Atopy, dry eye provide prime environment for development of corneal ulceration

Cheryl Guttman
in Vienna

Atopy and dry eye provide the prime environment for development of corneal ulceration. Management of this problem requires a careful differential diagnosis between sterile and infectious processes, said Mark J. Mannis, MD, at the Joint Congress of the European Society of Ophthalmology and American Academy of Ophthalmology.

“Both dry eye and atopy are associated with ocular surface and immune dysfunction and can lead to the development of corneal ulcers via mechanical or immune-mediated mechanisms. Clinicians face the task of accurately diagnosing the type of ulcer so they can provide appropriate treatment. However, they also need to manage the underlying features that predispose to ulcer development,” said Dr Mannis, chair, department of ophthalmology and vision science, University of California Davis, Sacramento, California.

Explaining the mechanisms underlying corneal ulcer development in dry eye, Dr Mannis noted that the normal tear film protects the ocular surface by providing a mechanical barrier, volumetric flushing, nutrition, and immune support.

“The tear film is a wonderful soup of proteins, lipids, immunoglobulins, cytokines, growth factors, and electrolytes. However, in dry eye, there is a shift to hyperosmolarity, altered cytokine content, decreased soluble mucin, activated proteases and decreased content of proteins and the normal immune components of the tear film,” he said.

This imbalance leads to deficiencies in tear production and secretory IgA accompanied by overgrowth of Staphylococcus aureus on the ocular surface, increased lipase production, and dysfunctional meibomian gland secretions that cause loss of surface integrity and ultimately corneal ulceration.

“Published studies highlight the risk of sterile ulceration in dry eye. In one review of 109 eyes of 56 patients with keratoconjunctivitis sicca (KCS), Hemady et al reported a statistically significant association between the presence of sterile corneal ulceration and an underlying disease state, especially rheumatoid arthritis. Another study from France of 134 patients with KCS seen over a six-year period provided corroborating results about the high risk of sterile corneal ulceration in dry eye, but also reported a significant proportion of patients manifested with bacterial keratitis,” Dr Mannis said.

Patients with atopic disease are also at increased risk for developing bacterial and sterile corneal ulcers, in part because dry eye is a common comorbidity in atopy patients. However, several other factors also play a role. Where in nonatopic, healthy individuals, there is a five per cent to 10 per cent rate of S. aureus colonisation on the ocular surface, that rate increases to between 40 per cent and 90 per cent in atopic individuals.

The suspected cause of this difference is that atopic patients have fewer protective skin fatty acids and more scars from ubiquitous scratching that facilitate bacterial adherence. Further favouring S. aureus colonisation is the presence of an immune imbalance characterised by increased interleukin-4 (IL-4) and decreased interferon on the ocular surface along with fewer T cells, abnormal T cell subpopulations, fewer natural killer cells, deficiencies in secretory IgA, and impaired monocyte and granulocyte chemotaxis, antibody-dependent cytotoxicity, and IL-1 production.

“The presence of an excessive eosinophil response, fibroblast and goblet cell damage, conjunctival squamous cell metaplasia, decreased mucin production, and poor ocular surface hydration in the presence of allergic conjunctivitis further increase the risk of infection and ulceration by creating a dysfunctional barrier,” Dr Mannis said.

In patients with viral keratoconjunctivitis (VKC), corneal involvement is common. While that usually presents as superficial punctate keratitis, the disrupted areas can coalesce to produce corneal ulceration leading to the development of a classic shield ulcer usually on the superior cornea.

“Differentiating these ulcers from superinfection can be problematic as the atopy patients are susceptible to both entities,” Dr Mannis said.

Treatment of the shield ulcer is multimodal and involves controlling the underlying inflammatory disease with antihistamines, decongestants, nonsteroidal anti-inflammatory agents, aspirin, corticosteroids and cyclosporine A.

“In selecting topical agents, it is important to avoid suspension formulations since they can worsen ulceration by working like grinding stones in a mill under the large tarsal papillae present in eyes with VKC. Supratarsal steroid injection, first introduced about a decade ago, has shown itself to be very useful in the management of shield ulcers,” Dr Mannis said.

These patients also need to be monitored closely for response. Excision or ablation of the tarsal papillae and patching may be necessary, along with tarsorrhaphy and antibiotic prophylaxis.

Björn O Bachmann

Animal model suggests activity of early VEGF Trap treatment for enabling corneal graft survival

Cheryl Guttman
in Fort Lauderdale, Florida

TRANSENT blockade of VEGF-A activity by VEGF Trap (Regeneron Pharmaceuticals, Inc.) treatment immediately following penetrating keratoplasty significantly improves graft survival, according to the results of a preclinical study presented at the annual meeting of the Association for Research in Vision and Ophthalmology.

Björn O Bachmann, MD, departments of ophthalmology and anatomy, University of Erlangen-Nuremberg, Germany, and colleagues assessed the effect of neutralising VEGF-A on postoperative revascularisation and keratoplasty outcomes in a mouse model of “low high-risk eyes”.

First, an inflammatory stimulus was created by placement of three interrupted 11-0 sutures in the corneal stroma. The sutures were left undisturbed for six weeks and then removed. Six months later, penetrating keratoplasty was performed using donor tissue from C57BL/6 mice. The animals were randomised to treatment via intraperitoneal injection with VEGF Trap 25 mg/kg or control (Fc protein). Injections were administered on the day of surgery and on postoperative days four, seven, and 14.

The animals were followed for graft survival over the next eight weeks. At the termination of the study, the corneas were processed for histomorphometric evaluation of corneal revascularisation using immunohistochemical markers to identify lymphatic and blood vessels.

The results showed that by two weeks, only 10 per cent of grafts were still surviving in the control group compared with a 75 per cent survival rate among the VEGF Trap-treated animals. At week eight, the graft survival rates in the control and treated groups were 10 per cent and 50 per cent, respectively (P < 0.05).

Despite the survival benefit associated with VEGF Trap treatment, there was no difference between the treated and control eyes with respect to vascularisation by blood and lymphatic vessels at the end of the study. There was also no difference in the extent of vascularisation when eyes were grouped based on whether the graft survived or not.

“We are hypothesising that anti-VEGF treatment after keratoplasty may have a benefit for limiting the early growth of vessels that might interfere with tolerance and ultimately graft survival. Presumably, delaying the time until the graft becomes connected with the vascular system affords a window of opportunity for tolerogenic mechanisms to become established,” said Dr Bachmann.

He noted that their assessment of vascularisation at eight weeks post-keratoplasty might have been too late to observe an effect of VEGF Trap treatment.

Earlier work showed that transient treatment with VEGF Trap suppressed angiogenesis for at least a week after normal-risk corneal transplantation (Cursiefen et al, IOVS, 45, 266, 2004). The researchers are now planning to repeat the study but with earlier assessment of vessel growth post-keratoplasty to investigate that hypothesis.

An initial study demonstrated that temporary placement of sutures in the corneal stroma induced an inflammatory response with pathological corneal hem and lymphangiogenesis, but that the vessels regressed over time. In that study, the sutures were left for two weeks before being removed and histomorphometric analysis for revascularisation was performed in groups of animals at one, two, three, four, six, and eight months after suture removal. The results showed that growth of lymphatic vessels regressed earlier and to a greater extent compared with blood vessels. However, by six months after suture removal, no lymphatic vessels were observed while there were only some partially perfused and “ghost” (nonperfused) blood vessels.

These findings established that the experimental methods used in the study of graft survival enabled a model of “low high-risk eyes,” Dr Bachmann explained.

bjorncbachmann@augen.imed.uni-erlangen.de