Clinical Issues:

Quality Use of Antifibrotics in Trabeculectomy

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Core Concepts

- Wound healing response is the most important determinant of long-term outcome for trabeculectomy
- Simple changes in surgical technique can considerably increase safety
- Current antifibrotic treatments include steroids and antimitabolites
- Antimitabolites such as 5-FU and MMC are associated with long-term failure and more effective and safer agents are required
- Improvements have occurred with anti-VEGF compounds, steroids or NSAIDs.
- Inhibitors of TGF-beta and its intermediates may be promising
- MMP inhibitors improve anti-scarring effects

Maximising outcomes with the use of anti-fibrotics in trabeculectomy

The wound healing response to surgery is the most important determinant of the long-term outcome of trabeculectomy. Wound healing is an immensely complex process that includes the activation and silencing of various mechanisms at different stages. Based on our recent understanding of these mechanisms, new anti-scarring approaches have been tried. The current treatments in the clinic include steroids and antimitabolites (5-FU and MMC) to control the scarring. However, if not used appropriately, these agents have significant risks. Simple changes in surgical technique, such as increasing the surface area of antimitabolite application and methods to control the rate and direction of aqueous flow can considerably increase the safety of surgery and are summarized in Figure 1.

Many of these measures have now been widely adopted around the world with good results. Nonetheless, antimitabolites are still associated with long-term failure and better anti-scarring agents with a higher safety profile are required.

The anti-VEGF medicines including bevacizumab have shown promise particularly when combined with 5-FU. Although the mechanism for this synergic effect is not clear, inflammation is one of the major contributors to scarring during wound healing. Anti-inflammatory drugs, either steroid or NSAID, have offered benefit for the control of scarring following surgery. Improvements have also resulted from the optimization of application protocols and new anti-inflammatory drugs.

Inhibition of the pro-fibrotic cytokines including TGF-beta has been studied extensively but with disappointing results. Different dosing, sustained release formulations, new antibodies and approaches to inhibit the TGF-beta family and its intermediates including CTGF and ALK-5 inhibitor may still be promising, as may be combinations of therapies.

The matrix metalloproteinase (MMP) family plays a key role in many stages of the wound healing from releasing sequestered cytokines in the extra cellular matrix to angiogenesis and scar formation. As a result the significance of the anti-scarring effects of MMP inhibitors such as Ilomastat to prolong experimental bleb survival has been shown to have great promise.

In summary, the use of antimitabolites has improved the success rate of glaucoma surgery, and with appropriate simple modifications to technique, complications can be greatly reduced. Many new therapeutic possibilities promise to improve long term outcomes for glaucoma surgery combined with entirely new surgical techniques, thereby lowering eye pressure safely to minimize progression for the majority of glaucoma patients.

References