PTERYGIA
Anti-angiogenic therapy supported by scientific rationale, but not by trial results
by Cheryl Guttman Krader in Milan

Although VEGF inhibition appears to be an attractive therapeutic target for preventing pterygium recurrence, randomised controlled trials investigating anti-VEGF treatment have produced disappointing results, said José L Güell MD.

Speaking at the 3rd EuCornea Congress during a symposium on cornea neovascularisation, Dr Güell noted that recurrent pterygia tend to have a more exuberant fibrovascular growth response than primary lesions and are much more difficult to handle surgically. Therefore, various strategies have been suggested for use at the time of pterygia excision or postoperatively as a means to prevent lesion recurrence. These modalities include anti-mitotic agents (5-fluorouracil or mitomycin-C), corticosteroids and beta-irradiation.

However, when used alone or in combination, none of these approaches has proven to be completely effective and each is accompanied by safety concerns. Therefore, the search for alternatives continues.

Interest in anti-VEGF therapy relates to evidence that angiogenesis plays a role in pterygium development and growth. In addition, researchers analysing pterygium tissue found elevated expression of a variety of proangiogenic factors along with decreased expression of various angiogenic inhibitors.

“We know that pterygium is a proliferative invasive conjunctival lesion characterised by chronic inflammation and angiogenesis with resultant connective tissue remodelling. Among the chemical mediators stimulating angiogenesis, VEGF appears to be the most important. Therefore, it was postulated some years ago that suppressing neovascularisation with anti-VEGF therapy might prevent pterygium recurrence or retard its progression,” said Dr Güell, professor of ophthalmology, Universidad Autonoma de Barcelona, and director, cornea and refractive surgery unit, Instituto de Microcirugia Ocular de Barcelona, Spain.

“Based on published reports describing use of topical or subconjunctival bevacizumab (Avastin, Genentech), anti-VEGF treatment appears to be safe. However, in controlled studies, any favourable effect of the anti-VEGF therapy for limiting conjunctival neovascularisation in impending pterygia was incomplete and temporary. Furthermore, the data show no advantage of treatment with bevacizumab for lessening symptoms of irritation, recurrence rate, or the thickness and size of recurrent lesions.”

Aside from his own personal experience, in reviewing the literature through the period ending July 2012, Dr Güell identified 12 articles reporting on the use of local anti-VEGF therapy with bevacizumab (Avastin, Genentech) as treatment for primary pterygium or to treat or prevent recurrence. The first five papers published on this topic were single case reports or small case series including no more than five eyes, and the treatment outcomes were mixed. Subsequently, five randomised, controlled clinical trials evaluating local bevacizumab were published along with two larger interventional series.

The randomised controlled studies included between 30 and 80 eyes. Bevacizumab was applied topically twice daily for one week in one study of patients with impending recurrent pterygium. The other studies investigated subconjunctival bevacizumab in doses ranging from 1.25 to 3.75 mg for the treatment of impending recurrent pterygium, primary pterygium treatment or to prevent recurrence after primary pterygium excision. However, none of the randomised controlled studies demonstrated any conclusive evidence of a significant benefit of bevacizumab.

“Favourable results were reported in two other papers, but both were uncontrolled studies and in one that investigated subconjunctival bevacizumab for advanced primary pterygium, patients received multiple injections,” Dr Güell said.

Why the failure? Dr Güell reviewed several possible reasons that might account for the lack of efficacy of anti-VEGF therapy in pterygium management and noted that the full explanation might be multifactorial. One factor to consider is that even though angiogenesis plays an important pathophysiological role in pterygium development and progression, VEGF inhibition by itself may be insufficient to stop neovascularisation in a milieu containing other proangiogenic growth factors and cytokines.

“Perhaps future research might find that the combination of an anti-VEGF agent with angiogenic inhibitors targeting other stimulators might be effective,” he said.

The fact that vascularisation in pterygia is a mixture of old and new vessels might also explain the lack of a better response to anti-VEGF therapy, recognising that mature vessels are less sensitive to the anti-angiogenic activity of VEGF inhibition. In addition, because the aetiology of recurrent pterygia is multifactorial, treatment aimed at only the vascular component may be ineffective. Furthermore, there may be unrecognised differences in the pathogenesis of primary and recurrent pterygia, Dr Güell said.

There is an obvious difference in response to anti-VEGF therapy for macular disease and pterygium. Dr Güell suggested this might be related to differences in the histopathological characteristics of retinochoroidal neovascularisation. In addition, the anti-VEGF agent has a much longer half-life at the target site when it is injected into the vitreous than when it is applied topically or subconjunctivally where the drug is cleared into the systemic circulation via absorption through the conjunctival vessels, he said.

“Increasing the dose of locally applied bevacizumab could improve its bioavailability at the target site when used to treat pterygia, but would also increase the risk of side effects,” Dr Güell added.

Based on the positive experience using anti-VEGF therapy in treating neovascular macular disease and considering the multifactorial aetiology of pterygia, Dr Güell suggested that future studies might evaluate combination approaches using an anti-VEGF agent together with anti-inflammatory corticosteroid therapy. He also reminded ophthalmologists that while the role of anti-VEGF treatment in pterygia management requires further study, available evidence supports VEGF inhibition for controlling corneal neovascularisation in other clinical situations.

“Anti-VEGF therapy has been shown to be an excellent strategy in controlling corneal neovascularisation associated with lipid degeneration, infectious keratitis, after penetrating keratoplasty to prevent graft rejection, and perhaps in the treatment of some superficial carcinomas,” Dr Güell said.

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