厚生労働科学研究費補助金（難治性疾患等克服研究事業）
分担研究報告書

重症多型滲出性紅斑眼障害の克服に向けた新規医療器具の開発

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分担研究者　小泉　範子　同志社大学生命医科学部

研究要旨：重症多形滲出性紅斑の眼後遺症に対する輪部支持型ハードコンタクトレンズの有効性と安全性を確認する、医師主導治験を実施し、患者のリクルート、診察、コンタクトレンズ処方、有効性、安全性の評価を行った。

A．研究目的

重症多形滲出性紅斑の眼後遺症に対する輪部支持型ハードコンタクトレンズの有効性と安全性を確認する医師主導治験を実施する。

B．研究方法

1、被験者リクルート

京都大学附属病院眼科角膜専門外来受診中の患者から重症多形滲出性紅斑の眼後遺症を持つ患者を検索した。問診および診察を行い、選択基準に合致する患者をリクルートした。

2、患者の診察

視力、眼圧測定、シルマーテスト、細隙灯顕微鏡検査を行った。判定基準に基づいて、眼後遺症の grading を行った。

3、コンタクトレンズ処方

患者の角膜曲率半径から適当と考えられるベースカーブのコンタクトレンズを試験装用し、細隙灯顕微鏡を用いて、フィッティングを確認した。ベースカーブが決定した後、患者の屈折度数及び視力検査から適切な頂点屈折力を決定した。

4、有効性評価

コンタクトレンズ装用前の最良矯正視力と装用後 13 週目における最良矯正視力を比較した。またアンケートの基づいた自覚症状の変化を評価した。

5、安全性評価

有害事象の発現、不具合の発現について評価を行った。

C．研究結果

1、被験者リクルート

重症多形性紅斑の眼後遺症を持つ患者２名（男性１名、女性１名）をリクルートすることができた。

2、患者の診察

症例 1. 51 才男性。4 歳時に重症多形滲出性紅斑を発症。H11 年に左眼に対しては羊膜移植を行われている。右眼は結膜が角膜の 1/2 の範囲に侵入。角膜混濁の程度は瞳孔が見える程度。左眼は結膜が角膜の 1/2 以上の範囲に侵入。混濁の程度は瞳孔が見えない状態。

症例 2. 58 才女性。30 年前に膀胱炎の治療の際に重症多形滲出性紅斑を発症。平成 24 年に左眼角膜穿孔に対する結膜被覆術を施行されている。右眼は結膜が角膜の 1/2 の範囲に侵入。角膜混濁の程度は瞳孔が見える程度。左眼は結膜が角膜の 1/2 以上に侵入。混濁の程度は瞳孔が見えない状態。

３、コンタクトレンズ処方

症例１.右眼に対し、ベースカーブ 760 サイズ OZ ベベル 13/8.5/N　カラーブルーを処方。

症例 2. 右眼に対し、ベースカーブ 760 サイズ OZ ベベル 13/8.5/N　カラーブルーを処方。いずれの症例も良好なフィッティングが得られ、十分なレンズ下での涙液交換が認められた。

４、有効性評価

症例 1. 対象眼の処方前最良矯正視力は 0.03、13 週目の最良矯正視力は 0.5。

症例 2. 対象眼の処方前最良矯正視力は 0.2、13 週目の最良矯正視力は 0.7。

５、安全性評価

いずれの症例においてもコンタクトレンズの終日装用が可能であり、角結膜上皮障害や感染症などの合併症を認めず、コンタクトレンズ装用休止の必要性はなかった。コンタクトレンズの破損も認めなかった。明らかな有害事象は認めていない。

D．考察

当院における 2 症例については、輪部支持型ハードコンタクトレンズは自覚症状の改善し、quality of life を向上する可能性があると考えられる。

E．結論

重症多形滲出性紅斑の眼後遺症 2 例に対して輪部支持型ハードコンタクトレンズを処方し、自覚症状の改善を確認し、明らかな有害事象の発現を認めなかった。

F．健康危険情報

該当なし

G．研究発表

１．論文発表

なし

２．学会発表

なし

H．知的財産権の出願・登録状況

特許取得：なし

実用新案登録：なし

その他：なし

I．参考文献

特になし

厚生労働科学研究費補助金（難治性疾患等克服研究事業）
分担研究報告書

病態のモニター法の検証

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研究要旨：重症多形滲出性紅斑の眼後遺症に対する輪部支持型ハードコンタクトレンズの有効性と安全性を確認する医師主導治験を実施した。本治験に並行する形で近未来の薬事承認・保険収載後の臨床研究に資するため、末梢血で病態をモニターできるか否かを検討した。重症多形滲出性紅斑の眼後遺症に対する輪部支持型ハードコンタクトレンズの有効性を末梢血もしくは眼部体液でモニターできる可能性を見出した。

A．研究目的

重症多形滲出性紅斑は難治稀少疾患として位置づけられており、高度の視力障害とドライアイが生涯続く後遺症となるが、その病態は十分に解明されていない。したがって、本疾患患者の眼後遺症に対する輪部支持型ハードコンタクトレンズ装用により装用前に比較して病態がどのように変動するかをモニターする客観的評価法を開発し、眼表面異常についての従来の有効性と安全性評価との対応付けにつなげる。

B．研究方法

重症多形滲出性紅斑は難治性角結膜疾患として位置づけられており、同類の疾患として全身の粘膜・皮膚に病変をきたす水疱症患者すなわち粘膜類天疱瘡（MMP: mucous membrane pemphigoid）がある。粘膜類天疱瘡のうち眼病変のみを示す患者（OcMMP: ocular mucous membrane pemphigoid と仮称する〕および、これらの異常のない正常人の血清を合計 37 例で採取した。病態は急性期のものも、慢性期のものも含む。

Biorad 社の Bioplex27 を用いて、27 種のサイトカイン、4 種のアジポカイン類の血清濃度を検定した。まずは、Bioplex の結果を概観し、正常人、患者で差異が認められるか検索し、患者と正常上の間に統計学的に有意の差の認められるサイトカイン、平均値と

しての有意差は認められないが患者において正常人以上に血清濃度に大きなばらつきのみられるサイトカインを選別し、重症多形滲出性紅斑患者の眼後遺症に対する輪部支持型ハードコンタクトレンズ装用後に装用前に比較して変動する可能性のあるサイトカインを絞り込んだ。同時に、MMP と OcMMP 患者で変動に大きな差のあるサイトカインも選別した。

C．研究結果

Bioplex31 種測定結果の概観で、正常人、患者で差異が認められるものとして IL6,IL8,IL10 などは明らかに患者において増加傾向が認められた。次に統計学的処理により IL10 (p=0.042), IL8 (p=0.0977)、b FGF (p=0.0680)が患者群で正常人群より有意に高値を示し、IP10 (p＝0.12)、MCP1 (p＝0.95)の 2 種が統計学的有意差は認められないものの低値を示す傾向であった。一方、正常人群に比較し、患者群で血清濃度のバラツキが著明に拡大しているものとして、IL4, IL5, IL6, IL10, bFGF, IFNg, Leptin, Adiponectin が選択された。60－70 歳台に比較し 80 歳以上で多くのサイトカインが低値を示し生理的加齢変化の存在を示唆したが、IL6, IL8 には本傾向は認められなかった。面白いことに MMP 患者よりも OcMMP 患者で有意に高値を示すものとして IP10 (p=0.0397), Leptin (p=0.0574)の 2 種、低値を示すものとして Eotaxin (p=0.0532)が選択された。

以上より、重症多形滲出性紅斑患者の眼後遺症に対する輪部支持型ハードコンタクトレンズ装用の有用性を病態学的に実践検証するには、IP10, Leptin,IL10,IL8,bFGF,IL6,IFNg の 7 種を候補として選択した。

D．考察

選択された候補サイトカインの有用性を最終的に決定するには重症多形滲出性紅斑患者の輪部支持型ハードコンタクトレンズ装用前後での末梢血並びに局所体液中を用いての実践検証が必要である。その際は上述の 7 種に、MCP1 も加えるべきと思われる。IP10, Leptin, IL10, IL8, bFGF, IL6, IFNg、 MCP1 の内 Leptin, IL10 を除く 6 種にはマクロファージ、好中球、間葉系細胞に対する遊走活性が知られており、病態との関連を示唆する。

E．結論

重症多形滲出性紅斑患者の眼後遺症に対する輪部支持型ハードコンタクトレンズ装用の有用性を病態学的に実践検証するのに末梢血中の IP10, Leptin, IL10, IL8, bFGF, IL6, IFNg, MCP1 をモニターすることに意義があると考えられる。

Ｆ．健康危険情報

該当なし

Ｇ．研究発表

１．論文発表

該当なし

２．学会発表

該当なし

Ｈ．知的財産権の出願・登録状況

特許取得：なし

実用新案登録：なし

その他：なし

Ｉ．参考文献

なし

厚生労働科学研究費補助金（難治性疾患等実用化研究事業）
分担研究報告書

新規臨床試験デザインの開発に関する研究

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研究要旨：重症多型滲出性紅斑眼障害などの希少疾病に関する多くの臨床試験は 2 値エンドポイントを用いた単群試験である。この設定において、私たちはベイズ流適応的デザイン（予測標本サイズ選択デザイン、PSSD: predictive sample size selection design）およびその拡張版を提案した。このデザインは、無益性または安全性による試験の早期中止のための中間解析、標本サイズ選択を許容し、効率的かつ柔軟性の高いデザインとして特に探索的臨床試験において有用である。

A．研究目的

本研究の目的は、2値エンドポイントを伴う探索的単群臨床試験において、効率的かつ柔軟性の高い臨床試験デザインを提供することである。

B．研究方法

2種類の事前分布（デザイン事前分布、解析事前分布）を用いるベイズ流の方法により、試験開始前に標本サイズを決定する。その際、臨床的デザイン事前分布に加えて、懐疑的デザイン事前分布を用いて、2つの標本サイズ（NおよびNmax）を決定する。

試験開始後、中間モニタリングを行い、効果発現確率が低い場合は早期中止を行い、必要に応じて標本サイズの選択（NまたはNmax）を行う。中間モニタリングおよび標本サイズの選択には、解析事前分布に基づくベイズ流予測確率を用いる。また、有効性に加えて安全性を同時に（より頻回に）モニタリングすることも可能である。

C．研究結果

シミュレーション研究により、頻度論的な動作特性を確認したところ、多くの状況において、第 I 種、第 II 種の過誤確率をそれほど増大させることなく、期待標本サイズを減少させることが示された。

また、安全性モニタリングを加えた拡張版デザインでは、検出力を大きく低下させることなく、有効性の劣る、または安全性に問題のある治療を早期に中止させることが可能であった。

D．考察

提案したデザインは、標本サイズ決定に

おける不確実性を考慮して、試験途中で標本サイズを見直すという適応型デザインである。今まで提案されたデザインにはない特長を有しており、効率的かつ柔軟性の高いデザインとして有用と考える。

E．結論

今後、本デザインを実際の臨床試験に適用し、その有用性について実地で検証していく必要がある。また、本デザインを他の型のエンドポイント、多群試験などに拡張していく予定である。

G．研究発表（平成 26 年度）

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H．知的財産権の出願・登録状況（予定を含む。）

特許取得：なし

実用新案登録：なし

その他：なし

III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍・総説

該当なし

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Sotozono C, Yamauchi N, Maeda S, Kinoshita S.	Tear Exchangeable Limbal Rigid Contact Lens for Ocular Sequelae Due to Stevens -Johnson Syndrome or Toxic Epidermal Necrolysis.	Am J Ophthalmol	158(5)	983-993	2014
手良向聡	臨床試験デザイン	京都府立医科大学雑誌	123	769-777	2014
Sumi E, Yamazaki T, Tanaka S, Yamamoto K, Nakayama T, Bessho K, Yokode M.	The increase in prescriptions of bisphosphonates and the incidence proportion of osteonecrosis of the jaw after risk communication activities in Japan: a hospital-based cohort study.	Pharmacoepidemiol Drug Saf.	23(4)	398-405	2014

Ⅳ．資料、研究成果の刊行物・別刷

Tear Exchangeable Limbal Rigid Contact Lens for Ocular Sequelae Resulting From Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis

CHIE SOTOZONO, NAOKI YAMAUCHI, SOSHUN MAEDA, AND SHIGERU KINOSHITA

• PURPOSE: To evaluate the therapeutic benefits of tear-exchangeable, limbal, rigid contact lenses (limbal CLs) in patients with Stevens-Johnson syndrome- or toxic epidermal necrolysis-associated ocular sequelae.

• DESIGN: Noncomparative, retrospective, interventional case series.

• METHODS: We enrolled 53 eyes of 42 patients (mean age, 51.8 ± 13.9 years; mean follow-up, 25.7 ± 15.7 months) with Stevens-Johnson syndrome- or toxic epidermal necrolysis-associated ocular sequelae and divided them into 3 groups according to the best-corrected visual acuity (BCVA) before limbal CL fitting: (1) BCVA worse than 20/2000 (11 eyes), (2) BCVA ranging from 20/200 to 20/2000 (31 eyes), and (3) BCVA of 20/200 or better (11 eyes). The BCVA and the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) composite score before fitting and after 3 months of limbal CL use were evaluated. The change in BCVA (in logarithm of the minimal angle of resolution [logMAR] units) and 25-item National Eye Institute Visual Function Questionnaire composite score change were compared among the 3 groups.

• RESULTS: Best-corrected visual acuity improved from 1.61 to 0.86 logMAR at 3 months after fitting CL use. Improvement in BCVA in groups 1, 2, and 3 was 0.95 logMAR, 0.82 logMAR, and 0.37 logMAR, respectively. The mean 25-item National Eye Institute Visual Function Questionnaire composite score for the 11 subscales improved from 37.6 ± 16.0 to 58.4 ± 17.4 ($P = .000001$). All 11 subscores, except that for driving ability, improved significantly. The general vision subscore improved most in group 3, yet the general health subscore improved most in group 1. No serious adverse events attributable to limbal CL use occurred.

• CONCLUSIONS: The tear-exchangeable limbal CL is safe and effective for the improvement of vision and quality of life in Stevens-Johnson syndrome or toxic epidermal necrolysis patients with severe ocular sequelae. (Am J Ophthalmol 2014;158:983–993. © 2014 by Elsevier Inc. All rights reserved.)

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STEVENS-JOHNSON SYNDROME (SJS), AND ITS SEVERE variant, toxic epidermal necrolysis (TEN), are acute, life-threatening diseases of the skin and mucous membranes.[1–3] Although the incidence of SJS and TEN is very low, that is, approximately 0.4 to 1 and 1 to 6 cases per 1 million persons, respectively, both can affect anyone at any age, usually as a consequence of adverse drug reactions.[4–7] In more than 50% of SJS or TEN patients, ocular complications are involved at the acute stage of the disease. In mild cases, bilateral acute conjunctivitis occurs before, or simultaneously with, acute fever and skin eruption. In severe cases, ocular surface epithelial defect, pseudomembranous conjunctivitis, or both are observed, and extensive ocular surface inflammation persists for more than several weeks after disease onset.[8–11] Coinciding with the remission of each disease, ocular sequelae associated with the loss of corneal epithelial stem cells such as conjunctivalization, neovascularization, opacification, and keratinization of the cornea appear. All of these cornea-related ocular sequelae disrupt visual function. Cicatrization resulting from fibrosis, symblepharon, trichiasis, and xerophthalmia cause ocular discomfort such as eye pain, dry eye, or foreign body sensation, and visual impairment and ocular discomfort continue throughout the life of the patient. In more than 50% of eyes with SJS- or TEN-associated ocular sequelae, best-corrected visual acuity (BCVA) reportedly is worse than 20/200.[11] Therefore, it is vital to improve the visual acuity (VA) of SJS or TEN patients with ocular sequelae.

The reported long-term outcomes of penetrating keratoplasty, lamellar keratoplasty, or limbal transplantation for SJS or TEN patients is poor.[12–14] Graft rejection or the loss of donor epithelial cells occurs easily, ultimately resulting in progressive conjunctivalization and scarring of the ocular surface, which once again causes severe vision loss. Amniotic membrane transplantation alone or in combination with limbal transplantation can be used for epithelialization, reducing pain, and reconstructing the conjunctival fornix in SJS or TEN patients.[15–17] Cultivated limbal epithelial transplantation or cultivated oral mucosal epithelial transplantation (COMET) are 2

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methods that improve visual function in eyes with SJS- or TEN-associated ocular sequelae.[18–24] However, it is impossible to restore the patient's ocular surface to its previous normal and healthy state.

Scleral contact lenses (CLs) originally were introduced in the 1880s in the form of a rigid contact lens made from glass. Well-designed scleral CLs with minimal clearance reportedly have been used for the treatment of severe dry eye of various causes.[25] However, nonmanageable sequelae such as corneal vascularization and ulceration were serious problems associated with the use of those lenses. The introduction of rigid gas-permeable materials to the construction of scleral CLs increased corneal oxygenation and improved the therapeutic efficacy of using scleral CLs for the treatment of ocular surface disorders.[26,27] At present, scleral CLs with high oxygen permeability are fitted for the treatment of a variety of diseases manifesting an irregularly shaped cornea, such as keratoconus or corneal ectasia, or in patients who have undergone penetrating keratoplasty.[28–30] In the use of scleral CLs, artificial tears are captured under the CL and remain trapped between the CL and the cornea until the CL is removed. Because artificial tears usually remain between the CL and the cornea for an extended period, an unhealthy physiologic status can arise.

Recent reports have demonstrated the therapeutic benefits of scleral CLs in the management of severe ocular surface diseases such as SJS and TEN.[31,32] In most of the patients in those studies, the initial VA before CL fitting was 20/200 or better. However, the findings of our previous study revealed that in more than 50% of eyes with ocular sequelae, VA is worse than 20/200.[11] Because the size of scleral CLs ranges from 16 to 23 mm, they are too large to be used on severely cicatrized eyes with conjunctival fornix shortening. Even in normal eyes, the depth of the fornix in Asians is smaller than that in white persons.

Recently, we developed a new type of rigid contact lens with a 13.0- or 14.0-mm diameter size (smaller and larger diameter sizes also can be made) that can be used in eyes with a short fornix, symblepharon, or both. Because severe dry eye is a frequent, long-term ocular sequelae caused by SJS or TEN,[33–35] the tear film plays a critical role in the homeostasis of the ocular surface in those patients. Thus, we designed this new CL to enable tear exchange under the CL during the blinking process. We named this new tear-exchangeable CL the *limbal rigid contact lens* (or limbal CL). The aim of this present study was to evaluate the safety and therapeutic benefits of the limbal CL in patients with ocular sequelae caused by SJS or TEN.

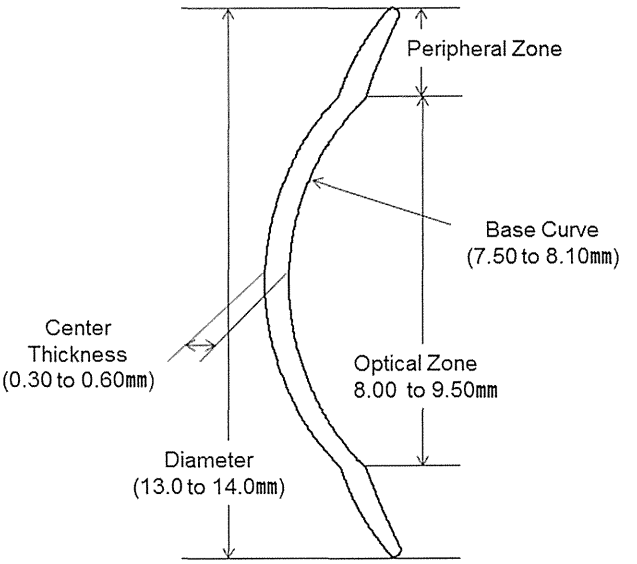

FIGURE 1. Diagram illustrating the limbal contact lens (CL) designed for eyes with ocular sequelae resulting from Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). The curvature design of the new limbal CL incorporates an 8.5- or 9.0-mm diameter optical zone at the center of the lens and a peripheral zone overlying the limbus. A peripheral zone is designed as a projecting edge, that is, like the brim of a hat, and consists of a quadcurve design that enables the inflow of tears under the CL at the time of blinking.

METHODS

THE STUDY WAS APPROVED BY THE ETHICS COMMITTEE AND Institutional Review Board of Kyoto Prefectural University of Medicine, Kyoto, Japan, and was carried out in accordance with the tenets set forth in the Declaration of Helsinki. Written informed consent was obtained from each patient before the initiation of the study. The study protocol was designed to evaluate the efficacy and safety of the limbal CL. The SJS or TEN patients with ocular sequelae seen at the SJS outpatient service at Kyoto Prefectural University Hospital were enrolled. The diagnosis of SJS was based on a confirmed history of the acute onset of high fever, serious mucocutaneous illness with skin eruptions, and the involvement of at least 2 mucosal sites, including the ocular surface. Patient inclusion criteria were as follows: (1) visual disturbance, severe dry eye, or both caused by SJS or TEN; (2) patients who can handle the CL by themselves, or with the support of family; and (3) age older than 7 years. Exclusion criteria were as follows: (1) patients with systemic or ocular infections, (2) patients with colonization of methicillin-resistant *Staphylococcus aureus* or methicillin-resistant *Staphylococcus epidermidis* on the ocular surface, (3) lost vision resulting from other reasons such as glaucoma or retinal diseases, (4) patients who are unable to come to the hospital at regular intervals, and (5) patients with dementia. Only the patients who met all of the inclusion criteria were enrolled in this study.

• **MATERIALS AND DESIGN OF THE LIMBAL CONTACT LENS:** The limbal CL is lathed from Hexafocon A (Bausch

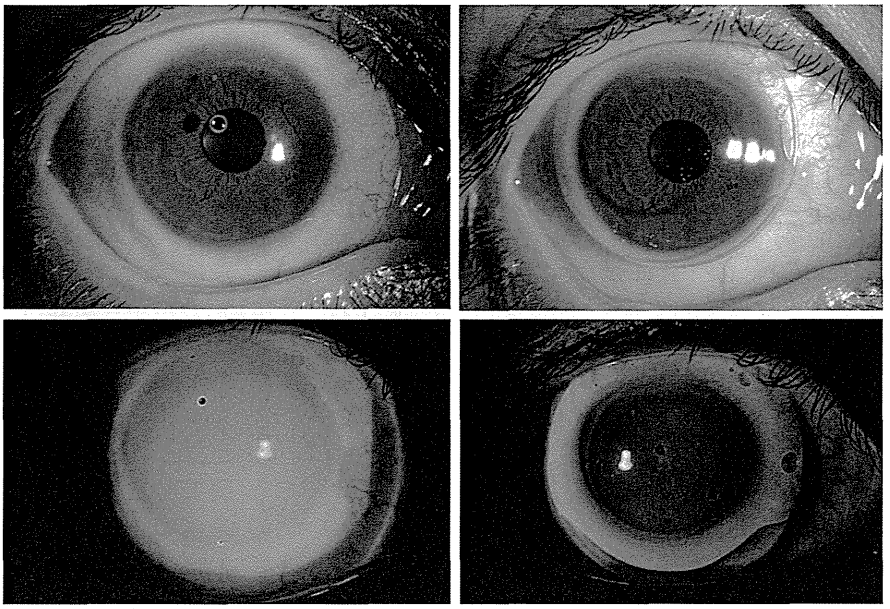

FIGURE 2. Images comparing a scleral contact lens (CL) and the limbal CL designed for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). (Top left and Bottom left) When using a scleral CL, the lens design causes fluid to be trapped between the lens and the cornea. The thick fluid coverage remains trapped beneath the CL and does not exchange with each blink. (Top right and Bottom right) In contrast, the design of the limbal CL allows for a fluid layer to exist at the peripheral zone of the lens and for the tear beneath the lens to be exchanged at every blink.

TABLE 1. Ocular Surface Grading Score of the Eyes With Ocular Sequelae Resulting From Sevens-Johnson Syndrome or Toxic Epidermal Necrolysis

		BCVA before Limbal Contact Lens Fitting		
	Total	Group 1: BCVA worse than 20/2000 (logMAR > 2), Average Grade	Group 2: BCVA 20/200 to 20/2000 (2 ≥ logMAR >1), Average Grade	Group 3: BCVA 20/200 or Better (1 ≥ logMAR), Average Grade
No. of eyes	53	11	31	11
Ocular surface grading score				
Corneal complications				
Epithelial defect	0.00	0.00	0.00	0.00
Loss of POV	2.89	2.91	2.94	2.73
Conjunctivalization	2.70	2.82	2.71	2.55
Neovascularization	2.02	2.64	1.94	1.64
Opacification	1.42	2.27	1.23	1.09
Keratinization	0.83	1.82	0.77	0.00
Conjunctival complications				
Hyperemia	1.17	1.00	1.16	1.36
Symblepharon formation	1.25	1.73	1.23	0.82
Eyelid complications				
Trichiasis	1.77	2.09	1.90	1.09
Mucocutaneous junction involvement	2.04	2.36	2.00	1.82
Meibomian gland involvement	2.94	3.00	3.00	2.73
Punctal damage	2.51	2.64	2.45	2.55
Total	21.7	25.3	21.5	18.5

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimal angle of resolution; POV = palisades of Vogt.

& Lomb, Inc, Rochester, New York, USA), a special polymer with an oxygen permeability value of 100 Dk. The curvature of the lens was designed with an 8.5- or 9.0-mm diameter optical zone at the center of the lens and a peripheral zone at the peripheral area of the lens (Figure 1). The peripheral zone is designed in the shape of a projecting

edge, for instance, like the brim of a hat, which consists of a quad-curve design that enables the inflow of tears under the CL at the time of blinking. In the use of scleral CLs, the edge of the CL touches the sclera and the thick fluid coverage beneath the CL remains trapped and does not exchange (Figure 2, Top left and Bottom left). In contrast, in the use of limbal CLs, a thin fluid layer exists under the CL with a fluid reservoir at the peripheral zone of the CL (Figure 2, Top right and Bottom right), thus allowing tear exchange beneath the CL at every blink.

Although patients using scleral CLs must remove and clean the CL several times per day, patients using the limbal CL do not need to remove and clean the lens because of the continual tear exchange. The diameter of the lens (13 or 14 mm; larger and smaller diameter sizes also can be made), the base curve (750 to 810 mm), the size of the optical zone (8.5 or 9 mm), and the peripheral-area design (2 available patterns: flat or tight) are selections that are determined by the physician at the time of the patient's trial fitting.

• TEAR EXCHANGE UNDER THE CONTACT LENS: Of the 53 total eyes involved in this study, 4 eyes of 3 patients who wear scleral CLs participated in the preliminary experiment to elucidate tear exchange via fluorescein staining patterns under the CL, that is, between the CL and the cornea. All 3 of those patients used a Boston Scleral Lens Prosthetic Device (The Boston Foundation for Sight, Inc, Needham, Massachusetts, USA) prescribed at other clinics. Those 4 eyes were examined and selected to wear either a scleral CL or the limbal CL. In the experiment, 50 μL of 0.001% sodium fluorescein dye (Fluorescite; Alcon Japan Ltd, Tokyo, Japan) was put into the concave side of the respective CLs before CL wear to elucidate the change in fluorescein pattern and concentration between the CL and the cornea associated with each type of CL. Each type of CL first was filled with fluorescein dye, and then placed on the patient's eye. The patient then was instructed to blink normally for 10 minutes. Artificial tears then were instilled in the eye at between 5 and 10 minutes after insertion of the CL, and the change in fluorescein staining pattern and concentration then was calculated by a fluorophotometer (Anterior Fluorometer FL-500; Kowa Company, Ltd, Nagoya, Japan) at the following 3 time points: (1) immediately after insertion of the CL, (2) after 5 minutes of CL wear, and (3) after 10 minutes of CL wear.

• OCULAR SURFACE GRADING SCORE: All enrolled patients underwent slit-lamp examinations to observe 12 components of the following 3 categories of ocular sequelae: (1) corneal sequelae consisting of epithelial defect, loss of the palisades of Vogt, conjunctivalization, neovascularization, opacification, and keratinization; (2) conjunctival sequelae consisting of hyperemia and symblepharon formation; and (3) eyelid sequelae consisting of

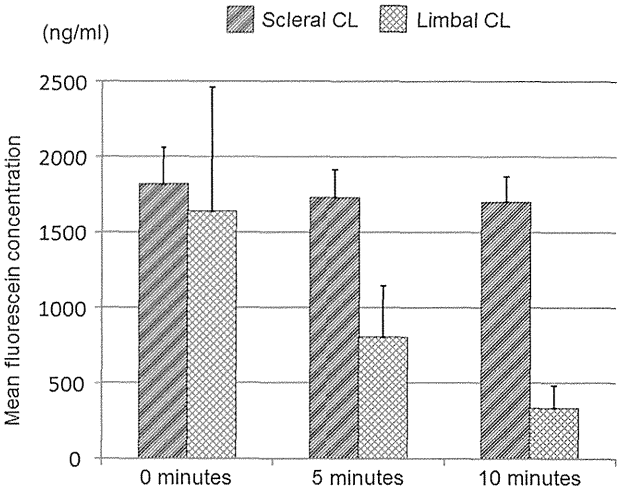

FIGURE 3. Bar graph showing the difference of fluorescein dilution between a scleral contact lens (CL) and the limbal CL. To investigate the difference of fluorescein dilution between a scleral CL and the limbal CL, 50 μL 0.001% sodium fluorescein dye was put on the concave side of each lens, and each lens was then put on a patient's eye. After 10 minutes of lens wear for each lens, no change of fluorescein concentration was observed in the eyes wearing the scleral CL; however, the fluorescein concentration gradually decreased in the eyes wearing the limbal CL (n = 4, mean ± SD). The top lines of each box represent the mean value, and the vertical lines extending from the top of each box represent the SD.

trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal damage in accordance with our previously reported grading system.[36] Each component was graded on a scale from 0 to 3, depending on the severity of involvement. The sum of each grading score was defined as the ocular surface grading score (maximum score, 36).

• OUTCOMES: The main outcome measure was the BCVA before CL fitting and after 3 months use of the limbal CL after fitting. The 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) composite score was defined as the secondary outcome. The SJS- or TEN-related ocular surface sequelae were graded on a scale from 0 to 3 according to their severity as described above. The patients were divided into 3 groups according to the BCVA before CL fitting: group 1, VA worse than 20/2000 (the logarithm of the minimal angle of resolution [logMAR] > 2); group 2, VA from 20/200 to 20/2000 (2 ≥ logMAR > 1); and group 3, VA 20/200 or better (1 ≥ logMAR). The ocular surface grading score, the change of VA, and the change of the NEI VFQ-25 composite score then were compared among the 3 groups.

• VISUAL ACUITY: Best-corrected visual acuity was measured at baseline (before fitting of the limbal CL) and after 3 months use of the limbal CL. Best-corrected visual

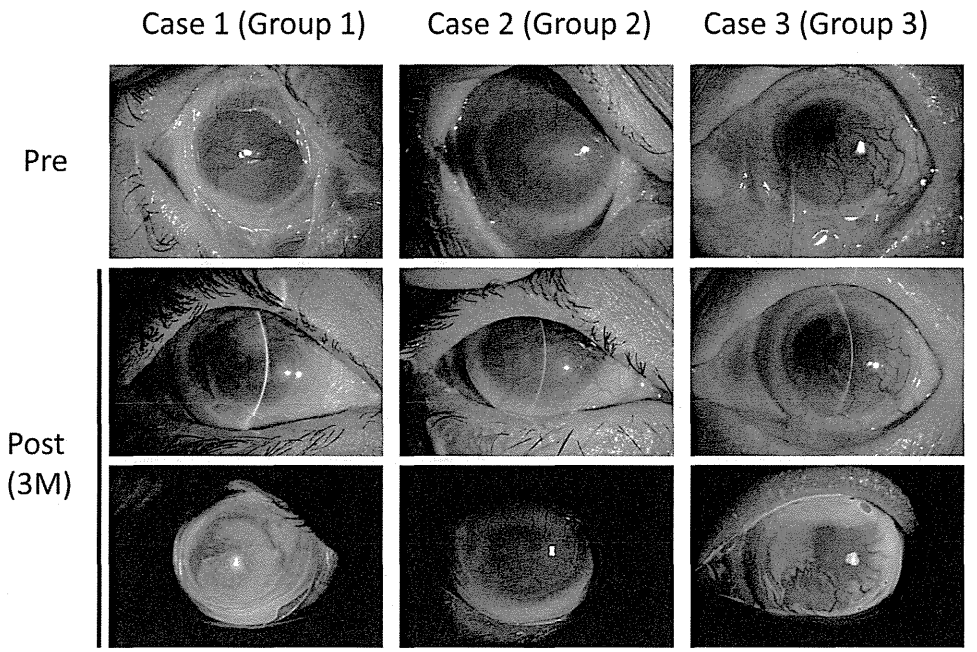

FIGURE 4. Representative appearances of the eyes with ocular sequelae resulting from Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) in each group. (Top row) Corneal appearances before fitting of the limbal CL. All 3 patients had ocular surface scarring, including fornix shortening, conjunctivalization, and neovascularization of the cornea and severe lacrimal dysfunction. (Middle and Bottom rows) Appearances at after 3 months use of the limbal CL. The thin fluid layer beneath the CL (Bottom row) is exchanged at every blink. Patient 1 was a 31-year-old man with SJS or TEN for 24 years. With the use of the limbal CL, his visual acuity (VA) improved from hand movements to 0.04. Patient 2 was a 36-year-old man with SJS or TEN for 19 years whose VA improved from 0.04 to 0.8 as a result of using the limbal CL. Patient 3 was a 59-year-old women with SJS or TEN for 29 years whose VA improved from 0.4 to 0.9 as a result of using the limbal CL.

acuity at baseline was best-corrected spectacle VA, and BCVA at after 3 months of CL use was measured with the CL fitted, and if needed, with spectacles. Improvements in VA were analyzed in relation to changes in logMAR BCVA. Counting fingers, hand movements, and light perception were determined to be 0.004, 0.002, and 0.001, respectively.

• VISUAL FUNCTION QUESTIONNAIRE: Each patient completed a Japanese language version of the NEI VFQ-25 at the baseline examination and after 3 months of limbal CL use to evaluate their vision-related quality of life.[37] The questionnaire was administered via a direct interview by a trained interviewer (S.M.) who was otherwise not involved in the patient's care.

• STATISTICAL ANALYSIS: The Wilcoxon signed-rank test was used to compare the NEI VFQ-25 data at baseline and after 3 months of limbal CL use. *P* values of less than .05 were considered statistically significant.

• ADDITIONAL COLLECTED DATA: For each patient, additional collected data included the diameter and the peripheral design of the CL, the base curve and the size of the optical zone, the length in time of CL wear, patient reports of symptoms, if any, during CL wear, and all adverse events that occurred during the period of CL use.

RESULTS

• PATIENT CHARACTERISTICS: This retrospective study involved a total of 53 eyes of 42 SJS or TEN patients (15 men and 27 women) ranging in age from 28 to 78 years (mean age ± standard deviation [SD], 51.8 ± 13.9 years). At disease onset, patient age ranged from 2 to 64 years (mean age ± SD, 22.4 ± 16.7 years), and 23 (53.5%) of the 41 patients were younger than 20 years. The duration of the illness ranged from 2 to 68 years (mean duration ± SD, 29.3 ± 15.7 years), and the mean ± SD patient follow-up period was 25.7 ± 15.7 months. The causative drugs were cold medicines in 13 patients, nonsteroidal anti-inflammatory drugs in 11 patients, antibiotics in 6 patients, anticonvulsants in 2 patients, and others in 6 patients.

Prior ocular surgeries had been performed in 37 (70.0%) of the 53 eyes at Kyoto Prefectural University of Medicine

or at a different medical facility. Corneal reconstruction was performed in 21 eyes: COMET in 9 eyes, cultivated limbal epithelial transplantation in 5 eyes, limbal transplantation or keratoepithelioplasty in 5 eyes, and penetrating keratoplasty or lamellar keratoplasty in 6 eyes. Conjunctival reconstruction was performed in 17 eyes: amniotic membrane transplantation in 11 eyes, COMET in 2 eyes, oral mucosal transplantation in 2 eyes, and other surgeries in 2 eyes. Cataract surgery was performed in 13 eyes. Entropion surgeries were performed in 12 eyes, and ptosis surgeries were performed in 4 eyes. Fitting and use of the limbal CL was initiated only when the ocular surface had been stable for at least 1 month after cataract or eyelid surgery and for at least 3 months after ocular surface reconstruction or keratoplasty.

• OCULAR SURFACE GRADING SCORE: As reported previously, the ocular surface grading score reflects the severity of sequelae caused by SJS or TEN.[36] The loss of the palisades of Vogt and meibomian gland involvement were grade 3 in 50 eyes (94.3%) and 51 eyes (96.2%), respectively. That is, more than 95% of eyes were limbal stem cell deficient and also had severe meibomian gland dysfunction. Mild to moderate neovascularization and opacification of the cornea existed (Supplemental Table, available at AJO.com).

There were 11 eyes in group 1, 31 eyes in group 2, and 11 eyes in group 3. All ocular surface grading scores (except those for hyperemia and punctal damage), as well as the total score, were highest in group 1 and lowest in group 3 (Table 1).

• TEAR EXCHANGE UNDER THE CONTACT LENS: The results of the tear-exchange experiment revealed substantial differences in fluorescein staining patterns and concentrations between the scleral CL and the limbal CL. Fluorescein patterns showed no change of fluorescein concentration over a 10-minute period in the eyes with the scleral CL, but did reveal a gradual decrease of fluorescein concentration in the eyes with the limbal CL (Figure 3).

• LIMBAL CONTACT LENS WEAR IN EYES WITH OCULAR SURFACE SCARRING: The limbal CLs were able to be used for eyes with fornix shortening, conjunctivalization, and neovascularization of the cornea, and there was no need to fill the CL with saline or artificial tears. During limbal CL wear, a thin fluid layer existed beneath the CL (Figure 4) and the precorneal fluid layer exchanged at every blink (Supplemental Video, available at AJO.com).

• VISUAL ACUITY: Best-corrected visual acuity improved from 1.61 to 0.86 logMAR after 3 months of limbal CL use, and in 43 eyes (81.1%), the BCVA improvement was more than 0.2 logMAR (Figure 5). The BCVA

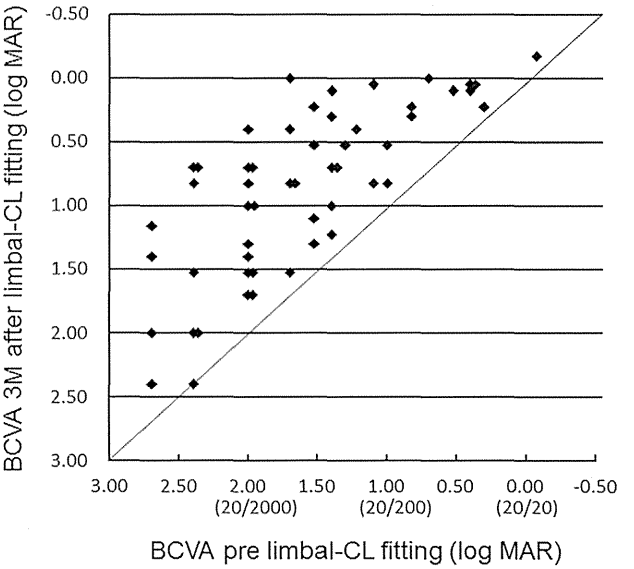

FIGURE 5. Scatterplot showing the change in best-corrected visual acuity (BCVA) measured in logarithm of the minimal angle of resolution (logMAR) units before and at after 3 months use of the limbal contact lens in 42 patients (53 eyes) with ocular sequelae resulting from Stevens-Johnson syndrome or toxic epidermal necrolysis. The diagonal line indicates the values at which the preoperative and postoperative visual acuity values were the same. Counting fingers, hand movements, and light perception were determined to be 0.004, 0.002, and 0.001, respectively.

improvement in groups 1, 2, and 3 was 0.95 logMAR, 0.82 logMAR, and 0.37 logMAR, respectively (Table 2). Mean BCVA after 3 months of CL use was 1.55 logMAR in group 1, the worst among the 3 groups. However, BCVA improvement was best in group 1. Of 29 cases in which the CL was fitted unilaterally, the CL was fitted in the eye with better VA in 26 cases and in the eye with worse VA in 3 cases. At the final examination, the eye fitted with the limbal CL was the eye with better VA in all 29 unilateral cases.

• VISUAL FUNCTION QUESTIONNAIRE: The mean NEI VFQ-25 composite score of the 11 subscores improved from 37.6 ± 16.0 to 58.4 ± 17.4 ($P = .000001$). Significant improvement was found in all 11 subscores, except for the score for driving ability (Table 3). Significant improvement was found not only in the vision-related subscores, but also in the behavioral subscores. It should be emphasized that the subscore for mental health (ie, patient well-being) was very low in group 1, but greatly improved after using the limbal CL.

Comparison of the subscores among the 3 groups revealed that the vision-related subscores most improved in group 3, except for the score for color vision. However, the subscores of general health most improved in group

TABLE 2. Comparison of the Change of Visual Acuity Among the 3 Groups Divided According to Best-Corrected Visual Acuity Before Limbal Contact Lens Fitting

		BCVA Before Limbal CL Fitting		
	Total	Group 1: BCVA Worse Than 20/2000 (logMAR >2), Average Grade	Group 2: BCVA 20/200 to 20/2000 (2 ≥ logMAR > 1), Average Grade	Group 3: BCVA 20/200 or Better (1 ≥ logMAR), Average Grade
No. of eyes	53	11	31	11
BCVA before limbal CL fitting (logMAR)	1.61	2.51	1.67	0.57
BCVA after 3 months of limbal CL use (logMAR)	0.86	1.55	0.85	0.20
BCVA improvement (logMAR)	0.75	0.95	0.82	0.37

BCVA = best-corrected visual acuity; CL = contact lens; logMAR = logarithm of the minimal angle of resolution.

1 (Table 4). Among the behavioral subscores, social functioning and dependence improved almost equally in the 3 groups. Both mental health and role difficulties (ie, role limitations) improved most in group 3, but the improvement of mental health in group 1 also was high.

• LIMBAL CONTACT LENS SIZE, BASE CURVE, AND PERIPHERAL DESIGN: Of the total 53 eyes, the diameter of the limbal CL was 14.0 mm in 45 eyes, 13.0 mm in 6 eyes, 12.5 mm in 1 eye, and 16 mm in 1 eye. The base curve of the lens ranged from 780 to 810 mm in 48 eyes (ie, 750 mm in 1 eye, 760 mm in 1 eye, 770 mm in 3 eyes, 780 mm in 18 eyes, 790 mm in 12 eyes, 800 mm in 7 eyes, and 810 mm in 11 eyes). The size of the optical zone was 8.0 mm in 2 eyes, 8.5 mm in 32 eyes, 9.0 mm in 17 eyes, and 9.5 mm in 2 eyes. The peripheral design was the flat-pattern type in 49 eyes and the tight-pattern type in 4 eyes.

Because of the highly irregular corneal surface in each patient, the corneal shape could not be evaluated by use of topography. To determine the CL size, base curve, and peripheral design, we first tested the CL fitting using the 790/0/14.0-8.5 flat-pattern type. Next, we changed and tested the CL, step by step, by evaluating the fluorescein staining pattern both at rest and during blinking. In the eyes with slight scarring of the ocular surface, the large optical zone CL was well fitted and the peripheral tight-pattern design was preferred.

• LENGTH OF TIME OF CONTACT LENS WEAR AND ADVERSE EVENTS: In 33 eyes, the limbal CL was used from morning into the evening, that is, more than 12 hours per day. In 3 eyes, the CL was used only during the part of the day when the patients left their house to go outside. In 3 eyes, the patients reported eye pain after several hours of CL wear; all 3 eyes had severe scarring of the upper fornix, and the symblepharon was asymmetrical between the upper and lower fornix. In 1 eye, a small epithelial erosion occurred, but healed within several days after the discontinuation of CL wear. No other complications or infections occurred as a result of CL wear. Seven patients lost their CL because of low VA, making it extremely difficult for them to find the CL by themselves.

DISCUSSION

THE OCULAR SEQUELAE RESULTING FROM SJS OR TEN CAN be devastating to a patient's vision, and the associated severe ocular discomfort is extremely serious and lasts throughout the patient's life. The improved VA and quality of life achieved through the use of the tear-exchangeable limbal CL are encouraging, because this CL has the potential of being a new treatment option that can provide better VA, improved ocular comfort, or both for patients with SJS or TEN.

It should be emphasized that before the initial use of this new CL, BCVA in 79% of the eyes (42 of the 53 eyes) was worse than 20/200 (groups 1 and 2). Moreover, BCVA in 21% of the eyes (11 of the 53 eyes) before CL use was worse than 20/2000, hand movements, or counting fingers (group 1). The mean change in BCVA was 0.95 logMAR, the greatest change being in group 1. Visual acuity improved immediately after the CL fitting, and the patients were surprised with the instant improvement. In fact, that improvement of VA allowed some of the patients to see their doctor's face for the first time.

With the use of this new CL, spontaneous exchange of tear fluids or artificial tears occurs during every blink. In contrast, with the use of scleral CLs (diameter, 16 to 23 mm), there is little or no exchange of tear fluids or artificial tears, and the CL must be cleaned every 4 to 6 hours. Our findings show that all-day wear of our new CL is possible, because there is no need to remove and clean the CL during that extended period.

In recent years, semiscleral CLs with a diameter of 15.0 to 18.0 mm were reported to offer the benefit of improving VA in eyes with severe dry eye or an irregular cornea.[38,39]

TABLE 3. Twenty-five-Item National Eye Institute Visual Function Questionnaire Results for the Patients With Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis Before and After 3 Months of Limbal Contact Lens Use

	Before CL Fitting	After CL Fitting	Mean Change	*P* Value[a]
Composite score 11				
Mean ± SD	37.6 ± 16.0	58.5 ± 17.4	20.8 ± 15.8	.000001
Median (range)	35.2 (8.4 to 69.4)	58.4 (23.2 to 92.7)	21.6 (–17.2 to 59.7)	
Composite score 7				
Mean ± SD	35.7 ± 16.0	58.4 ± 17.6	22.7 ± 17.6	.000001
Median (range)	35.1 (4.3 to 67)	57.2 (17.0 to 93.9)	20.7 (–17.4 to 67)	
Subscale scores				
General health				
Mean ± SD	47.4 ± 21.2	58.8 ± 15.1	11.4 ± 21.6	.006265
Median (range)	50 (0 to 100)	60 (5 to 85)	0 (–27.5 to 65)	
Vision-related subscales				
General vision				
Mean ± SD	32.6 ± 15.8	65.1 ± 20.3	32.6 ± 22.6	.000001
Median (range)	30 (0 to 75)	70 (0 to 100)	35 (–15 to 75)	
Near vision				
Mean ± SD	31.1 ± 17.0	53.1 ± 21.7	22 ± 19.9	.000007
Median (range)	29.2 (0 to 66.7)	54.2 (8.3 to 100)	22.5 (–16.7 to 66.7)	
Distance vision				
Mean ± SD	29.9 ± 17.2	53.4 ± 18.3	23.5 ± 18.7	.000003
Median (range)	33.3 (0 to 62.5)	50 (12.5 to 95)	25 (–12.5 to 60)	
Color vision				
Mean ± SD	62.9 ± 24.2	77.1 ± 21.0	14.3 ± 24.1	.003496
Median (range)	75 (0 to 100)	75 (0 to 100)	0 (–50 to 75)	
Peripheral vision				
Mean ± SD	33.1 ± 24.0	50.0 ± 23.9	16.9 ± 25.5	.000447
Median (range)	25 (0 to 100)	50 (0 to 100)	25 (–75 to 75)	
Ocular pain				
Mean ± SD	43.9 ± 29.9	65.7 ± 25.9	21.8 ± 24.7	.000061
Median (range)	50 (0 to 100)	75 (12.5 to 100)	12.5 (–25 to 87.5)	
Behavioral subscales				
Mental health				
Mean ± SD	28.9 ± 21.1	52.8 ± 22.8	23.9 ± 21.5	.000003
Median (range)	25 (0 to 80)	55 (10 to 95)	20 (–15 to 75)	
Social function				
Mean ± SD	51.8 ± 16.8	66.9 ± 17.5	15.1 ± 20.9	.000661
Median (range)	50 (25 to 91.7)	66.7 (33.3 to 100)	16.7 (–25.0 to 58.3)	
Role limitation				
Mean ± SD	36.3 ± 22.6	57.4 ± 20.9	21.2 ± 20.6	.000009
Median (range)	37.5 (0 to 81.3)	56.3 (0 to 100)	18.8 (–18.8 to 68.8)	
Dependency				
Mean ± SD	39.5 ± 25.6	60.4 ± 22.4	20.9 ± 21.7	.000009
Median (range)	43.8 (0 to 87.5)	62.5 (12.5 to 100)	18.8 (–18.8 to 93.8)	
Ability to drive				
Driving				
Mean ± SD	6.1 ± 18.7	14.6 ± 29.8	9.9 ± 20.5	.278517
Median (range)	0 (0 to 75)	0 (0 to 100)	0 (0 to 75)	

CL = contact lens; SD = standard deviation.
[a]Wilcoxon signed-rank test.

The limbal CL presented in this study may seem to be similar to a large-diameter rigid gas permeable CL or a semiscleral CL. However, the chief difference between our new CL and a semiscleral or large-diameter CL is the entrapment of the fluid reservoir beneath the flange that extends beyond the limbus when using this CL. To bring the tear under the CL automatically, the CL design includes a multicurve zone at the periphery of the CL, thus

TABLE 4. Comparison of the Change of the 25-Item National Eye Institute Visual Function Questionnaire Scores Before and After 3 Months of Limbal Contact Lens Use among the 3 Groups Divided According to Best-Corrected Visual Acuity before Limbal Contact Lens Fitting

	Total	Group 1: BCVA Worse Than 20/2000 (logMAR > 2), Average Grade	Group 2: BCVA 20/200 to 20/2000 (2 ≥ logMAR > 1), Average Grade	Group 3: BCVA 20/200 or Better (1 ≥ logMAR), Average Grade
No. of cases	35	8	18	9
Composite score 11	20.8	18.1	20.2	24.5
Composite score 7	22.7	20.8	21.5	26.9
Subscale scores				
General health	11.4	13.8	12.6	6.9
Vision-related subscales				
General vision	32.6	26.3	30.8	41.7
Near vision	22.0	19.6	19.5	29.1
Distance vision	23.5	23.8	22.2	25.8
Color vision	14.3	9.4	18.1	11.1
Peripheral vision	16.9	12.5	17.6	19.4
Ocular pain	21.8	21.9	20.1	25.0
Behavioral Subscales				
Mental health	23.9	25.6	19.5	31.1
Social function	15.1	14.6	16.2	13.4
Role limitation	21.2	18.0	20.1	26.2
Dependency	20.9	18.0	22.2	20.8
Ability to drive				
Driving	9.9	0.0	2.1	28.3

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimal angle of resolution.

establishing a thin tear layer on the entire corneal surface that can bring relief to the patients with severe ocular discomfort.

Our new CL comprises an 8.5- or 9.0-mm diameter central zone and a peripheral zone that lies on the corneal and conjunctival limbus. During the lens design process, we found that in the eyes with severe cicatrization of the ocular surface, the shape of the sclera beyond the limbus is flatter than that of normal eyes. Therefore, the peripheral zone in our limbal CL was designed to be flatter than the central optical zone, and it incorporates a projecting multicurve edge design that is like the brim of a hat. Although our limbal CL with an 8.5-mm diameter central zone was well fitted in the severely cicatrized eyes in comparison with the moderately affected eyes, the CL with a 9.0-mm diameter central zone was well fitted in moderately damaged eyes or in the eyes without fornix shortening. The peripheral design with the flat-pattern type was well fitted in the moderate to severe cicatrized eyes. In contrast, the peripheral design with the tight-pattern type was well-fitted in the eyes with slight or no cicatrized eyes.

As reported previously, the quality of life in SJS or TEN patients is worse than that in the patients with Sjögren syndrome.[35,40] Use of our limbal CL not only increased the patients' VA, but also improved their general health and mental health. In fact, even the end-stage blind patients (group 1) experienced improved vision and general health. Moreover, because of the decrease of tear evaporation, eye pain also decreased during CL wear. The use of scleral CLs reportedly reduces symptoms related to severe dry eye,[31,32] and our findings show that using our new limbal CLs also reduces those same symptoms.

It should be noted that COMET is reportedly a reliable option for obtaining improved vision in eyes with end-stage SJS or TEN.[24] However, the damage in the eyes treated by COMET in that study was more severe than in the eyes enrolled in this present study. In this study, 11 cases used this CL after ocular surface reconstruction using the COMET technique. These patients were able to obtain improved vision by COMET alone, yet use of the limbal CL enhanced that improvement of vision. Thus, the use of this CL alone, or the 2-step treatment of COMET and limbal CL use, are safe and reliable treatment methods for ocular sequelae resulting from SJS or TEN. In conclusion, the findings of this study show that our new tear-exchangeable, limbal CL increases VA and also increases general health and mental health in SJS or TEN patients, especially those with end-stage blindness.

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