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Is Combined Photodynamic Therapy and Subconjunctival Bevacizumab Injection Useful for Corneal Neovascularization?

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Corneal neovascularization caused by various ocular conditions such as infectious, inflammatory, degenerative, or traumatic diseases of the cornea and the injury of the limbal stem cell barrier. It is often accompanied by corneal scarring, stromal edema, lipid deposition, and inflammation and is associated with significant visual impairment and poor prognosis after subsequent penetrating keratoplasty. Conventional treatments for corneal neovascularization, including medications such as steroids or angiogenesis inhibitors, laser photocoagulation, fine needle diathermy, and surgery, have clinical limitations and adverse effects. Gene therapy is effective in experimental models of corneal neovascularization, however disadvantages such as short duration of effect, technical problems, and safety concerns limit the application in clinical fields [1,2].

Recently, both photodynamic therapy (PDT) with verteporfin and anti-vascular endothelial growth factor (VEGF) therapies have been effectively used to treat intraocular neovasularization. Although combined PDT with intravitreal anti-VEGF injection have been known to be safe and effective to inhibit chorioretinal neovascularization in many chorioretinal diseases, including age-related macular degeneration, it is unclear whether combined PDT and anti-VEGF therapies can be also useful in the treatment of corneal neovascularization [3,4].

PDT with a photosensitizer can produce microvascular thrombosis with minimal damage to surrounding normal tissue. With PDT, the generation of oxygen free radicals from the interaction of light, oxygen, and the photosensitizer induces damage to endothelial cells and thrombus formation, resulting in occlusion of neovascular vessels. Verteporfin (Visudyne; Novartis, Basel, Switzerland), a benzoporphyrin derivative monoacid ring A photosensitizer, is a commercially available photosensitizer. PDT with verteporfin has been used safely and effectively for corneal neovascularization [5,6].

Agents that block the action of VEGF can reduce angiogenesis and vascular permeability, and thereby inhibit growth of new vessels potently. Topical or subconjunctival administration of bevacizumab (Avastin; Roche, Basel, Switzerland) has been applied for the management of corneal neovascularization [7,8].

However, both therapies have several limitations. Verteporfin PDT has a risk for a rebound phenomenon which is associated with increased VEGF expression and enhanced inflammation, increasing the risk of neovascular recurrence. A large dose of laser energy or simultaneous use of steroids may induce viral recurrence in the cornea after the procedure [9]. Although anti-VEGF therapy inhibits new, fresh corneal blood vessels, it is less effective in large, existing vessels. Subconjunctival bevacizumab may not lead to complete vascular occlusion and requires several injections to induce regression. According to a previous study, subconjunctival injection of bevacizumab could partially reduce corneal neovascularization in the short term and the efficacy correlated with the injection dose [8].

Combined therapy with PDT and anti-VEGF has several advantages and can improve treatment outcomes of corneal neovascularization. PDT results in direct closure of existing corneal vessels and contributes to long-term success. The increased VEGF expression and inflammation caused by PDT can be countered by an anti-VEGF agent. Combined therapy is effective in a variety of vessels, irrespective of caliber or chronicity. Therefore, combined therapy may provide complete and persistent obstruction of corneal neovascularization, leading to reduction in neovascular recurrence and retreatment rates. Although the cost of combination therapy increased, the decreased need for retreatment is of great benefit to patients and clinicians.

In a pilot study by Yoon et al. [10], the efficacy of combined PDT with verteporfin and subconjunctival bevacizumab therapy was evaluated in patients with corneal neovascularization. During one year follow-up, vascular regression was maintained in most cases. The mean cumulative vessel length and area of neovascularization significantly decreased after treatment. Compared with previous results after verteporfin PDT or bevacizumab monotherapy, the success rate was higher without additive complication [6,8].

In conclusion, combined verteporfin PDT and subconjunctival injection of bevacizumab are safe and effective for the management of corneal neovascularization. Combined therapy can inhibit not only new, fresh, and small blood vessels but also old, stabilized, and larger vessels, thereby increasing a success rate of complete vascular occlusion.

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