HHS Public Access

Author manuscript

Mol Cell Pharmacol. Author manuscript; available in PMC 2010 March 25.

Published in final edited form as:

Mol Cell Pharmacol. 2009 January 1; 1(4): 222–227. doi:10.4255/mcpharmacol.09.27.

Novel Pharmacologic Approaches for the Management of Diabetic Retinopathy

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Abstract

Diabetic retinopathy is the leading cause of vision loss among working-age people in the United States. The hallmark of diabetic retinopathy is vascular compromise. Increased vascular permeability leads to the development of diabetic macular edema, which is the major cause of vision loss in patients with diabetic retinopathy. Vascular occlusion causes retinal ischemia and subsequent angiogenesis (proliferative diabetic retinopathy), which increases the risk for vitreous hemorrhage and retinal detachment. Over the past 30 years our understanding of the pathophysiology of diabetic retinopathy has evolved greatly and has fostered the development of many novel treatments for this condition. This article will review promising new local and systemic pharmacologic treatments for diabetic macular edema and proliferative diabetic retinopathy.

Keywords

Corticosteroid; Diabetes; Diabetic retinopathy; Macular edema; Proliferative diabetic retinopathy; Vascular endothelial growth factor

Introduction

Diabetic retinopathy is the leading cause of visual loss among working-age people in the United States (1). The prevalence of diabetic retinopathy increases with the duration and severity of diabetes (2, 3) and with the degree of hypertension and hyperlipidemia (4). The hallmark of diabetic retinopathy is vascular injury. Increased vascular permeability leads to the development of retinal hemorrhages and fluid accumulation in the macula, which is referred to as diabetic macular edema. Vascular occlusion causes retinal ischemia and subsequent angiogenesis, which defines proliferative diabetic retinopathy.

Diabetic macular edema (Figure 1) is the principal cause of visual loss in persons with diabetes (3). Thirty years ago, laser photocoagulation was demonstrated effective for limiting vision loss in patients with diabetic macular edema (5) and proliferative diabetic

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Conflicts of Interest

Stephen G. Schwartz, M.D., M.B.A. has previously received research funding from Genentech, owns equity in Pfizer, and is co-holder of a patent pending entitled “Molecular targets for modulating intraocular pressure and differentiation of steroid responders versus nonresponders.” Jaclyn L. Kovach, M.D. is a consultant for Allergan.

retinopathy (Figure 2) (6). However, some patients continue to lose vision despite intervention. Since that time, our understanding of the pathophysiology of diabetic retinopathy has evolved greatly and has fostered the development of many novel treatments for this condition. This article will review promising new local and systemic pharmacologic treatments for diabetic macular edema and proliferative diabetic retinopathy.

Local Therapies

Anti-inflammatory agents

Intravitreal triamcinolone acetonide (IVTA) has potent anti-inflammatory effects and yields short-term anatomic and visual improvements in diabetic macular edema (7-11). Given its anti-angiogenic properties, IVTA also could be a valuable adjunct to treating proliferative diabetic retinopathy (12). Branded preservative-free formulations of triamcinolone acetonide, Triesence (Alcon, Fort Worth, Texas, US) and Trivaris (Allergan, Irvine, California, US) were developed to in an effort to lessen the incidence of noninfectious endophthalmitis and other complications.

The Diabetic Retinopathy Clinical Research (DRCR) Network investigated the anatomic and visual outcomes of two doses (1mg and 4mg) of Trivaris vs. macular photocoagulation for the treatment of diabetic macular edema in a large, multicenter randomized clinical trial (RCT). After 3 years of follow-up, treatment with macular photocoagulation was associated with better vision and fewer complications. Two of the major complications of IVTA are cataract formation and ocular hypertension. In the above study, the 3 year cumulative probability of cataract surgery was 31% in the laser group, 46% in the 1mg IVTA group and 83% in the 4mg IVTA group. Among patients followed for 3 years, 4 % of the laser group, 18% of the 1mg group and 33% of the 4mg group experienced an intraocular pressure increase of greater than 10mmHg. Four patients (all in the 4mg IVTA group) required a glaucoma procedure (13). The rate of endophthalmitis in patients enrolled in the DRCRnet and SCORE (Standard care versus COrticosteroid for REtinal vein occlusion study) trials was 1/2009 injections (0.05%) (14).

Given the chronic nature of diabetic macular edema, there may be a role for sustained-release corticosteroid therapy. Several sustained-release delivery systems are currently in clinical trials. The triamcinolone-eluting intravitreal implant, I-vation (Surmodics, Inc., Eden Prairie, Minnesota, US) has been studied for the treatment of diabetic macular edema, and a Phase II clinical trial is planned. A fluocinolone acetonide intravitreal implant, Retisert (Bausch & Lomb, Rochester, New York, US) is FDA-approved for the treatment of chronic, non-infectious uveitis. A phase III clinical trial conducted in patients with DME reported high rates of cataract and glaucoma. A phase III clinical trial is underway for a smaller fluocinolone acetonide intravitreal implant, Iluvien (Alimera Sciences, Alpharetta, Georgia, United States) that can be administered in an office setting. Ozurdex (Allergan, Irvine, California, US) is an extended release biodegradable dexamethasone intravitreal implant that has recently received FDA approval in treating macular edema secondary to retinal vein occlusions. Promising results from the Phase II trial involving DME patients have led to the Phase III trial which is underway.

Nepafenac (Nevanac, Alcon, Fort Worth Texas, US) is an FDA-approved topical non-steroidal anti-inflammatory drug that has demonstrated efficacy against DME in one case report (15).

Etanercept (Enbrel, Amgen, Inc., Thousand Oaks, California, US and Wyeth, Madison, New Jersey, US) is a recombinant fusion protein with activity against TNF-α and is FDA-approved for the treatment of psoriasis (16). A small series of patients with refractory DME were treated with intravitreal etanercept with no statistically significant improvement (17). Infliximab (Remicade, Centocor, Horsham, PA, US) is another TNF-α antagonist that is FDA-approved to treat Crohn's disease. An investigation of systemic treatment of DME with infliximab (18) has led a study of administration via intravitreal injection.

Anti-Vascular Endothelial Growth Factor (VEGF) agents

Bevacizumab (Avastin, Genentech, Inc., South San Francisco, California US) is a full-length recombinant humanized antibody against VEGF-A and is an FDA-approved systemic treatment for metastatic colon cancer. Several prospective RCTs of intravitreal bevacizumab have demonstrated favorable anatomic and visual outcomes in patients with DME, including a Phase II clinical trial from the DRCR network (19-21). In two small, comparative trials, intravitreal triamcinolone was associated with better efficacy and longer duration of action in the treatment of DME than was bevacizumab (22, 23). Avery et al (2006) reported regression/resolution of iris and retinal neovascularization following intravitreal Avastin. However, recurrence of neovascularization was noticed as early as two weeks after treatment, which is its major shortcoming when compared to panretinal photocoagulation (24). Bevacizumab is gaining popularity as a clinical adjunct to panretinal photocoagulation in certain patients with PDR (25). Of note, patients have reportedly experienced traction retinal detachments following treatment with bevacizumab for PDR (26).

Ranibizumab (Lucentis, Genentech, Inc., South San Francisco, California US) is a recombinant humanized antibody fragment against VEGF-A and is FDA-approved for the treatment of exudative age-related macular degeneration (27, 28). Ranibizumab demonstrates some efficacy in the treatment of DME (29). The READ-1 study was a prospective, nonrandomized case series of 10 patients with chronic DME who were treated with ranibizumab at baseline and months 1, 2, 4, and 6. An improvement in visual acuity and mean foveal thickness was noted at month 7 (30). A larger phase II trial is currently underway (READ-2) that will compare laser photocoagulation and a combination of ranibizumab plus laser for DME. RESOLVE is a randomized double-masked, multicenter, phase II study that will assess the safety and efficacy of two concentrations of intravitreal ranibizumab compared with nontreatment control for the treatment of center-involving DME. Phase III trials (RISE and RIDE) will compare intravitreal ranibizumab to laser photocoagulation for DME. The DRCR network has several studies in progress that investigate the role of ranibizumab in the treatment of diabetic retinopathy, including IVTA vs. ranibizumab as an adjunct to panretinal photocoagulation for PDR and ranibizumab vs. IVTA in combination with laser for DME.

Anti-VEGF agents, like bevacizumab and ranibizumab, are appealing alternative treatments given their lower risks of intraocular pressure elevation and cataract formation when

compared to intravitreal corticosteroids. The cumulative rates of endophthalmitis in the major ranibizumab trials, where scheduled dosing was monthly for two years, was 5/477 (1.0%) (27) and 2/277 (0.7%) (28) per eye over the course of the studies. The per-injection rates of endophthalmitis were much lower, about 0.05% per injection.

VEGF Trap-Eye (Regeneron, Tarrytown, New York, US) is a potential treatment for diabetic retinopathy that has demonstrated anti-VEGF activity (Regeneron, Tarrytown, New York, US). VEGF Trap-Eye is a recombinant fusion protein active against VEGF-A and placental growth factor. Results from the phase I trial show short-term efficacy for the treatment of DME (31).

Sirolimus, also known as rapamycin (Rapamune, Wyeth, Madison, New Jersey, US) is a macrolide with immunosuppressive and anti-VEGF activity. Systemic rapamycin has been shown to inhibit choroidal neovascularization in mice (32). A National Eye Institute sponsored pilot trial of intravitreal sirolimus is currently recruiting patients (http://clinicalstudies.info.nih.gov/detail/A_2008-EI-0175.html).

Vitreolytic agents

Intravitreal purified ovine hyaluronidase (Vitrase, ISTA Pharmaceuticals, Irvine, California, US) has shown efficacy and safety in a Phase III clinical trial to investigate its promotion of the clearance of vitreous hemorrhage from PDR, (33,34) although the agent is not FDA-approved for this purpose. The induction of a posterior vitreous detachment also could be beneficial in the treatment of DME and PDR (35). A multicenter study to compare multiple doses of intravitreal microplasmin versus sham injection for treatment of patients with DME (MIVI-II) is currently underway.

Systemic Therapies

Ruboxistaurin

Ruboxistaurin (Arxxant, Eli Lilly and Company, Indianapolis, Indiana, US) is an oral antagonist of the beta subunit of protein kinase C which may be important in the pathogenesis of diabetic retinopathy (36, 37). Therapy with ruboxistaurin is associated with a reduction in the progression of DME and a reduction in the rate of vision loss in patients with DME, (38, 39) although ruboxistaurin has not received FDA approval.

Fenofibrate

Fenofibrate is most commonly used as a treatment for hyperlipidemia. Patients treated with fenofibrate have been shown to require less photocoagulation for PDR and DME (40). This result was unrelated to serum lipid levels, which were statistically similar in both the group treated with fenofibrate and the control group (41).

Somatostatin analogues

Somatostatin is an endogenous growth hormone inhibitor with anti-angiogeneic properties. The somatostatin analogue octreotide (Sandostatin, Novartis, Basel, Switzerland) has been associated with decreased rates of progression to high-risk PDR, (42) vitreous hemorrhage

and the need for vitrectomy (43) in patients with at least severe nonproliferative diabetic retinopathy (NPDR).

Conclusion

Laser photocoagulation partnered with improved glycemic, blood pressure, and cholesterol control are the standard treatments for diabetic retinopathy. However, diabetic macular edema can be chronic and refractory to standard treatments. Vitreous hemorrhage, dense cataract, and neovascular glaucoma may prevent timely laser treatment of proliferative diabetic retinopathy. For these reasons, alternative and adjunctive therapies are being explored. Over the next few years, more information will be gained regarding efficacy and safety of investigational treatments. We await the clarification of their role in our future treatment algorithms.

Acknowledgement

Partially supported by NIH center grant P30-EY014801 and by an unrestricted grant to the University of Miami from Research to Prevent Blindness, New York, NY.

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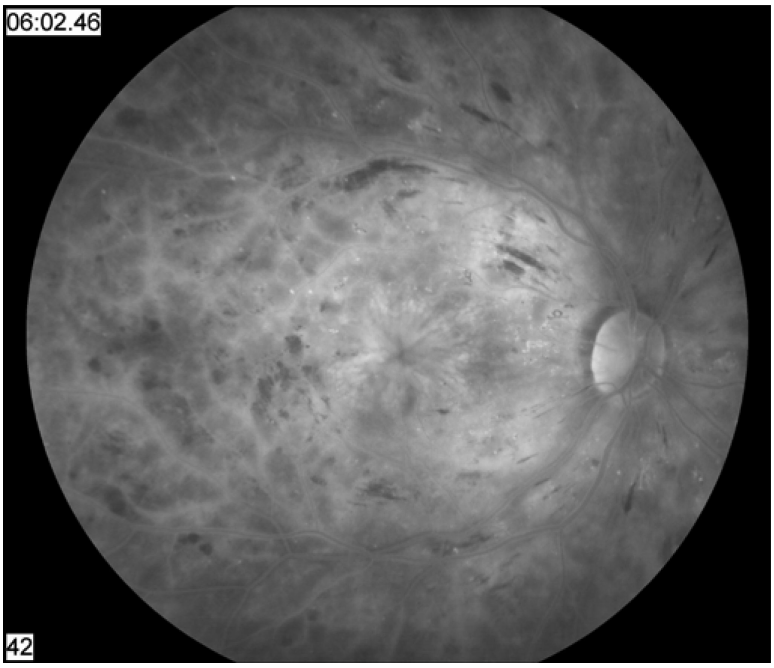

Figure 1. Florid diabetic macular edema in the right eye of a young patient with type I diabetes demonstrated by hyperfluorescent macular leakage late in the fluorescein angiogram

Note the increased vascular permeability of the retinal vessels as a result of increased levels of vascular endothelial growth factor.

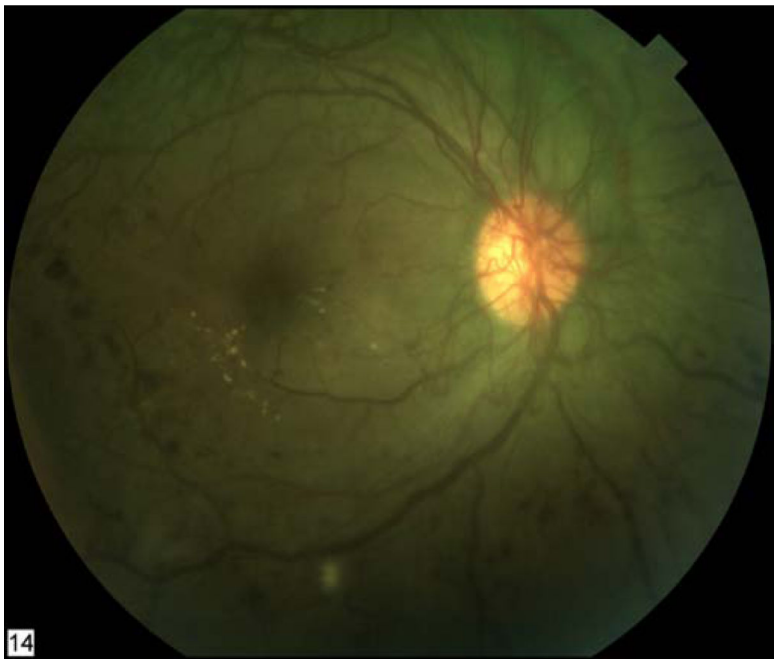

Figure 2. Advanced proliferative diabetic retinopathy with neovascularization of the disc
Scattered retinal hemorrhages, macular exudates, and a cotton-wool spot are present. This fundus image of the right eye appears green because of the increased permeability of the abnormal vessels to fluorescein following an angiogram.