REVIEW ARTICLE

Exciting directions in glaucoma

Carol A. Rasmussen, MS, Paul L. Kaufman, MD

ABSTRACT • RÉSUMÉ

Glaucoma is a complex, life-long disease that requires an individualized, multifaceted approach to treatment. Most patients will be started on topical ocular hypotensive eyedrop therapy, and over time multiple classes of drugs will be needed to control their intraocular pressure. The search for drugs with novel mechanisms of action, to treat those who do not achieve adequate intraocular pressure control with, or become refractory to, current therapeutics, is ongoing, as is the search for more efficient, targeted drug delivery methods. Gene-transfer and stem-cell applications for glaucoma therapeutics are moving forward. Advances in imaging technologies improve our understanding of glaucoma pathophysiology and enable more refined patient evaluation and monitoring, improving patient outcomes.

Le glaucome est une affection complexe et chronique qui comporte plusieurs façons d'aborder le traitement. La plupart des patients commenceront par recevoir une goutte hypotensive oculaire et auront éventuellement besoin de plusieurs classes de médicaments pour maitriser la pression intraoculaire (PIO). La recherche de médicaments ayant de nouveaux modes d'action, pour soigner ceux qui n'arrivent pas à maitriser adéquatement la PIO avec les thérapies courantes ou en deviennent réfractaires, se poursuit, de même que la recherche d'une plus grande efficacité, concernant les modes de prestation des médicaments. Le transfert des gènes et l'application des cellules souches dans les thérapies du glaucome progressent. Les progrès des technologies d'imagerie améliorent notre compréhension de la pathophysiologie du glaucome et permettent de raffiner davantage l'évaluation et le suivi des patients, améliorant leurs résultats.

New Glaucoma Drugs in the Pipeline

Targeting the trabecular meshwork

Current glaucoma therapeutics decrease intraocular pressure (IOP) by reducing aqueous humor formation or increasing outflow of fluid through the uveoscleral pathway. A novel strategy is targeting the trabecular meshwork (TM) cytoskeleton, aiming to increase fluid outflow through the TM/conventional outflow pathway.[1,2] There are several targets for this approach: (*i*) TM–cytoskeleton-actin microfilament disruption using marine macrolides such as latrunculins (Lat-A/B; Wisconsin Alumni Research Foundation, Madison, WI, USA)[3–9] (Fig. 1), swinholide A, and jasplakinolide[10] (WARF); (*ii*) protein kinase inhibition using serine-threonine kinase inhibitors such as H-7 (WARF),[11] myosin light chain kinase inhibitor ML-7[12] and rho kinase inhibitors including Y-39983/SNJ-1656/RKI-983 (Senju, Osaka, Japan/Novartis, Basel, Switzerland),[13–15] AR-12286 (Aerie, Bedminster, NJ, USA),[16,17] AR-13324 (Aerie),[18] PG324 (which is AR-13324 combined with latanoprost) (Aerie), K-115 (Kowa, Morrisville, NC, USA),[19,20] and AMA0076 (Amakem, Diepenbeek, Belgium)[21]; and (*iii*) targeting actomyosin contractility using nonmuscle caldesmon (WARF)[22,23] or focal adhesions and cell–cell adhesions with exoenzyme C3 transferase (C3) (WARF).[24] A number of these compounds are moving through clinical trials with a mechanism of action that features relaxation of the TM, expansion of juxtacanalicular spaces, dilation of Schlemm's canal (SC), and inhibition of actomyosin contractility. Although they comprise different classes, many of these compounds can be effective at increasing conventional outflow because the real target is perturbing the overall system contractility, cell–matrix/cell–cell adhesion tension, all of which constitute a regulatory system, with efferent/afferent arms, that is likely responsive to IOP differential across the TM tissue.[25–27]

Various classes of adenosine agonists may also reduce IOP by increasing trabecular outflow,[28] with several receptor subtypes (A_1, A_{2A}, and A_3) in development as glaucoma therapeutics. Selective adenosine A_1 agonist INO-8875 (Inotek, Lexington, Mass, USA) is thought to increase trabecular outflow by reducing cell volume and remodeling the extracellular matrix after secretion of matrix metalloproteinases.[29] Novel adenosine A_{2a} receptor agonist OPA-6566 (Acucela, Seattle, WA, USA and Otsuka Pharmaceuticals, Tokyo, Japan) is thought to decrease IOP in human patients by stimulating aqueous humor outflow via the TM.[30] A_{2A} receptors mediate vasodilatation, coupling through G proteins to stimulate adenylyl cyclase, and may be downregulated after chronic exposure to an agonist.[31,32] A_3/A_1 receptor agonist

From the Department of Ophthalmology & Visual Sciences, School of Medicine & Public Health, University of Wisconsin-Madison, Madison, WI, USA.

Presented in part at the Glaucoma Management Review Course, 53rd Annual Walter Wright Day, Toronto, Ont., Dec. 6-7th, 2013.

Originally received May 13, 2014. Accepted Aug. 13, 2014

Correspondence to Carol A. Rasmussen, Department of Ophthalmology & Visual Sciences, University of Wisconsin-Madison, 600 Highland Avenue, K3/401 Clinical Sciences Center, Madison, WI 53792; crasmussen@wisc.edu

Can J Ophthalmol 2014;49:534–543
0008-4182/14/$-see front matter
http://dx.doi.org/10.1016/j.jcjo.2014.08.007

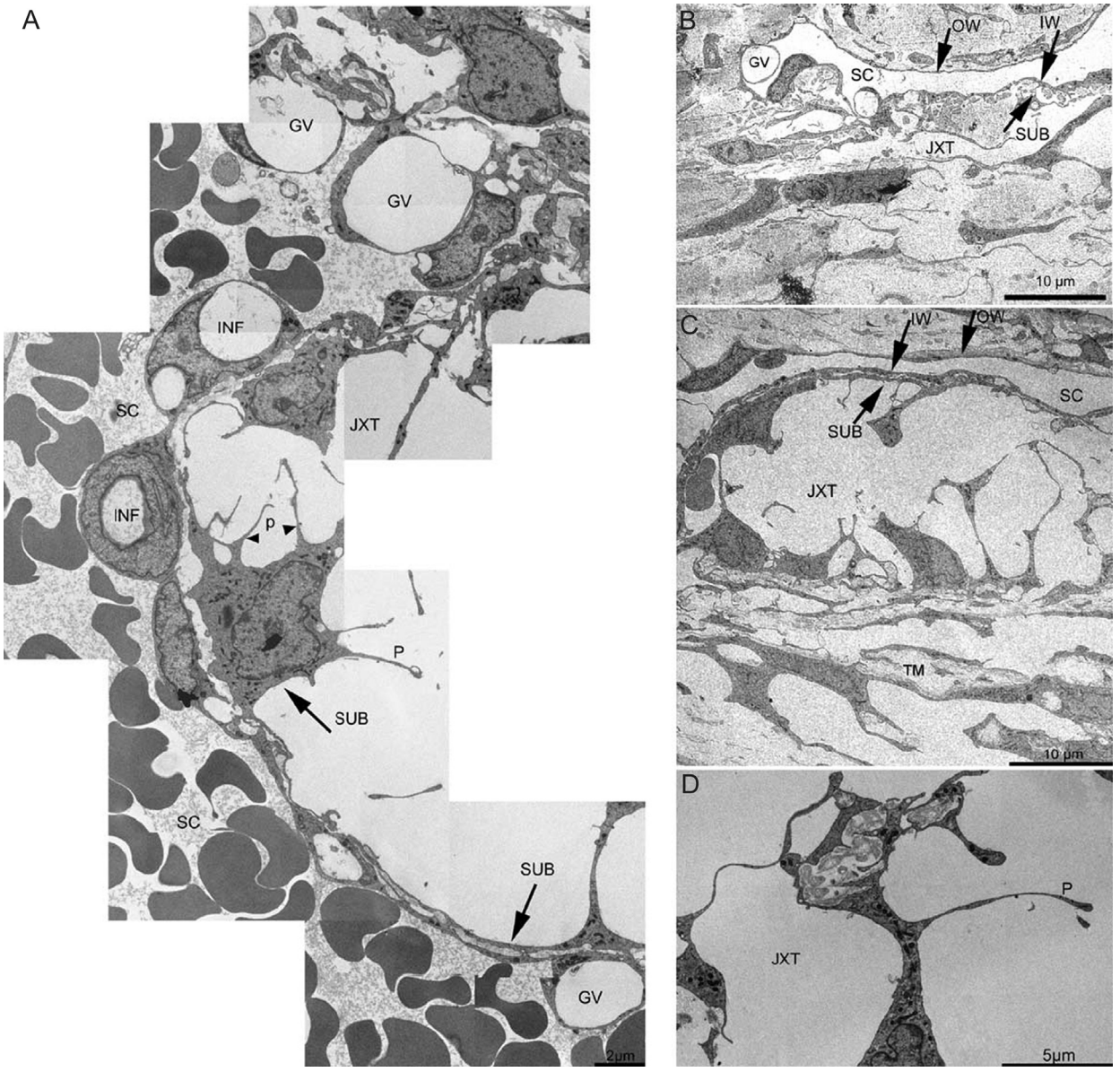

Fig. 1—Transmission electron micrograph of the trabecular meshwork (TM) after LAT-B (A, C, D) (K554) or vehicle (B) (K596). A, A long "montage" of images is shown, depicting the IW-JXT regions of the TM after LAT-B. B, Normal JXT region and its circumjacent structures. C, Indicates the massive "ballooning" of the JXT region and the retention of close contact between IW and SUB (compare with B). D, Absence of organelles from processes, irregular diameter of processes, and the entrapment of extracellular matrix deposits in intercellular spaces. GV, giant vacuoles; INF, membrane infoldings; IW, inner wall; JXT, juxtacanalicular region; OW, outer wall; P, cellular processes; SC, Schlemm's canal; SUB, subcanalicular cells. (Reprinted from Sabanay et al.,[6] by permission.)

CF-101 (Can-Fite BioPharma, Petah-Tikva, Israel) is an orally administered compound that showed IOP-lowering efficacy in a phase II clinical trial aimed at reducing symptoms of dry eye.[33] A_3 receptor agonists are thought to reduce IOP by inhibiting Cl^- channels of the non-pigmented ciliary epithelial cells at the aqueous surface of the ciliary epithelium, reducing aqueous humor production.[34–36]

Prostaglandin analogs (PGs) that target the prostaglandin E_2 receptor (EP_2) and EP_4 receptors may also increase outflow through the TM pathway. A selective prostanoid EP_4 receptor agonist (3,7-dithia PGE1) lowered IOP and increased total outflow facility in monkeys. No effect was seen on uveoscleral outflow or aqueous flow, suggesting that a substantial proportion of the ocular hypotensive activity was due to increased trabecular outflow facility.[37] Further studies with 3,7-dithia PGE using human cell cultures and a whole-eye organ perfusion system showed that human SC and TM cells do express PG-EP_4 receptors and their activation in the human conventional pathway results in a significantly increased outflow facility.[38] The prostanoid EP_2 receptor agonist butaprost is thought to decrease IOP by increasing uveoscleral outflow,[39] but other EP_2 receptor agonists (e.g., taprenepag isopropyl