Incidence and outcomes of LASIK with diffuse lamellar keratitis treated with topical and oral corticosteroids

Richard S. Hoffman, MD, I. Howard Fine, MD, Mark Packer, MD

Purpose: To analyze the incidence and clinical outcomes of patients developing diffuse lamellar keratitis (DLK) after laser in situ keratomileusis (LASIK) treated with topical and oral corticosteroids.

Setting: Oregon Eye Institute, Eugene, Oregon, USA.

Methods: A retrospective analysis of the last consecutive 1000 LASIK cases was performed. Eyes developing stage 3 DLK or at risk for progressing to stage 3 were treated with a combination of high-dose prednisolone acetate 1% and oral prednisone and evaluated for corneal scarring, loss of best spectacle-corrected visual acuity (BSCVA), and deviation from the intended refractive outcome.

Results: Diffuse lamellar keratitis developed in 40 eyes (4%). It progressed to stage 3 in 7 eyes (17%). Oral and topical steroids were used in 22 eyes (55%). The mean variation from the desired refractive outcome was 0.14 diopter ± 0.53 (SD). There were no instances of corneal scarring or permanent loss of BSCVA. No eye had interface irrigation.

Conclusion: Treatment of severe DLK with high-dose topical and oral corticosteroids produced excellent results without flap lifting and interface irrigation.

J Cataract Refract Surg 2003; 29:451–456 © 2003 ASCRS and ESCRS

Diffuse lamellar keratitis (DLK) or interface keratitis is a noninfectious condition that develops within the keratectomy interface shortly after laser in situ keratomileusis (LASIK).[1] The condition can also develop many months after LASIK when subsequent trauma, epithelial abrasions, or iritis develops.[2–10] The possible etiologies of DLK include interface debris in the form of meibomian secretions, blood, microkeratome oil, silicates, wax, povidone–iodine, and bacterial endotoxins.[11–15]

Diffuse lamellar keratitis can occur in sporadic cases or in epidemic clusters.[16] Currently, the most widely accepted approach for staging DLK is the classification system of Linebarger and coauthors.[17] Diffuse lamellar keratitis classically begins on the first or second postoperative day with a faint sterile infiltration of inflammatory cells at the flap edge within the interface (stage 1). It commonly progresses to migration of the inflammatory cells within the interface in a more central and diffuse pattern (stage 2). If the inflammation worsens, aggregation of the inflammatory cells within the visual axis can occur and is often associated with a subjective decline in visual quality (stage 3). In rare instances, collagenase release and stromal melting with subsequent scarring, hyperopic shifting, and loss of best spectacle-corrected visual acuity (BSCVA) can develop (stage 4).

Accepted for publication September 18, 2002.

From a private practice, Eugene, Oregon, USA.

Presented in part at the Symposium on Cataract, IOL and Refractive Surgery, Philadelphia, Pennsylvania, USA, June 2002.

None of the authors has a proprietary or financial interest in any product mentioned.

Reprint requests to Richard S. Hoffman, MD, Drs. Fine, Hoffman, & Packer, LLC, 1550 Oak Street, Suite 5, Eugene, Oregon 97401, USA. E-mail: rshoffman@finemd.com.

0886-3350/03/$–see front matter
doi:10.1016/S0886-3350(02)01835-7

The current treatment recommendations for DLK include the initiation of high-dose topical steroids (prednisolone acetate 1%, prednisolone phosphate 1%, or dexamethasone alcohol 0.1%) every hour for stages 1 and 2, with a slow taper over several weeks once the inflammation begins to subside. When stage 3 DLK develops, the current standards recommend flap lifting and interface irrigation to debulk the interface of inflammatory cells and collagenases to prevent progression to stage 4 with its associated ocular morbidity.[18]

Reports of the use of oral steroids to treat recalcitrant DLK in patients with allergic and atopic conditions[19] led us to use a combination of frequent topical and oral corticosteroids to treat patients who developed stage 3 DLK or appeared to be at risk for developing stage 3 (presenting on the first postoperative day with severe stage 2). We report a retrospective analysis of the incidence of DLK after LASIK and the outcomes in patients treated with a topical or a combination of topical and oral corticosteroids without the intervention of flap lifting or interface irrigation.

Patients and Methods

A retrospective analysis of the last 1000 LASIK cases was performed. All eyes in which DLK was diagnosed were identified and reviewed. Analysis included age, preoperative refractive error (spherical equivalent [SE]), incidence of concomitant corneal abrasions, postoperative day (POD) of diagnosis and stage at diagnosis, and POD on which the maximum stage was achieved. In addition, corneal scarring, permanent loss of BSCVA, and the last reported variation from the desired refractive error were recorded.

All patients had a complete preoperative examination including manifest and cycloplegic refractions, corneal topography, pachymetry, and slitlamp and dilated fundus examinations. Special attention was given to ensure an absence of corneal anterior basement membrane dystrophy and diagnosis and treatment of significant blepharitis.

On the day of surgery, all patients were prepped with povidone–iodine (Betadine®) and the eyelids were draped with Tagaderm® to isolate the lids and lashes from the operative field. A nonaspirating lid speculum was placed, followed by placement of a Hansatome® microkeratome (Bausch & Lomb) and creation of the keratectomy. Eight percent of eyes had an enhancement procedure that was performed by lifting the edge of the flap with a sterile instrument at the slitlamp followed by flap lifting under the operating microscope. Laser treatment was performed with the Visx S2 or S3 excimer laser. Treatments were based on the patient's manifest refraction using a modified Hardten nomogram (David Hardten, MD, personal communication, April 1999). The intended final refractive error was recorded for all eyes and used as the reference to compare to the final refractive outcome and determine the variation from the intended result.

Following treatment, all flap interfaces were irrigated with a balanced salt or lactated Ringer's solution. After the flap was repositioned, patients were given several drops of ofloxacin (Ocuflox®), prednisolone phosphate 1%, and diclofenac sodium 0.1% (Voltaren®) intraoperatively. Postoperatively, they were started immediately on a regimen of prednisolone acetate 1% (Pred Forte® 1%) 4 times a day, Ocuflox 4 times a day, Voltaren 4 times a day as needed for discomfort, and frequent nonpreserved artificial tears. Patients with concomitant corneal abrasions were treated with a Plano-T bandage contact lens (Bausch & Lomb) if more than 20% of the corneal epithelium was abraded.

Patients were seen on POD 1 and then 1 week later if no complications developed. Patients with corneal abrasions were followed every 1 to 2 days until epithelial healing was complete. If DLK was diagnosed, patients were followed every 1 to 2 days until the DLK appeared to reach its maximum stage and was beginning to regress. Once regression was observed, follow-up was usually performed weekly until the DLK resolved.

Although no standardized treatment protocol was used, patients were generally instructed to increase the frequency of topical steroids to every 1 to 2 hours at the time DLK was diagnosed. If DLK progressed to stage 3, oral prednisone was prescribed at a dose ranging from 40 to 80 mg a day. Patients who presented with stage 2 DLK on POD 1 were generally treated with frequent topical and oral corticosteroids. High-dose oral corticosteroids were reduced quickly to 20 to 30 mg/day once DLK regression began. Topical and oral corticosteroids were then tapered slowly depending on the clinical response. No eye, regardless of stage or BSCVA, was treated with flap lifting and interface irrigation.

Results

Forty of the 1000 LASIK eyes (4%) developed DLK. In most, the DLK occurred in epidemic clusters rather than sporadic instances. The mean age of the patients who developed DLK was 37 years. The mean preoperative SE was -3.44 diopters (D) $\pm$ 1.74 (SD). Bilateral presentation occurred in 30 of the 40 eyes (75%). The bilateral presentation corresponded to 15 of 25 patients (60%). Corneal abrasions were present in 11 DLK eyes (28%), and 3 of the abraded eyes (27%) progressed to stage 3 DLK. Sixteen of the 1000 LASIK eyes (1.6%) had associated corneal abrasions that did not result in DLK compared to the 11 eyes (1.1%) that did develop DLK.

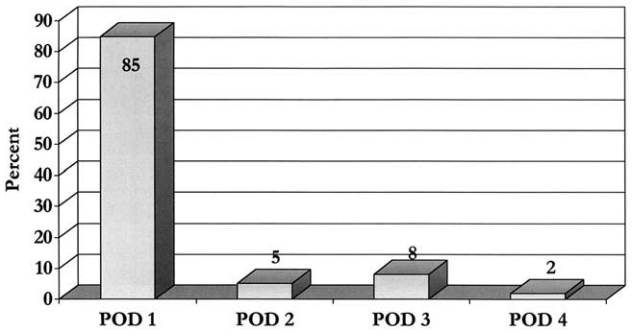

Figure 1. (Hoffman) Postoperative day of DLK diagnosis.

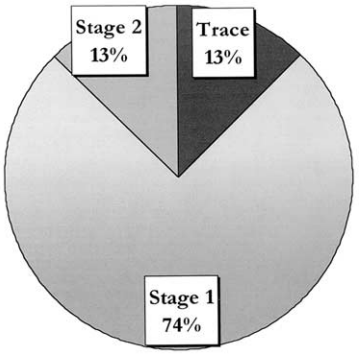

Figure 2. (Hoffman) Stage at time of DLK diagnosis.

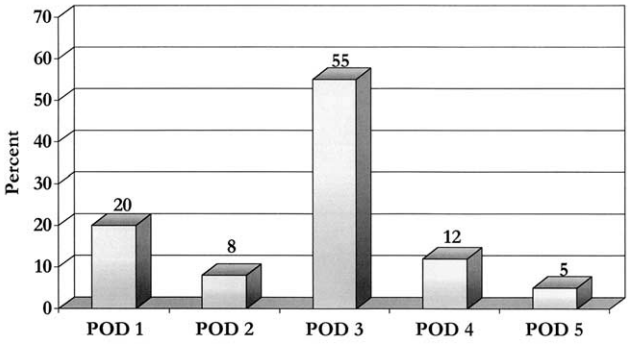

Figure 3. (Hoffman) Postoperative day of maximum DLK.

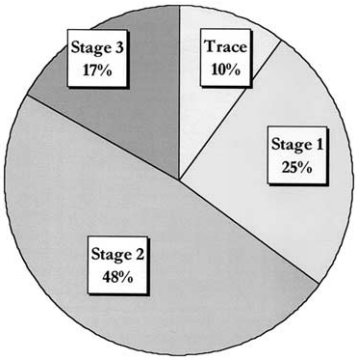

Figure 4. (Hoffman) Maximum DLK stage achieved.

Figure 1 shows the POD on which DLK was diagnosed and Figure 2, the stage at the time of diagnosis. Fifty-five percent of eyes with DLK were ultimately treated with topical and oral steroids. Thirty-two percent of these eyes were started on oral steroids on POD 1, 9% on POD 2, and 59% on POD 3. The mean duration of topical steroid use was 18 days (range 7 to 28 days) and of oral steroid use, 18 days (range 4 to 45 days).

Figure 3 shows the POD on which DLK reached its maximum stage and Figure 4, the maximum DLK stage achieved. Most DLK eyes (55%) reached their maximum stage on POD 3. Twenty percent did not progress after POD 1. No eye progressed to stage 4 DLK.

The mean variation from the intended postoperative refractive result was 0.14 ± 0.53 D. The mean postoperative follow-up was 5.2 months. (The follow-up was affected by the requirement that if a secondary enhancement procedure was performed, the follow-up of the primary procedure [in addition to all other recorded parameters] would end on the last examination before the secondary procedure.) There were no instances of corneal scarring or permanent haze, and there was no loss of BSCVA. Ten percent of eyes gained 1 or more lines of BSCVA.

A separate analysis of the 7 eyes (17%) that progressed to stage 3 DLK was performed to determine whether this more severe subset of DLK eyes had a different prognosis in terms of the variation from the intended refractive result (hyperopic deviation) and corneal clarity. The variation from the intended refractive outcome was −0.10 ± 0.60 D. The mean follow-up was 3.3 months. Two eyes had a transient decrease in BSCVA to 20/50 during the DLK period; however, there was no loss of final BSCVA and no corneal scarring in any stage 3 DLK eye (Table 1). Forty-three percent of the eyes that progressed to stage 3 had concomitant corneal abrasions.

Discussion

Diffuse lamellar keratitis has routinely been described as a serious sight-threatening condition requiring aggressive treatment to prevent the permanent visual

Table 1. Outcome in 7 eyes with stage 3 DLK.

Patient	Eye	Age (Y)	Preop SE (D)	Abrasion	POD/ Dx	Oral Steroids (mg)	Lowest BSCVA	Scarring	Loss of BSCVA	Variation from Desired SE (D)	Follow-up (Mo)
1	OS	46	2.50	−	1	80, taper	20/20	−	−	0.75	3
2	OD	52	−4.50	+	1	40, taper	20/50	−	−	0.12	7
2	OS	52	−3.50	+	1	40, taper	20/25	−	−	−0.25	7
3	OD	39	−6.25	−	1	80, taper	20/25	−	Gain 1	−0.25	8
3	OS	39	−7.00	−	1	80, taper	20/30	−	−	0.12	8
4	OD	28	−1.50	+	3	60, taper	20/50	−	−	−1.25	3
5	OS	23	−4.50	−	1	80, taper	20/20	−	−	0.00	2

SE = spherical equivalent; POD = postoperative day; BSCVA = best spectacle-corrected visual acuity

sequelae of stromal tissue loss, irregular astigmatism, corneal scarring, hyperopic refractive errors, and loss of BSCVA.[17,18] The proposed mechanism of this ocular morbidity is believed to be the release of collagenases from the abundant white blood cells (WBCs) that accumulate within the central keratectomy interface in stage 3 DLK. When stage 3 develops, flap lifting and irrigation, in addition to frequent topical corticosteroids, are recommended to prevent the progression to stage 4.[18]

There is some controversy within the ophthalmic community as to whether stage 4 DLK is a rare progression from stage 3 or whether it is a completely different entity. Parolini and coauthors[20] describe 4 cases of central necrotic inflammation developing 2 days after LASIK that led to central stromal opacification, flap striae, a hyperopic shift, and loss of BSCVA. These cases had some of the associated morbidity of stage 4 DLK but differed in that a natural progression through the developing stages of DLK did not occur. These cases of severe postoperative interface inflammation can be construed as stage 4 DLK but in reality may represent a different condition. Maloney has observed similar cases and believes these isolated cases are not stage 4 DLK but rather a condition he terms "central toxic keratopathy," an entity characterized by early severe inflammation with stromal melting, induced hyperopia, and eventual slow regression to emmetropia (R. Maloney, MD, cited in "Could DLK Lead to Corneal Ectasia?" Review of Ophthalmology, March 2002, page 5). However, an early report of DLK describes instances of stromal thinning, corneal haze, and resultant hyperopia[21] consistent with a diagnosis of stage 4 DLK with an appropriate chronological progression through the stages of DLK, adding confusion to this debate.

Assuming the possibility that stage 4 DLK exists, the question is whether it can be avoided using a combination of frequent topical and high-dose oral corticosteroids without flap lifting and interface irrigation. MacRae and coauthors[22] report favorable outcomes in stage 2 and higher DLK treated with a short intensive course of an oral corticosteroid combined with an hourly topical steroid. In their study of 13 eyes, a best corrected visual acuity (BCVA) of 20/30 or worse was used as the criterion to begin oral prednisone. In addition, eyes with a BCVA of 20/50 or worse were treated with flap relifting and irrigation of the flap interface.

In our study, we found that combination therapy resulted in excellent outcomes without the use of interface irrigation. Additional findings included a high association of bilateral presentation and corneal abrasions in patients developing DLK. The diagnosis of DLK was most commonly determined on POD 1, and in 87% of eyes, the stage at the time of diagnosis was mild, recorded as trace or stage 1. Oral prednisone was begun in addition to frequent topical steroids in 55% of eyes, and all patients were started on oral prednisone before POD 4. Treated patients received intensive oral steroids for 1 to 2 weeks only, followed by a rapid taper, the duration of which depended on the clinical response. Although 1 patient was maintained on oral prednisone for 45 days, high-dose steroids were only used for the first 2 postoperative weeks in this patient followed by a prolonged taper at lower doses. Diffuse lamellar keratitis achieved its maximum severity in most eyes by POD 3 and progressed to stage 3 in 17% of the eyes.

One of the main concerns about DLK is the potential for stromal loss and a consequent hyperopic result from collagenases released by WBCs within the interface. When all patients with DLK were analyzed, the mean hyperopic deviation from the intended refractive target was clinically negligible, averaging only −0.14 D. One might expect stage 3 DLK patients to have a worse prognosis when analyzed separately since there is a more concentrated accumulation of inflammatory cells within the central interface. However, the mean variation from the intended refractive outcome in the 7 eyes with stage 3 DLK demonstrated a mean undercorrection of −0.10 D.

No patient in this study developed permanent loss of corneal clarity, and none lost BSCVA. This was accomplished with a combination of topical and oral steroids in all eyes progressing to stage 3 DLK and in the eyes threatening to progress to stage 3; ie, those presenting with significant stage 2 DLK on POD 1. No eye was treated with interface irrigation, suggesting that excellent outcomes may be achieved using combination therapy without the need for flap lifting in eyes progressing to stage 3 DLK. This is further supported by the fact that in 2 of the 7 stage 3 eyes, the BSCVA deteriorated to 20/50 and recovered fully without loss of BSCVA or a hyperopic deviation.

It is important, however, to consider that this study is a retrospective review of only 1000 LASIK cases. Linebarger and coauthors[17] report an incidence of stage 4 DLK of 1:5000. Thus, a larger review may be required to truly establish that a combination of high-dose oral and topical steroids begun promptly can reduce or eliminate serious ocular morbidity and the occurrence of stage 4 DLK.

References

1. Smith RJ, Maloney RK. Diffuse lamellar keratitis; a new syndrome in lamellar refractive surgery. Ophthalmology 1998; 105:1721–1726
2. Weisenthal RW. Diffuse lamellar keratitis induced by trauma 6 months after laser in situ keratomileusis. J Refract Surg 2000; 16:749–751
3. Schwartz GS, Park DH, Schloff S, Lane SS. Traumatic flap displacement and subsequent diffuse lamellar keratitis after laser in situ keratomileusis. J Cataract Refract Surg 2001; 27:781–783
4. Haw WW, Manche EE. Late onset diffuse lamellar keratitis associated with an epithelial defect in six eyes. J Refract Surg 2000; 16:744–748
5. Shah MN, Misra M, Wilhelmus KR, Koch DD. Diffuse lamellar keratitis associated with epithelial defects after laser in situ keratomileusis. J Cataract Refract Surg 2000; 26:1312–1318
6. Yavitz EQ. Diffuse lamellar keratitis caused by mechanical disruption of epithelium 60 days after LASIK [letter]. J Refract Surg 2001; 17:621
7. Chang-Godinich A, Steinert RF, Wu HK. Late occurrence of diffuse lamellar keratitis after laser in situ keratomileusis. Arch Ophthalmol 2001; 119:1074–1076
8. Yeoh J, Moshegov CN. Delayed diffuse lamellar keratitis after laser in situ keratomileusis. Clin Exp Ophthalmol 2001; 29:435–437
9. Harrison DA, Periman LM. Diffuse lamellar keratitis associated with recurrent corneal erosions after laser in situ keratomileusis. J Refract Surg 2001; 17:463–465
10. Keszei VA. Diffuse lamellar keratitis associated with iritis 10 months after laser in situ keratomileusis. J Cataract Refract Surg 2001; 27:1126–1127
11. Fogla R, Rao SK, Padmanabhan P. Diffuse lamellar keratitis: are meibomian secretions responsible? [letter] J Cataract Refract Surg 2001; 27:493–495
12. MacRae S, Macaluso DC, Rich LF. Sterile interface keratitis associated with micropannus hemorrhage after laser in situ keratomileusis. J Cataract Refract Surg 1999; 25: 1679–1681
13. Kaufman SC, Maitchouk DY, Chiou AGY, Beuerman RW. Interface inflammation after laser in situ keratomileusis; sands of the Sahara syndrome. J Cataract Refract Surg 1998; 24:1589–1593
14. Holland SP, Mathias RG, Morck DW, et al. Diffuse lamellar keratitis related to endotoxins released from sterilizer reservoir biofilms. Ophthalmology 2000; 107:1227–1233; discussion by EJ Holland, 1233–1234
15. Peters NT, Iskander NG, Penno EEA, et al. Diffuse lamellar keratitis: isolation of endotoxin and demonstration of the inflammatory potential in a rabbit laser in situ keratomileusis model. J Cataract Refract Surg 2001; 27: 917–923
16. Johnson JD, Harissi-Dagher M, Pineda R, et al. Diffuse lamellar keratitis: incidence, associations, outcomes, and a new classification system. J Cataract Refract Surg 2001; 27:1560–1566
17. Linebarger EJ, Hardten DR, Lindstrom RL. Diffuse lamellar keratitis: diagnosis and management. J Cataract Refract Surg 2000; 26:1072–1077
18. Steinert RF, Swami AU. Diffuse interface keratitis. Rev Ophthalmol 2001; 8(suppl to Jan):46–52
19. Macaluso DC, Rich LF, MacRae S. Sterile interface keratitis after laser in situ keratomileusis: three episodes in

one patient with concomitant contact dermatitis of the eyelids. J Refract Surg 1999; 15:679–682
20. Parolini B, Marcon G, Panozzo GA. Central necrotic lamellar inflammation after laser in situ keratomileusis. J Refract Surg 2001; 17:110–112
21. Schneider DM, Khanna R. Interface keratitis-induced stromal thinning: an early postoperative complication of laser in situ keratomileusis. J Cataract Refract Surg 1998; 24:1277–1279
22. MacRae SM, Rich LF, Macaluso DC. Treatment of interface keratitis with oral corticosteroids. J Cataract Refract Surg 2002; 28:454–461