Journal Reading

TREATMENTS FOR CORNEAL NEOVASCULARIZATION: A REVIEW

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Treatment—medicine

Anti-VEGF agents

- VEGF was required for inflammatory NV of the rat cornea and identified as a functional endogenous corneal angiogenic factor
- VEGF-A is known to increase migration and mitosis of endothelial cells, increase methane monooxygenase activity, and play a role in the creation of blood vessel lumen and vessel fenestrations.

Treatment

Anti-VEGF agents

- The clinical focus at the present time for CNV is in the use of antibodies to VEGF
- Clinical studies using Avastin are case reports and case series.
- The methods of application were

1. Topical (range: 5–25 mg/mL, 2–5/d)
2. Subconjunctival injection (range: 1.25 mg/0.05 mL to 5 mg/0.2 mL, single monthly injections)

- Most studies reported a partial and transient reduction in NV

Treatment

Anti-VEGF agents

- Avastin seems to be most effective for small-to-medium sized vessels that recently developed (VEGF would be actively secreted in newly forming vessels rather than established vessels)
- Less effective in treatment of established blood vessels because they may become less dependent on VEGF for survival.
- Combination treatments may be more effective. (platelet-derived growth factor B, CD-36 receptor agonists, etc.)

Treatment

Anti-VEGF agents

- Currently, many studies are small, uncontrolled, and provide little evidence.
- None of the studies reported any significant side effects, so it may be safer than corticosteroids
- However, because of the highly specific effect of anti-VEGF agents, it seems likely that in most situations, they will be used as an adjunct to steroids rather than as a replacement.

Treatment

Cyclosporine

- A high specificity for T-cell lymphocytes and inhibits cell-mediated immune response, probably inhibition of IL-2 induced CNV.
- Has a role in situations of steroid glaucoma, herpetic corneal disease, and where topical steroids need to be tapered.

Treatment

Cyclosporine

- Many published reports were in the context of experimental graft rejection, but not all reports showed an inhibition of CNV
- Corneal deposits have also been reported in clinical use
- Improved CNV in treatment of nonnecrotizing HSV stromal keratitis in 8 of 16 patients

Treatment

Experimental Gene Therapy Strategies

- Direct application of naked DNA, an electric pulse, ballistic transfer with a gene gun, non-viral vector, and replication-deficient viral vectors
- Viral vectors — concern viral toxicity and insertional mutagenesis
- Non-viral vectors — low transfection rate and relatively short life

Treatment

Experimental Gene Therapy Strategies

- Need to be resolved with gene therapy include:

1. Which of the therapeutic transgenes most effective
2. The level of transgene expression required to produce a therapeutic effect
3. The time frame over which expression will be needed.

Treatment—Laser and conventional surgical treatment

- Laser
- Photodynamic therapy (PDT)
- Superficial keratectomy
- Needle diathermy / cautery.

Treatment

Argon Laser

- Uses light-induced thermal damage to ablate vessels and is established in the treatment of retinal NV
- Hemoglobin has a very high absorption rate of argon energy and can coagulate hemoglobin-filled corneal vessels.
- Important parameters to consider not damaging the adjacent tissue when treating CNV

Treatment

Argon Laser

- The clinical application of AL has been mostly used in lipid keratopathy and penetrating keratoplasty.
- Sixty-three cases of LK were treated (settings were 50-mm aperture, 0.1-s exposure, and 0.2–0.8 W power), reduced in extent in 62% and in density in 49%; VA improved in 48%.

Treatment

Argon Laser

- In graft rejection, a series of post-PK patients with stromal CNV that were unresponsive to topical steroid.
- 8 of 13 patients had regression of CNV and reversal of rejection. Two underwent pre-PK laser treatment went on to have PK with nil rejection over the 21-month follow-up period.

Treatment

Argon Laser — problems have been reported:

- Feeding arteries of CNV are difficult to identify
- Impermanence of the occlusive effect and vessel recurrence
- Thermal destruction of vessels trigger the activation of inflammatory mediators and VEGF
- complications such as peripheral corneal hemorrhage, iris atrophy and pupillary ectasia, corneal thinning, and necrotizing scleritis
- Therefore, AL not gained widespread acceptance.

Treatment

Yellow Laser

- Described for treatment of CNV in the context of graft rejection
- Yellow laser was absorbed more by oxy-hemoglobin and reduced hemoglobin, therefore requiring less total energy.
- However, yellow laser is not routinely used clinically.

Treatment

Nd:YAG Laser

- Case series of 30 eyes using the frequency-doubled Nd:YAG (532 nm) laser for the treatment of quiet CNV (setting: 120~480MW power, 50~150 mm size, 0.05 seconds pulse duration)
- At the 3-month follow-up, 80 vessels (54.15%) were totally occluded, 14 (9%) partially occluded, 52 (35.14%) recanalized, and 2 shunt vessels appeared.
- the laser was a safe and effective means of reducing CNV in quiet eyes

Treatment

Nd:YAG Laser

- a comparative study of continuous wave Nd:YAG (1064 nm), argon and yellow lasers (570 nm), noted that the Nd:YAG required tissue necrosis to occlude the vessels, thus making it a potentially poorer choice.
- A case series: in 8 of 9 herpetic keratitis patients, CNV was markedly reduced with a resulting decrease in corneal opacity.

Treatment

Photodynamic Therapy (PDT)

- Requires 3 components: a photosensitizing compound, light, and oxygen.
- The photosensitizing compound is selectively absorbed and retained by neovascular and inflammatory tissues. The compound is activated by laser triggering the release of cytotoxic free radicals that cause tissue damage, vascular endothelial damage, and intravascular thrombosis.
- Mechanism of the PDT response may involve both apoptosis and necrosis

Treatment

Photodynamic Therapy (PDT)

- A case series of fluorescein-potentiated argon laser treatment of CNV in 15 patients demonstrated a significant reduction in corneal edema secondary to inflamed vessels.
- Dihematoporphyrin in a series of 7 patients with CNV concluded that the agent was effective in reducing NV, but significant side effects of the dye (both systemic and and local)

Treatment

Photodynamic Therapy (PDT)

- At the 12-month follow-up of verteporfin in 18 eye with established CNV, 9 were classified as have completely occluded; 5 partially occluded; 2 recanalized; and 2 were regarded as failures.
- There were no systemic or ocular complications noted with the dye
- Overall, PDT has achieved limited acceptance in the treatment of CNV because of high costs of the dyes and diode lasers, and the potential local and systemic complication.

Treatment

Superficial Keratectomy

- Superficial keratectomy is described in 2 patients of superficial CNV combined with Avastin use.
- The epithelium and superficial vessels was scraped, leaving the Bowman layer intact, and followed by an injection of Avastin into the sub-conjunctiva.
- There were no signs of recurrence at the 3-month follow-up.

Treatment

Needle Diathermy and Cautery

- Fine needle diathermy (FND) occlusion of corneal vessels involved a stainless steel 3/8 circle side-cutting, single-armed needle attached to a 10-0 nylon suture, held with microsurgical needle holder. (setting: lowest unipolar diathermy 0.5–1.0 mA)
- The needle was inserted close to the limbus and at the level of the blood vessel to be occluded
- For larger vessels, the needle was inserted into the vessel lumen.

Treatment

Needle Diathermy and Cautery

- In 3 cases, use of an electrolysis needle involves direct thermal cautery rather than electrical currents as in diathermy.
- Vessels were occluded in all patients up to 8 months, with repeat cautery required at months 9 and 10 in 2 patients.

Treatment

Needle Diathermy and Cautery

- In 14 cases of CNV due to different etiology, the graft rejection were successfully reversed; the corneal opacity due to LK stabilized, but not reverse; and the inflammation resolved in disciform keratitis.
- The technique seems to be simple, safe, and effective, but limited conclusions could be drawn because of the small number of cases.

Summary

- Key clinical indications for anti-angiogenic treatments include preventing and treating vision-threatening CNV and improving graft survival after penetrating keratoplasty
- Research in basic sciences to understanding of the angiogenic cascade to allow targeting of specific molecular pathways

Summary

- Steroids have traditionally been used of managing new vessels, but can elicit a variable clinical response and well-known side effects.
- NSAIDs are not considered clinically effective and are not used as first-line agents
- Anti-VEGF treatments in CNV need prospective multicenter clinical trials to prove the efficacy
- Gene therapy has been proven to be successful in regressing CNV and prolonging graft survival, but it is far from clear which of potential therapeutic transgenes