Rapid Response of Refractory Ocular Surface Dysplasia to Combination Treatment With Topical All-trans Retinoic Acid and Interferon Alfa-2b

Topical treatments of ocular surface dysplasia are attractive because these conditions tend to recur.1-3 Traditional surgical procedures such as excision and cryotherapy are destructive and can have long-term consequences, particularly with limbal involvement.2,3 Interferon alfa-2b is a well-tolerated and generally efficacious topical therapy option for ocular surface dysplasia.1-3 The combination of interferon with retinoic acid may be a useful alternative for treating interferon-unresponsive lesions.

Report of a Case. A 64-year-old woman had a history of long-term exposure to sunlight. On examination, a keratinized lesion at her left temporal limbus was noted, extending from the 3-o’clock position to the 5-o’clock position and measuring 3.5 x 2.0 mm. Best-corrected visual acuity was 6/5 OU.

A clinical diagnosis of limbal dysplasia was made and treatment was commenced with topical all-trans retinoic acid (ATRA), 0.01%, 1 eyedrop applied every second day. The lesion grew slowly and the patient was reassessed after 9 months of treatment with topical ATRA. The clinical diagnosis was confirmed (Figure, A) and the patient was treated with 2 intralesional injections of $3 \times 10^6$ IU of recombinant interferon alfa-2b (Schering Plough, Kenilworth, New Jersey) in 0.5 mL, 2 months apart, followed by topical interferon alfa-2b ($1 \times 10^6$ IU/mL) 4 times a day.

Three months later, the lesion appeared larger despite continuous use of topical interferon alfa-2b. The patient was reluctant to undergo surgery, and it was decided to continue with combined topical interferon alfa-2b ($1 \times 10^6$ IU/mL 4 times a day) and ATRA, 0.01% (1 eyedrop applied every second day). After 1 month of combination treatment, the lesion had totally resolved (Figure, B). Furthermore, limbal architecture had returned to normal in the previously affected area.

Combination treatment was continued for a further 1 month, with no lesion visible. Unfortunately, the lesion had returned on follow-up 3 months later, so the patient elected to undergo surgery. A wide excision specimen was sent for histopathologic analysis. This demonstrated a partial-thickness lesion positive for cornea and conjunctiva intraepithelial neoplasia with no evidence of invasive squamous cell carcinoma. The patient has remained disease free for longer than 2 years.

Figure. A dysplastic lesion was noted at the left temporal limbus at the initial visit (A), and the limbal lesion had resolved 1 month following combined treatment with topical interferon and retinoic acid (B).
Comment. Topical interferon was first described by Maskin1 in 1994 as being effective in the treatment of ocular neoplasia. A limited number of cases in the literature also show the cytostatic effect of ATRA on ocular surface dysplasia.4

Our early experience with topical ATRA alone was consistent with early reports of effectiveness, with no response occurring in certain patients. Our early experience with topical interferon alfa-2b demonstrated a more consistent clinical response, and recent studies have documented an 80% treatment efficacy using topical interferon alfa-2b.2 Mitomycin C and fluorouracil are alternative topical therapies for ocular surface dysplasia. However, interferon has fewer ocular adverse effects compared with these topical chemotherapeutic agents.2 Retinoic acid is known to irritate the conjunctiva in higher doses.4

In our patient, neither ATRA nor interferon alfa-2b alone was effective in slowing growth of the ocular lesion. Longer treatment with interferon alfa-2b may have led to a better response. The rapid clinical response to the combined therapy with topical interferon alfa-2b and ATRA seems remarkable. However, previous studies have described the synergistic effects of interferon alfa-2b and ATRA in combination, both in vitro and in vivo. These same studies, although not of an eye or eye model, reported that ATRA can permit growth inhibition by interferons in interferon-unresponsive cells.3

Prospective studies with more patients and longer follow-up are needed to confirm the treatment efficacy and safety profile of this combination therapy as a well- tolerated alternative to topical mitomycin C and fluorouracil. Appropriative further studies may reveal a benefit for both dysplastic and neoplastic lesions.

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Financial Disclosure: None reported.


Methods. This study was approved by the Institutional Review Board of Kyoto Prefectural University of Medicine, Kyoto, Japan. For reverse transcription–polymerase chain reaction assay, we obtained human conjunctival epithelial cells from healthy volunteers by brush cytology using previously described methods. The primers were (forward) 5’-TCA ACC ATG CCT ATT TCT ACA GCC ACT ACG-3’ and (reverse) 5’-AGG TCT CTA ATA TCT CAA CAA AAG TCC CTA GTG-3’ for human PTGER4 and (forward) 5’-CCA TCA CCA TCT TCC AGG AG-3’ and (reverse) 5’-CCT GCT TCA CCA CCT GTG-3’ for human GAPDH. For immunohistochemistry, we used nearly normal bulbar conjunctival tissues obtained during surgery for conjunctivochalasis as a control, and human conjunctival tissues were also prepared from samples obtained during surgery to reconstruct the ocular surface such as treatment for various ocular surface diseases including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), ocular cicatricial pemphigoid (OCP), and pterygium. For EP4 staining, we used the rabbit polyclonal antibody to EP4 (Cayman Chemical Co, Ann Arbor, Michigan).

Results. The presence of PTGER4 messenger RNA and EP4 protein in human conjunctival epithelium was examined by reverse transcription–polymerase chain reaction and immunohistological analysis, respectively. The PTGER4 messenger RNA was detected in normal human conjunctival epithelium (Figure, A). The sequences obtained from these polymerase chain reaction products were identical to the human PTGER4 complementary DNA sequence. The EP4 protein was also detected in the nearly normal conjunctival epithelium obtained from the patients with conjunctivochalasis (Figure, B). Next, we examined the conjunctival tissues with various ocular surface diseases. The EP4 protein was detected in conjunctival epithelium from patients with pterygium as well as in the conjunctival epithelium from...