulative vessels and area of corneal neovascularization showed to be maintained as 3.5 $\pm$ 5.1 mm ($p < 0.01$) and 2.1 $\pm$ 2.8 mm^2 ($p < 0.01$) (Table 2, Fig. 1).

Among five patients who were followed up for more than 1 year, two eyes maintained complete vascular regression, one eye maintained partial vascular regression and two eyes showed vascular recanalization at the one-year follow-up. Three eyes with severe chronic ocular manifestation revealed revascularization in two eyes and partial vascular regression in one eye (Fig. 2).

Table 1 Baseline characteristics of patients with corneal neovascularization in Stevens–Johnson syndrome

Patient number	Age (years)	Sex	Eyes	VA (LogMAR)	IOP (mmHg)	COMS	Cumulative length of vessels (mm)	Neovascular area (mm^2)	Follow-up duration (months)
1	53	M	Lt.	1.85	14	7	14.2	8.3	6
2	69	F	Lt.	0.30	16	8	8.6	5.6	12
3	38	M	Rt.	0.40	18	9	12.1	8.9	8
4	78	M	Rt.	0.52	17	7	7.6	6.3	13
5	74	F	Lt.	2.30	12	13	18.4	11.5	14
6	38	F	Rt.	1.00	13	18	8.3	4.6	18
7	68	F	Rt.	1.85	15	8	11.3	6.7	10
8	74	F	Rt.	0.40	18	13	6.2	4.6	16

VA visual acuity, *IOP* intraocular pressure, *LogMAR* logarithm of minimal angle of resolution, *COMS* chronic ocular manifestation score, *Lt.* left, *Rt.* right

Discussion

Patients with SJS are characterized by severe inflammation and ulceration of the tarsal conjunctiva and lid margin in the acute stage. If left unattended, lid margin keratinization and tarsal scarring, together with lipid tear deficiency, contribute to corneal complications due to blink-related microtrauma. Sustained microtrauma damage from abnormal blinking and ocular surface problems leads to corneal neovascularization accompanied by LSCD which is a particularly prominent feature of SJS that results in visual loss [1–8].

Anti-VEGF therapy to prevent corneal neovascularization in SJS has been tried. Bevacizumab is a recombinant humanized monoclonal immunoglobulin G1 antibody directed against all isoforms of VEFG-A; its use inhibits abnormal blood vessel formation and decreases vascular permeability [20, 21, 26]. Kesawani et al. [27] described a 14-year-old patient with SJS in whom subconjunctival injection of bevacizumab in one eye achieved bilateral regression of corneal neovalscularization. In addition, Uy et al. [7] showed that topical bevacizumab was well tolerated and effective in improving ocular comfort and inducing the regression of ocular surface neovascularization and opacification caused by SJS. In addition, histologic findings of bevacizumab-treated conjunctiva in patients with SJS revealed markedly less stromal vascularization in the conjunctiva and an absence of perivascular inflammatory cells [28].

However, anti-VEGF therapy has several limitations. First, bevacizumab treatment for cornea neovascularization may not lead to complete occlusion and requires several injections to induce regression [20, 21]. Second, bevacizumab usually inhibits smaller minor blood vessels rather than larger major vessels [29]. Third, bevacizumab may cause spontaneous loss of epithelial integrity and progression of stromal thinning due to disruption of the wound healing process [30]. Anti-VEGF monotherapy can require multiple injections in cases of severe corneal neovascularization, and it may be inappropriate for SJS with severe ocular surface and lid problems.

Combined therapy with verteporfin PDT and anti-VEGF offers the dual effects of vessel destruction and anti-angiogenesis to prevent recurrence of corneal neovascularization. Verteporfin binds to endogenous low-density lipoproteins in serum, forming a complex that can then bind to low-density lipoprotein receptors on vascular endothelial cells [16]. PDT destroys endothelial cells and the vascular basement membrane by generating reactive oxygen species and cascading oxidative damage, leading to vessel thrombosis and architectural remodeling [15, 16]. The increased VEGF expression and enhanced inflammation caused by PDT can be countered by an anti-VEGF agent [22]. We previously reported that combined PDT with verteporfin and subconjunctival bevacizumab therapy was an effective treatment for corneal neovascularization with various etiologies in human [22]. Lanzetta et al. [31] reported that the combination of PDT with verteporfin and subconjunctival bevacizumab and triamcinolone acetonide led to complete vascular regression for the six-month follow-up duration in a

Table 2 Treatment outcomes of patients with corneal neovascularization in Stevens–Johnson syndrome who were treated with combined photodynamic therapy with verteporfin and intrastromal injection of bevacizumab

Patient number	3 months after treatment					6 months after treatment				
	VA (LogMAR)	IOP (mmHg)	Cumulative length of vessels (mm)	Neovascular area (mm^2)	Outcome	VA (LogMAR)	IOP (mmHg)	Cumulative length of vessels (mm)	Neovascular area (mm^2)	Outcome
1	1.85	15	1.5	0.4	CR	1.85	14	1.7	0.5	CR
2	0.30	15	0.7	0.6	CR	0.30	16	0.8	0.7	CR
3	0.30	17	0.6	0.2	CR	0.30	16	0.6	0.2	CR
4	0.40	19	1.2	0.7	CR	0.30	19	1.3	0.8	CR
5	2.30	14	14.5	8.4	PR	2.30	13	15.6	8.9	PR
6	1.00	15	6.9	3.2	PR	1.00	13	7.2	3.4	PR
7	1.85	13	0.2	0.1	CR	1.85	14	0.2	0.1	CR
8	0.40	17	0.3	1.8	PR	0.50	16	0.4	1.9	PR

Patient number	1 year after treatment		Ocular complications
	VA (LogMAR)	Outcome	
1	–	–	Corneal edema
2	0.30	CR	
3	0.30	CR	Intracorneal hemorrhage
4	–	–	Corneal edema
5	2.30	Revascularization	
6	1.00	Revascularization	
7	–	–	
8	0.40	PR	

VA visual acuity, *IOP* intraocular pressure, *LogMAR* logarithm of minimal angle of resolution, *CR* complete regression, *PR* partial regression

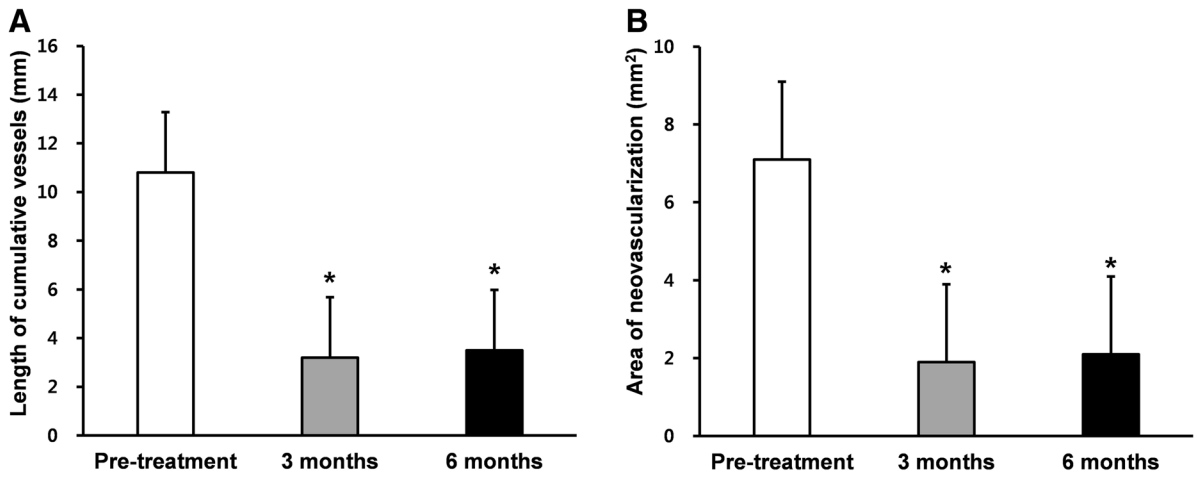

Fig. 1 Comparisons of **a** the length of cumulative vessels and **b** area of neovascularization before, 3 and 6 months after combined photodynamic therapy with verteporfin and intrastromal injection of bevacizumab. *$p < 0.05$ compared with pretreatment values

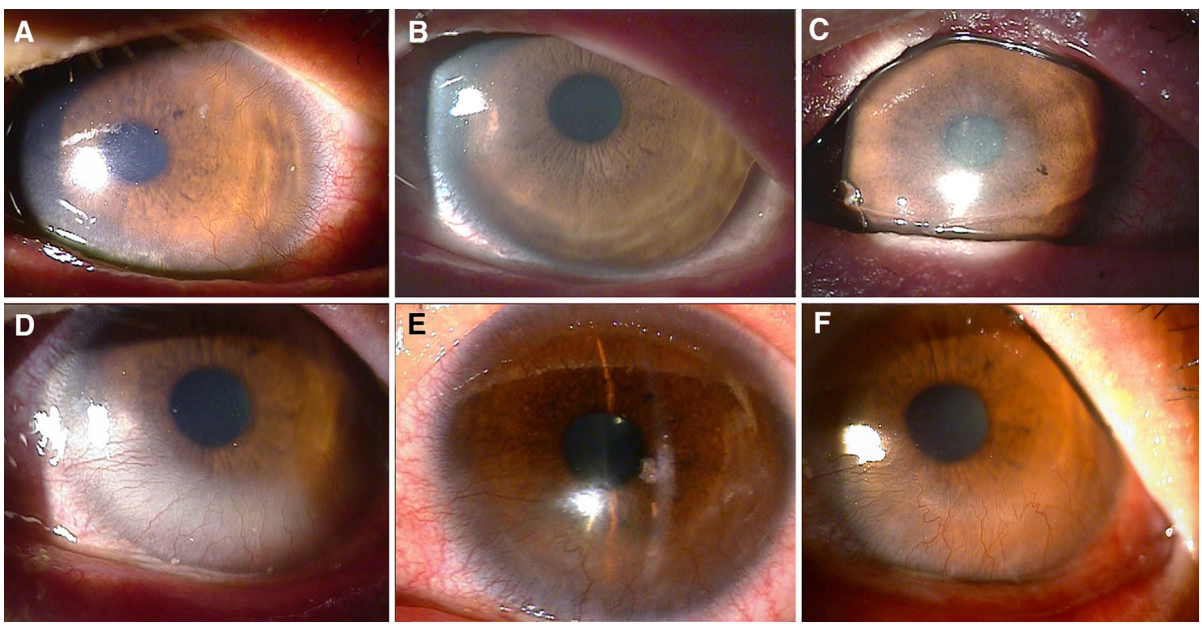

Fig. 2 Slit-lamp photographs before and after combined photodynamic therapy with intrastromal injection of bevacizumab. In patient 2, **a** multiple blood vessels were observed in the cornea. **b** Three months after treatment, the corneal vessels significantly decreased. **c** Complete regression of corneal neovascularization was maintained 1 year after treatment. In patient 6, **d** multiple blood vessels with conjunctivalization were detected in the eye. **e** Three months after treatment, the corneal vessels were partially regressed. **f** One year after treatment, revascularization with stromal haziness occurred

patient with corneal neovascularization secondary to graft failure. In addition, Ra et al. [32] investigated that combined PDT and topical bevacizumab treatment were effective for the treatment of corneal neovascularization in rabbits.

At 3 and 6 months, the results of our study demonstrated the effectiveness of combined PDT with intrastromal bevacizumab injection for the treatment of corneal neovascularization in SJS patients. The cumulative length of blood vessels and the area of corneal neovascularization significantly decreased

after treatment. In addition, complete or partial regression of corneal neovascularization was achieved in all eyes. Three eyes with partial regression manifested a high COMS. No significant systemic or ocular complications associated with the treatment were observed.

However, in chronic stage, among five patients who could be followed for more than 1 year, two patients showed vascular recanalization and one patient showed partial regression. These three patients had severe chronic ocular manifestation with a high COMS. Sustained blink-induced microtrauma and LSCD related to a high COMS may not be resolved by combination treatment of PDT with verteporfin and intrastromal bevacizumab, resulting in revascularization. In addition, visual acuity did not change despite neovascular regression after combined treatment. This may be due to epithelial irregularity and stromal opacification of the inflamed cornea in the chronic stage of SJS.

Our study had several limitations, including a small number of patients and a variable follow-up period. In addition, comparison with other treatment was not performed. Further studies with a larger sample size, a longer follow-up duration and a controlled design are needed. Despite these limitations, our results suggest that combined treatment of PDT with verteporfin and intrastromal bevacizumab injection is effective for the treatment of refractory corneal neovascularization in patients with SJS. However, cases of SJS with severe chronic ocular manifestation have a high possibility of vascular recanalization in the chronic stage despite combined treatment.

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Compliance with ethical standards

Conflict of interest All authors declare that he/she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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