

¹ Department of Ophthalmology, Sveti Duh General Hospital, Zagreb, Croatia

² Department of Diabetic Complications, Division for Ophthalmology, University Clinic for Diabetes, Endocrinology and Metabolic Diseases, School of Medicine, University of Zagreb, Vuk Vrhovac Institute, Zagreb, Croatia

³ University Department of Ophthalmology, Zagreb University Hospital Center, Zagreb, Croatia

PHARMACOTHERAPY FOR DIABETIC RETINOPATHY – IT IS NOT JUST A DREAM

Snježana Kaštelan¹, Martina Tomić², Višnja Mrazovac³

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SUMMARY

Diabetic retinopathy is a major cause of new blindness among working-age individuals in developed countries and remains one of the most serious complications of diabetes. At the time, primary prevention with intensive glycemic control, strict blood pressure regulation and lipid-modifying therapy, as well as local ocular treatment (laser photocoagulation and pars plana vitrectomy) are the proven standard treatments for diabetic retinopathy. However, more recently, many researchers have directed their efforts towards better understanding of microvascular changes in diabetic retinopathy in order to develop more effective pharmacologic prevention and treatment, and to determine new treatment strategies. The three major classes of agents currently being studied are corticosteroids, vascular endothelial growth factor (VEGF) antagonists and agents that are involved in biochemical pathways (polyol pathway activation, diacylglycerol, protein kinase C pathway

activation, and changes in macromolecule structure and function via the formation of AGE products). As further prospective randomized clinical trials accumulate data, the role and guidelines of pharmacologic treatments will become clearer.

INTRODUCTION

Diabetes mellitus is the most common endocrine disease in developed countries, estimated to have affected 171 million people worldwide in 2006 and is projected to affect 366 million by 2030 (1). It was the fifth leading cause of death in 2000, and diabetic microvascular complications account for a significant portion of the morbidity and mortality (2). Diabetic retinopathy, the main long-term and visually devastating diabetic complication, is estimated to be the most frequent cause of new blindness among working-age adults (20-74 years) in developed countries (3,4). The prevalence of retinopathy increases with the duration of diabetes and is related to hyperglycemia, hypertension, hyperlipidemia, pregnancy, nephropathy and anemia (5,6). The retina is a metabolically active tissue, and hyperglycemia, with associated relative or absolute insulin deficiency, is thought to adversely affect the normal physiology. Various biochemical, hemorheological, and immune mechanisms have been implicated to explain vascular

Corresponding author: Snježana Kaštelan, MD, PhD, Department of Ophthalmology, Sveti Duh General Hospital, Sveti Duh 64, HR-10000 Zagreb, Croatia
E-mail: snjezanakastelan@yahoo.com

disruption in retinopathy (7-9). Vascular disruptions are characterized by abnormal autoregulation of retinal blood flow caused by the loss of pericytes that normally regulate vessel caliber, breakdown of the inner blood-retinal barrier, thickening of the capillary basement membrane, and damage and proliferation of endothelial cells. Characteristic clinical manifestations are the result of four main processes: the occurrence of microaneurysms, increased vascular permeability, capillary occlusion, and fibrous and neovascular proliferation (10). Fluid leakage can range from microexudates to the most severe form, macular edema, which can seriously reduce vision. The leakage of blood cells and platelets causes the foci of intraretinal hemorrhage. Another lesion that can appear is capillary occlusion (non-perfusion with retinal ischemia), which leads to the proliferation of new vessels (neovascularization) that seek out new routes to irrigate the ischemic area. These new vessels are often surrounded by fibrous tissue, and the fibrovascular complex adheres to the posterior part of the vitreous body. Traction on the vitreous, which usually happens with age or with rapid eye movement during sleep, can rupture the fragile structure of the new vessels and lead to vitreous hemorrhage or even retinal detachment. New vessels and fibrous tissue can also close the anterior chamber angle, which leads to neovascular glaucoma with severe elevations in intraocular pressure.

The primary goal of diabetic retinopathy treatment is to improve or protect vision by reducing vascular leaking and macular edema, retinal ischemia and growth of fragile new vessels, thus preventing vitreous hemorrhages and tractional retinal detachment.

The first step in managing diabetic retinopathy is to reduce the risk of retinopathy development and progression by controlling the underlying risk factors: hyperglycemia, hypertension and hyperlipidemia. The DCCT and UKPDS trials have shown that strict glycemic control is associated with a lower risk of retinopathy compared with conventional therapy in both type 1 and type 2 diabetes (11,12). The UKPDS trial has also demonstrated that intensive blood pressure control reduces microvascular complications compared with less intensive control (13). Lipid-lowering therapy, especially the levels of serum

cholesterol, low-density lipoprotein (LDL) and triglycerides, is shown to decrease the severity of retinal hard exudates as well as the risk of developing proliferative diabetic retinopathy (14,15). In addition to controlling these modifiable risk factors, regular dilated eye examinations have been shown to reduce the incidence of blindness due to diabetic retinopathy through early detection and treatment (16). However, not all cases of diabetic retinopathy can be prevented, thus highlighting the need for effective treatment.

Currently, laser photocoagulation is the primary method of treatment in patients with diabetic retinopathy that are at a high risk of vision loss, but it is not always effective for improving vision (17). In many cases when retinal damage and vision loss have already occurred, laser treatment can just maintain vision and avoid further vision loss. In about 50% of patients, retinopathy will progress despite laser photocoagulation. The procedure is uncomfortable and often-repeated treatments are required. Moreover, laser photocoagulation is an ablative procedure destroying retinal tissue, leaving scars that always enlarge with time, leading to a decrease in night vision, color vision and peripheral vision as well as loss of 1 or 2 lines of visual acuity in some patients (18,19).

Pars plana vitrectomy (PPV) is a microsurgical procedure designed to remove vitreous gel, usually in order to achieve access to a diseased retina. It is the main method of treating severe complications of proliferative diabetic retinopathy, such as severe persistent vitreous hemorrhages and tractional retinal detachment (20).

However, despite standard intervention, vision loss from diabetic retinopathy still occurs at a frightening rate. Therefore, many researchers have recently directed their efforts towards better understanding the microvascular changes in diabetic retinopathy in order to develop more effective pharmacological prevention and treatment, and to establish new treatment strategies. The three major classes of pharmacological agents currently being studied are corticosteroids, vascular endothelial growth factor (VEGF) antagonists and agents that are involved in biochemical pathways (polyol pathway activation, diacylglycerol, protein kinase C (PKC) pathway

activation, stimulation of cellular oxidative stress, and changes in macromolecule structure and function *via* the formation of advanced glycation end products).

CORTICOSTEROIDS

Corticosteroids have multiple mechanisms of action. In addition to their well-known potent anti-inflammatory effects, corticosteroids cause down-regulation of VEGF. They have been shown to inhibit the expression of VEGF and transforming growth factor- β (TGF- β) (21) and to reduce the induction of VEGF by proinflammatory mediators (22). Steroids directly affect retinal endothelial cell barrier properties and decrease vascular permeability, thus preventing blood-retinal barrier breakdown (23).

Intravitreal injection of triamcinolone acetonide (IVTA) (Kenalog 40), a slow-release steroid, is a promising therapy for diabetic macular edema, which suppresses inflammation, reduces vascular leakage and inhibits fibrovascular proliferation (24). In eyes with diabetic macular edema, it reduced foveal thickness and improved visual acuity in several case series (25,26). Intravitreal administration of triamcinolone acetonide is also an effective treatment for proliferative diabetic retinopathy (27). However, the treatment effect lasts for only approximately 6 months, so often-repeated treatments may be required, and there is a limit how often it is safe to enter the vitreous cavity. The possible complications of using triamcinolone acetonide include intraocular pressure (IOP) elevation, cataract and endophthalmitis (27). The most important complication of IVTA is elevation of IOP resulting in secondary open-angle glaucoma, which may sometimes be severe and intractable (28). IOP elevation up to 24 mm Hg may occur in about 40% of patients, usually within 3 months (29). The second most important complication of IVTA is cataract formation, which may become visually significant in about 50% of eyes within 1 year (30). The rates of injection-related endophthalmitis following IVTA have been reported to range between 0.09% and 0.87% *per* injection (31). Other reported complications of IVTA (and of any intravitreal injection) are rare and include retinal detachment, lens trauma and vitreous hemorrhage. The use of peribulbar

rather than intravitreal triamcinolone acetonide offers reduced risks of endophthalmitis and perhaps other complications, but this administration of the same agent has some limitations and is less effective than IVTA (32). Neither peribulbar nor intravitreal triamcinolone appears to offer long-term efficacy for diabetic macular edema, which has led to the investigation of various extended-release corticosteroids. The fluocinolone acetonide intravitreal implant (Retisert) is Food and Drug Administration (FDA)-approved for the treatment of chronic, noninfectious posterior segment uveitis (33), and studies in patients with diabetic macular edema are currently in progress and will assess its efficacy and side effects. A biodegradable, extended-release dexamethasone implant (Posurdex) has shown promising outcomes in the treatment of macular edema of various etiologies including diabetic macular edema (34).

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) INHIBITORS

Vascular endothelial growth factor (VEGF), primarily isoform VEGF_{164/165}, is a key mediator of blood-retina barrier breakdown and angiogenesis in the ischemic retina (35). VEGF is produced by pericytes, the pigment epithelial cells, and endothelial cells of the retina in response to hypoxia from capillary loss and/or microaneurysm formation. Clinical studies have shown that intravitreal VEGF concentration increased in eyes as they progressed from nonproliferative diabetic retinopathy to active proliferative diabetic retinopathy (36). Similarly, successful panretinal photocoagulation reduced intraocular VEGF levels by 75% in patients treated for ocular neovascularization (36). These data suggest that specific inhibition of VEGF activity may prevent retinal neovascularization and associated blood flow abnormalities. The role of VEGF in retinal neovascularization has encouraged the development of inhibitors such as VEGF-specific antibodies (bevacizumab, pegaptanib, ranibizumab).

Pegaptanib

Pegaptanib (Macugen) is a selective aptamer directed against the VEGF-A 165 isoform. It was the first FDA-approved ophthalmologic anti-VEGF agent for the treatment of choroidal neovascularization in age-related macular degeneration (37). In a phase 2 prospective clinical trial, pegaptanib appeared to improve anatomic and visual outcomes in patients with diabetic macular edema, and to induce regression of neovascularization (38,39). Phase 3 trials of pegaptanib for diabetic macular edema are currently under way.

Bevacizumab

Bevacizumab (Avastin), a full-length recombinant humanized antibody, is active against all isoforms of VEGF-A. It is FDA-approved as a systemic treatment for metastatic colorectal cancer (40). Case reports and small, nonrandomized pilot studies have documented the efficacy of using off-label intravitreal bevacizumab against exudative age-related macular degeneration, macular edema from nonischemic central retinal vein occlusion, iris neovascularization as well as diffuse diabetic macular edema and various complications of proliferative diabetic retinopathy (41,42). The Diabetic Retinopathy Clinical Research network (DRCR.net) has completed a phase 2 prospective randomized multicenter clinical trial to determine the safety and possible benefits of this agent.

Ranibizumab

Ranibizumab (Lucentis), a recombinant humanized antibody fragment, is active against all isoforms of VEGF-A. Intravitreal ranibizumab is FDA-approved for the treatment of exudative age-related macular degeneration (43). Two pilot studies of ranibizumab demonstrated efficacy in the treatment for diabetic macular edema (44,45). Two phase 3 prospective randomized multicenter comparing clinical trials, one in patients with diabetic macular edema and no proliferative diabetic retinopathy, and another one in patients with diabetic macular edema and proliferative diabetic retinopathy, are under way.

PROTEIN KINASE C (PKC) INHIBITORS

PKC plays an important role in hyperglycemia-induced microvascular dysfunction in diabetes. Activation of PKC results in many cellular changes including increased expression of matrix proteins such as collagen and fibronectin, and increased expression of vascular mediators such as endothelin. The final effects of these changes are thickening of the capillary basement membrane and changes in vascular permeability and/or blood flow (46). Moreover, PKC is an integral component of cellular signaling by VEGF, an important mediator of ocular neovascularization seen in ischemia. Although the activity of multiple PKC isoforms (α , β 1, β 2 and ϵ) is increased in vascular tissue in diabetes, studies suggest that PKC β 2 isoform is specially activated (46). Two PKC inhibitors are currently in development in order to reduce microvascular diabetic complications.

LY333531 (ruboxistaurin, RBX) is a specific oral inhibitor of PKC β 1 and β 2. In animal models, it was found to block vascular complications of diabetes, including abnormalities in retinal blood flow, neovascularization, and VEGF-mediated effects on permeability (47). PKC-DRS2 has shown efficacy of RBX against diabetic macular edema by reducing diabetes-induced retinal vascular leakage, but no significant effect on prevention of diabetic retinopathy progression (48). Although Lilly received an approvable letter from FDA on August 18, 2006, the FDA requested an additional, 3-year phase 3 clinical trial to collect additional efficacy data.

PKC412 (midostaurin) is a nonspecific oral kinase inhibitor. It was found to block VEGF receptors 1 and 2, platelet-deriving growth factor β , and the α , β and γ isoforms of protein kinase C. In animal models of neovascularization, PKC412 inhibited ischemia-induced angiogenesis as well as retinal vessel formation during development. A recent phase I/II placebo-controlled human trial resulted in significant decreases in retina thickness and volume and increased visual acuity (49).

SOMATOSTATIN ANALOG

Growth hormone, secreted from the anterior pituitary, is associated with the progression of diabetic retinopathy, thus hypophysectomy was long ago proposed as an intervention for severe, treatment-resistant diabetic retinopathy (50). Insulin-like growth factor-1 (IGF-1), a cytokine structurally similar to proinsulin and stimulated by growth hormone, directly induces diabetic angiogenesis, which in diabetic models may be suppressed by IGF-1 receptor inhibitors. Therefore, somatostatin, an endogenous growth hormone releasing inhibitor from the hypothalamus, was evaluated for the treatment of diabetic retinopathy. Early results in patients with proliferative diabetic retinopathy were encouraging, although some evidence of resistance to the agent was noted. In a recent trial in patients with severe nonproliferative diabetic retinopathy or early proliferative diabetic retinopathy, therapy with octreotide (a somatostatin analog and growth hormone/insulin-like growth factor-1 antagonist; Sandostatin) decreased the need for retinal photocoagulation compared with conventional treatment (51). However, the incidence of progression to advanced proliferative diabetic retinopathy was not significantly different between the treatment groups (52). A large clinical trial is currently under way to evaluate the ability of an intramuscular injection of octreotide to treat proliferative diabetic retinopathy.

ALDOSE REDUCTASE AND AGE INHIBITORS

Aldose reductase is the rate-limiting enzyme in the conversion of glucose to sorbitol, an energy-dependent process that uses nicotinamide-adenine dinucleotide phosphate (NADPH). Excessive amounts of glucose activate this enzyme, which increases sorbitol formation, decreases NADPH, and can cause oxidative stress and inflammation. The rise in sorbitol can lead to osmotic damage to vascular cells. Sorbitol is finally converted to fructose. Nonenzymatic glycation of fructose results in high levels of advanced glycation end products, which finally activate PKC and cause cell damage and dysfunction. Decrease of NADPH

reduces nitric oxide formation, which can alter blood flow. Several aldose reductase inhibitors have been studied over the past two decades. Their usefulness has been limited by minimal efficacy and significant toxicity (liver and kidney damage) (53). Epalrestat, fidarestat and ranirestat are aldose reductase inhibitors recently studied for the treatment of diabetic peripheral neuropathy (54). No studies of these aldose reductase inhibitors in patients with diabetic retinopathy have been performed to date, but there is hope that a member of this class of drugs will prove useful for both diabetic peripheral neuropathy and retinopathy.

High serum glucose can also lead to protein modification. Binding of glucose to protein side chains results in the formation of nonfunctional products termed advanced glycation end (AGE) products. The consequence of AGE products formation is activation of PKC, which causes cell damage and dysfunction. The use of a complex that inhibits AGE formation, such as aminoguanidine, has been investigated in the prevention of microvascular damage in diabetes. In the retinas of diabetic rats treated with aminoguanidine, AGE accumulation and microaneurysm formation were inhibited, and pericyte loss was significantly reduced (55). In another rodent model of diabetic retinopathy, aminoguanidine reduced retinal oxidative stress and PKC activity (56). A clinical trial of aminoguanidine in humans has been initiated. Preliminary results from phase 3 trials suggest that aminoguanidine reduced the progression of retinopathy but was associated with an increase in anemia (57).

OTHER PHARMACOLOGICAL AGENTS

Other potential therapeutic agents for the treatment of diabetic retinopathy and diabetic macular edema include inhibitors of the renin-angiotensin (RAS) system (angiotensin converting enzyme inhibitors/angiotensin II receptor blockers), antioxidant agents (vitamin A, glutathione, aminoguanidine), anti-thrombotic agents (aspirin, clopidogrel), agents that modulate nitric oxide pathway (calcium dobesilate), pigment endothelium-derived factor (PEDF) inducers, cyclooxygenase (COX)-2 inhibitors, integrins, hyaluronidase, endothelin and erythropoietin inhibitors.

Many prospective randomized clinical trials are currently under way and will evaluate the effects of these agents on diabetic retinopathy in type 1 and type 2 diabetic patients.

CLINICAL GUIDELINES

Although none of these pharmacological agents is FDA-approved for the treatment of patients with diabetic retinopathy, off-label treatment may be considered for patients with advanced proliferative diabetic retinopathy unresponsive to traditional standard therapy (35).

In patients with diabetic macular edema not responsive to laser photocoagulation, either intravitreal triamcinolone (IVTA) or an intravitreal anti-VEGF agent may be considered as second-option treatment. At this time, there is no report on comparison data of IVTA *versus* anti-VEGF agents for this disease. Literature data suggest that triamcinolone is more efficacious for diabetic macular edema, while anti-VEGF agents appear more efficacious for proliferative diabetic retinopathy. Triamcinolone is less expensive than the anti-VEGF agents, but is associated with the risk of IOP elevation, cataract and endophthalmitis.

In patients with complications of proliferative diabetic retinopathy not amenable to laser photocoagulation, intravitreal anti-VEGF agents should be applied in order to produce short-term

stabilization and/or regression of iris neovascularization. In most patients, afterwards, panretinal photocoagulation will finally be necessary.

Intravitreal anti-VEGF agents may also be helpful in patients with advanced complications of proliferative diabetic retinopathy, such as dense vitreous hemorrhage or/and neovascular glaucoma. If there is no evidence of retinal detachment on B-scan echography, these agents may provide useful anatomic improvement, until definitive panretinal photocoagulation can be done, or to reduce intraoperative bleeding in eyes with neovascular glaucoma.

CONCLUSION

Diabetic retinopathy is a major cause of blindness in developed countries and remains one of the most serious complications of diabetes. Thus, many researchers have recently directed their efforts towards better understanding the microvascular changes in diabetic retinopathy in order to develop more effective pharmacological prevention and treatment, and to determine new treatment strategies. However, at this time, primary prevention with strict glycemic control, strict blood pressure regulation and lipid-modifying therapy, as well as local ocular treatment (laser photocoagulation and pars plana vitrectomy) remain the proven treatments for diabetic retinopathy, through evidence-based medicine. As prospective randomized clinical trials accumulate data, the role and guidelines of pharmacological treatments will become clearer.

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