Novel treatment (new drug/intervention; established drug/procedure in new situation)

Topical dobesilate eye drops for ophthalmic primary pterygium

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Summary

Selective inhibition of fibroblast growth factor and vascular endothelial growth factor signalling pathways is effective in causing regression of pterygia. Prompt regression of fibrovascular mass and conjunctival angiogenesis was documented 2 weeks after topical administration of dobesilate eye drops twice daily. At 3-month follow-up, no recurrence was seen and no ocular irritation and burning were noted. The authors believe that this is the first known successful use of topical dobesilate in primary pterygium.

CASE PRESENTATION

A 53-year-old man presented with primary pterygium in the nasal side of his left eye. This study was performed with patient consent after the Ethical Committee approval of our Institution. Pterigium was visualised at baseline and after treatment by slit-lamp biomicroscopy. The patient was given a sterile eye drops bottle containing potassium dobesilate (25 mg/ml). Dobesilate was applied in an artificial tear solution (Dacrolux, M4 Pharma SL Barcelona, Spain). Vessels from the conjunctiva crossed from the limbus towards the cornea. The head of pterygium depicted Fuch's islets (figure 1A). These cell clusters were described by Ernst Fuchs more than a century ago.¹ These clusters could be visualised by slit-lamp examination,² and the presence of these patches may indicate an invasive pterygium behaviour.² After self administration of two drops of dobesilate twice a day for 2 weeks, prominent decreased limbal-conjunctival neovascularisation was achieved parallel with regression of the fibrovascular mass. No vessels were observed at the same eye area after dobesilate

treatment (figure 1B). At 2 months follow-up, no recurrent pterygium was noted. Patient's symptoms resolved without ocular irritation or burning.

OUTCOME AND FOLLOW-UP

Two weeks of treatment decreased conjunctival neovascularisation and regression of fibrosis in pterygium.

DISCUSSION

Pterygium is a common ocular surface lesion thought to originate from limbal stem cells altered by chronic ultraviolet (UV)-B exposure that can sometimes extend and encroach upon the papillary axis and cause vision loss. Recently, it has been postulated that ophthalmic pterygium is a stem cell disorder with premalignant features.² It is histologically characterised by tissue remodelling, cellular proliferation, angiogenesis, inflammation and fibrosis. Despite various surgical approaches for pterygia treatment, recurrence remains the major postoperative problem. Medical approaches to prevent recurrence of surgically excised

Figure 1 Anterior segment slit-lamp photograph of the patient demonstrating pterygium on the nasal side of the left eye at time of presentation (A) (note the intense neovascularisation and presence of Fuch's islets (asterisks)) and after 2 weeks of treatment with dobesilate (B).

pterygium include adjunct therapy with β radiation, thiopeta, mitomycin C, 5-fluorouracil and corticosteroids.³ The value of such therapy, however, is limited because of potential ocular side effects, including superficial punctate keratitis, poor epithelial healing, scleral ulceration, bacterial infection and increased intraocular pressure.

It has been reported that UV-B exposure induces, in pterygium epithelial cells, the synthesis of a wealth of cytokines and growth factors that have been proposed to be implicated with earlier pterygia formation.^{4–5} Several studies have shown that the increased levels of two of these growth factors, fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), indeed correlate with the formation and recurrence of pterygia.^{6–8} The overexpression of these two proteins in pterygium tissue prompted us to develop new therapeutic strategy based in the inhibition of their activities.^{9–11} FGFs are potent, broad-spectrum mitogens, which induce endothelial cell mitogenesis and promote angiogenesis.¹² In addition, FGF can induce the release of inflammatory mediators by endothelial cells, and the expression of adhesion molecules at their surface, thereby favouring migration of inflammatory cells such as neutrophils.¹³ Furthermore, FGF is a well-known fibrotic growth factor.¹⁴ Thus, targeted blockage of FGF/FGFR signal pathways seems a correct approach to treat diseases with the features of pterygia. Dobesilate is the active principle of Doxium an old drug of quite poor therapeutic applications, but of very save profile.¹⁵ Dobesilate is a quite unstable chemical, clearly not too appropriate for both oral administration and systemic transportation to its biological targets. These findings could explain the inefficacy of dobesilate when orally administered in diabetic patients.¹⁵ Nevertheless, quite recently dobesilate has been characterised as a potent inhibitor of FGF and its plasmalemmal receptor.¹⁶ In addition, being FGF a necessary mediator of VEGF activity, dobesilate also inhibits this last signalling system, as it has been also recently reported.¹⁷

We present a case of primary pterygium that displays prominent fibrovascular mass with a high count of microvessels that was treated with dobesilate. The treatment decreased limbal-conjunctival vascularisation as well as induces the regression of fibrovascular mass. Currently, data on antiangiogenic treatments of pterygia using bevacizumab (Avastin) does not seem conclusive.^{10–11} In addition, this treatment only achieves neovessels regression without any apparent reduction of fibrotic pterygium mass, and furthermore is expensive and requires repeated injections, conferring therefore ocular risks. Obviously, the actual clinical value against primary and recurrent pterygia of the dobesilate treatment described here needs to be further investigated in a prospective randomised clinical trial with a longer follow-up.

Learning points

- Ophthalmic pterygium is a stem cell disorder with premalignant features.
- FGF and VEGF are implicated in pterygium pathology.
- Dobesilate inhibits FGF and VEGF activities.
- Topical dobesilate promotes angiogenesis and fibrotic inhibition in pterygium mass.

Competing interests None.

Patient consent Obtained.

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Cuevas P, Outeiriño LA, Angulo J, Giménez-Gallego G. Topical dobesilate eye drops for ophthalmic primary pterygium. *BMJ Case Reports* 2012; 10.1136/bcr.12.2011.5449, Published XXX

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