Advances in the Medical Treatment of Diabetic Retinopathy

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Proliferative diabetic retinopathy (PDR) remains the leading cause of blindness among working-age individuals in developed countries (1). Diabetic macular edema (DME), another important event that occurs in diabetic retinopathy, is more frequent in type 2 than type 1 diabetes (2). Whereas PDR is the most common sight-threatening lesion in type 1 diabetes, DME is the primary cause of poor visual acuity in type 2 diabetes. Because of the high prevalence of type 2 diabetes, DME is the main cause of visual impairment for diabetic patients (2). In addition, DME is almost invariably present when PDR is detected in type 2 diabetes (3). Neovascularization caused by severe hypoxia is the hallmark of PDR, whereas vascular leakage caused by the breakdown of the blood retinal barrier (BRB) is the main event involved in the pathogenesis of DME (4,5).

STANDARD TREATMENT— Although tight control of both blood glucose levels and hypertension is essential to prevent or arrest progression of the disease, the recommended goals are difficult to achieve in many patients and, consequently, diabetic retinopathy develops during the evolution of the disease. When PDR or clinically significant DME do appear, argon-laser photocoagulation is currently indicated, which the efficacy of has been widely demonstrated (6). However, the optimal period for laser treatment has frequently passed; moreover, it is not uniformly successful in halting visual decline. In addition, argon-laser photocoagulation is associated with moderate visual loss, some diminished visual field, reduced color vision, and reduced contrast sensitivity. The presence of these symptoms led to the prevailing thinking that laser treatment prevents vision loss but rarely results in visual improvement.

Intravitreal corticosteroids have been successfully used in the eyes of patients with persistent DME and loss of vision following the failure of conventional treatment (i.e., focal laser treatment and attention to systemic risk factors). However, reinjections are commonly needed, and there are substantial adverse effects such as infection, glaucoma, and cataract formation (6). In addition, recent reports have shown that focal/grid photocoagulation is more effective and has fewer side effects than intravitreal triamcinolone for DME (7,8).

Vitreoretinal surgery is an expensive and complicated treatment that should be carried out only by vitreoretinal specialists experienced in this procedure, and it is normally reserved for the ultimately blinding complications of PDR, such as severe vitreous hemorrhage and secondary retinal detachment. For these reasons, new pharmacological treatments based on the understanding of the pathophysiological mechanisms of diabetic retinopathy are needed.

The paucity of relevant clinical studies addressed to testing new drugs in diabetic retinopathy is due, in part, to the necessity of long-term studies performed in large cohorts of diabetic patients by means of standardized masked grading of retinal photographs. Although there is no fixed rule, the duration of the trial must be consistent with the natural history of diabetic retinopathy and, consequently, at least 5 years seems to be necessary for separating the behavior of retinopathy in the intervention and control groups. In addition, most clinical trials have been aimed at evaluating the progression of diabetic retinopathy, whereas there have been few studies targeting prevention. All these caveats should be kept in mind when analyzing clinical trials on diabetic retinopathy because they can significantly contribute to false-negative results. The presence of diabetic retinopathy in nondiabetic subjects is another challenge. Wong et al. (9), in a study that included more than 11,000 participants from three population cohorts, provide evidence that with the current fasting plasma glucose cutoff of 7.0 mmol/l used to diagnose diabetes, 7.4–13.4% of nondiabetic patients had diabetic retinopathy. This finding, apart from questioning the current diagnostic criteria of diabetes, suggests a potential limit to the risk reduction for diabetic retinopathy that should be taken into consideration when interpreting the results of clinical trials.

Recently, two pivotal studies have been published regarding the beneficial effects of two types of drugs (fenofibrate and candesartan) on diabetic retinopathy (10–12). These studies fulfill all the main requirements for obtaining a valid result: long-term follow-up (~5 years), a large cohort of diabetic patients, retinopathy assessed by standardized methods, and a significant number of patients without diabetic retinopathy at study entry, thus allowing evaluation of the effectiveness of prevention. In advanced stages of diabetic retinopathy, intravitreous anti–vascular endothelial growth factor (VEGF) agents have emerged as new treatments. These drugs are yet to be approved for diabetic retinopathy treatment, but they are currently used by ophthalmologists in selected cases of PDR and DME (13,14). This article discusses the current state of knowledge concerning these novelties in the medical treatment of diabetic retinopathy and highlight areas where further studies and evidence are required.

FENOFIBRATE— Fenofibrate is a peroxisome proliferator–activated receptor (PPAR)-α agonist indicated for the treatment of hypertriglyceridemia and mixed dislipidemia. Its main action is to lower plasma triglyceride levels, but it also reduces total and LDL cholesterol, raises HDL cholesterol, and decreases

concentration of small LDL cholesterol particles and apolipoprotein B (15). Recently, Keech et al. (10) have reported results concerning laser treatment for diabetic retinopathy from the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study. The main aim of this randomized controlled trial was to assess whether long-term lipid-lowering therapy using fenofibrate (a PPAR-α agonist) could reduce the need for laser treatment in a large cohort (n = 9,795) of type 2 diabetic patients. The average follow-up was 5 years, and the end point was the need for laser treatment (a tertiary end point of the main study). In an intention-to-treat analysis, fenofibrate (200 mg once daily) reduced the frequency of laser treatment for macular edema by 31% and for proliferative retinopathy by 30%. In addition, in a substudy performed on patients in whom retinal status was graded by fundus photography, fenofibrate was able to reduce the progression of existing retinopathy. Although this study has some limiting factors (16,17), the substantial benefits obtained from reducing the need for laser treatment argue for consideration of using fenofibrate in the management of diabetic retinopathy. However, our poor knowledge of the mechanisms involved in its beneficial effects in diabetic retinopathy might limit its potential impact on clinical practice. Theoretically, another PPAR-α apart from fenofibrate can also be beneficial for diabetic retinopathy; however, at present this has been only demonstrated with fenofibrate.

The rationale for FIELD was that elevated lipid levels in systemic circulation constitute a risk factor for diabetic retinopathy; therefore, long-term lipid-lowering therapy with fenofibrate could reduce the progression of diabetic retinopathy and the need for laser treatment in patients with type 2 diabetes. However, no relationship between serum lipids and the appearance or progression of diabetic retinopathy was detected. This is in agreement with other prospective studies showing that serum lipids are unrelated to the progression of diabetic retinopathy or the development of PDR (18,19). In addition, the Collaborative Atorvastatin Diabetes Study (CARDS), a randomized controlled trial of 2,830 patients with type 2 diabetes, did not find atorvastatin to be effective in reducing diabetic retinopathy progression (20). However, this study was limited by substantial missing data (only 65% of patients had retinopathy status recorded at baseline) and lack of photographic grading for diabetic retinopathy. Another randomized trial, the ACCORD-EYE study that is now in progress, could shed light on this issue (21). In this study, the effects of lipid control (statin vs. fenofibrate added to a statin) on the progression of diabetic retinopathy will be evaluated. There will be 4,065 participants recruited to the study at baseline for whom fundus photographs will be taken within 4 months of randomization and again 4 years later. Although in the FIELD study there was no relationship between the quantitative levels of serum lipids and diabetic retinopathy, it is unknown whether the effectiveness of fenofibrate in modulating the qualitative properties of lipoproteins (i.e., reducing remnants and small dense LDL particles) can contribute to its beneficial effects. In addition, it should be noted that the mechanisms regulating intraretinal lipid transport rather than serum levels might be more important in the pathogenesis of diabetic retinopathy. In this regard, we have recently shown that apolipoprotein A1 (apo-A1) is overexpressed in the retina of diabetic patients (22). Apo-A1 is a key factor for the intraretinal transport of lipids, thus preventing lipid deposition and lipotoxicity, and it is also a potent scavenger of reactive oxygen species. Therefore, apo-A1 could play an important role in protecting the retina from oxidative stress. These findings have led us to hypothesize that the retinas from diabetic patients have a higher content of apo-A1 as a protective mechanism; consequently, patients with less capacity for apo-A1 production by the retina will be more prone to develop lipid deposition (hard exudates) and retinal damage induced by oxidative stress. Fenofibric acid was shown to enhance transcription of the gene of apo-A1 in the liver (23), macrophages, and fibroblasts (24), but whether this is also true at the retinal level remains to be elucidated.

Other nonlipidic mechanisms by which fenofibrate could be effective in preventing or arresting diabetic retinopathy might be the following:

1) PPAR-α is present in endothelial cells (25), and its activation by means of PPAR-α agonists has recently been shown to inhibit expression of VEGF receptor 2 (VEGFR2) and neovascularization in human umbilical endothelial cells (26). Varet et al. (27) have demonstrated that fenofibrate inhibits angiogenesis in vitro and in vivo as well as basic fibroblast growth factor–induced angiogenesis in vivo. In addition, in cells derived from human ovarian cancer, clofibric acid (a PPAR-α agonist) downregulates VEGF expression (28). Apart from its antiproliferative effects, fenofibrate inhibits the apoptosis induced by high glucose concentrations in human umbilical endothelial cells (29). Moreover, it has been demonstrated that fenofibrate prevents the apoptosis of human retinal endothelial cells induced by serum deprivation through a PPAR-α–independent but AMP-activated protein kinase–dependent pathway (30). This activation of the AMP-activated protein kinase pathway in endothelial cells could lead to an increase in endothelial nitric oxide synthase phosphorylation and nitric oxide production, thus resulting in beneficial effects on endothelial function (31).

2) PPAR-α is associated with anti-inflammatory and antioxidant activity (32). It has been reported that PPAR-α activation induces the expression and activation of antioxidant enzymes, such as superoxide dismutase and glutation peroxidase (33), and that activation of PPAR-α induces apoptosis of human monocyte–derived macrophages (34). In addition, PPAR-α activators inhibit the expression of vascular cell adhesion molecules on the endothelium (35). This effect might be useful in preventing leukostasis (the inappropriate adherence of leukocytes to the endothelium), which is essential in the pathogenesis of PDR.

3) PPAR-α activation also has a neuroprotective effect (33,36). This could be important in preventing neuroretinal degeneration, an early and crucial event that occurs in diabetic retinopathy even before vascular abnormalities can be detected (37).

4) The breakdown of the BRB, caused by the disruption of tight junctions and subsequent leakage, is the main factor accounting for DME (6). Because of the notable effect of fenofibrate in preventing DME progression, it would be worthwhile to explore whether fenofibrate is able to reduce the increased permeability that exists in diabetic retinopathy.

Future research on the potential effects of fenofibrate in all these areas will be essential for understanding its beneficial effects in diabetic retinopathy, and it will also be critical for using this drug as an adjunct in the management of diabetic retinopathy.

BLOCKING THE RENIN-ANGIOTENSIN SYSTEM — Observational and clinical trials have shown that blood pressure is an important modifiable risk factor for diabetic retinopathy and that lowering high blood pressure significantly reduces the development and progression of retinopathy in both type 1 and type 2 diabetic patients (38,39). The blockade of the renin-angiotensin system (RAS) with an ACE inhibitor or by using angiotensin II type 1–receptor (AT1-R) blockers is one of the most used strategies for hypertension treatment in diabetic patients. Apart from the kidney, the RAS system is expressed in the eye (40). In addition, there is growing evidence that RAS activation in the eye plays an important role in the pathogenesis of diabetic retinopathy (40). Therefore, apart from lowering blood pressure, the blockade of the RAS could also be beneficial per se in reducing the development and progression of diabetic retinopathy.

The major components of RAS have been identified in ocular tissues and are overexpressed in the diabetic retina. Angiotensin II (AT) binds and activates two primary receptors, AT1-R and AT2-R. In adult humans, activation of the AT1-R expressed in endothelial cells and pericytes dominates the pathological states (40). AT1-R activation by AT produced by the retina stimulates several pathways involved in the pathogenesis of diabetic retinopathy such as inflammation, oxidative stress, cell proliferation, pericyte migration, remodelling of extracellular matrix by increasing matrix metalloproteinases, angiogenesis, and fibrosis (40). The RAS is upregulated concomitant with hypoxia-induced retinal angiogenesis and is linked to AT-mediated induction of inflammatory mediators and growth factors, including VEGF and platelet-derived growth factor (40,41). In addition, AT1-R activation by AT promotes leukostasis and neurodegeneration (40), two key elements in the pathogenesis of diabetic retinopathy. Most of these pathogenic actions are inhibited or attenuated by pharmacological blockade of the RAS either at levels of ACE or the AT receptors

and are accompanied by downregulation of VEGF and VEGFR-2 (40). Recently, Kim et al. (42) have shown that perindopril (an ACE inhibitor) attenuates VEGF-mediated BRB breakdown in rats with streptozotocin-induced diabetes. In addition, it is also worthy of mention that candesartan inhibited retinal accumulation of the advanced glycation end product pentosidine in spontaneously diabetic Torii rats (43). Apart from reducing microvascular disease, there is growing evidence pointing to neuroprotection as a relevant mechanism involved in the beneficial effects of angiotensin receptor blockers in diabetic retinopathy (44–46).

On these experimental bases, it would be reasonable to postulate that RAS blockade can promote higher beneficial effects in diabetic retinopathy than other antihypertensive agents. However, studies in type 2 diabetic patients with hypertension suggest that ACE inhibitors and angiotensin receptor blockers are not superior in preventing or arresting diabetic retinopathy to other drugs equally effective in reducing blood pressure such as the β-blocker atenolol (47) or calcium channel blocker nisoldipine (48). These prospective randomized studies suggest that lowering blood pressure seems to be much more important than the potential effect of RAS blockade in the diabetic eye. However, the question concerning the potential effect of RAS blockers in normotensive diabetic patients remains to be elucidated. In the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID), it was reported that in normotensive patients (blood pressure ≤140/90 mmHg), either normoalbuminutic (85% of patients) or microalbuminuric, lisinopril (an ACE inhibitor) had no effect in reducing the incidence of diabetic retinopathy but decreased its progression by two or more grades and decreased the progression to PDR (49). However, these results have been criticized because the placebo group had significantly higher levels of mean A1C than the treatment group. In fact, after adjusting for A1C, the observed differences in progression by two levels and progression to PDR disappear and only the progression by one level remained significant. Other limiting factors of this study were the short period of follow-up (2 years) and the fact that diabetic retinopathy was not the primary end point of the study. Therefore, although the EUCLID study supported the idea of an additional benefit of ACE inhibitors on

diabetic retinopathy progression, it was underpowered for the eye-related outcome measures used. Furthermore, in the normotensive type 2 diabetic patients of the Appropriate Blood Pressure Control in Diabetes (ABC) study, Schrier et al. (50) showed that intensive blood pressure control decreased the progression of diabetic retinopathy. However, the results were the same whether enalapril or nisoldipine was used as the initial antihypertensive agent. Therefore, the specific antihypertensive agent again appears to be less important than the achievement of the lower blood pressure values.

The Diabetic Retinopathy Candesartan Trials (DIRECT) program was therefore designed to answer the question of whether the blockade of RAS with AT1-R blocker candesartan could prevent the incidence and progression of retinopathy in type 1 and type 2 diabetes independent of lowering blood pressure (11,12). This program consisted of three randomized double-blind placebo-controlled parallel-group studies: *1*) a primary prevention study involving 1,241 type 1 diabetic patients without diabetic retinopathy (DIRECT-Prevent 1), *2*) a secondary prevention study involving 1,905 type 1 diabetic patients with diabetic retinopathy (DIRECT-Protect 1), and *3*) a secondary prevention study involving 1,905 type 2 diabetic patients with diabetic retinopathy (DIRECT-Protect 2). In each trial, patients were randomized to receive candesartan (16–32 mg/day) or placebo and the median follow-up was 4.7 years. Patients with type 1 diabetes were eligible for inclusion if they were normoalbuminuric and normotensive (blood pressure ≤130/85 mmHg). For patients with type 2 diabetes, the inclusion criteria were normoalbuminuria and either normal blood pressure without antihypertensive therapy or blood pressure ≤160/90 mmHg during treatment. The primary end point was the incidence of diabetic retinopathy in the primary prevention study and progression of diabetic retinopathy in the secondary prevention studies. In the DIRECT-Prevent 1 study, a nonsignificant reduction (18% relative risk reduction; $P = 0.051$) in the risk of incidence of diabetic retinopathy was observed. However, in a post hoc analysis in which the primary end point was changed from a two-step increase to at least a three-step increase in the ETDRS scale, a significant difference was detected (35% relative risk reduction; $P = 0.003$). This beneficial effect was attenuated but still significant af-

ter the data were adjusted for duration of diabetes, A1C, and systolic blood pressure (26% relative risk reduction; $P = 0.046$) (11). In DIRECT-Protect 1, an identical progression of diabetic retinopathy was found in the placebo and in the candesartan groups, thus suggesting that candesartan is not effective in preventing diabetic retinopathy progression (11). DIRECT-Protect 2 showed a nonsignificant reduction in the progression of diabetic retinopathy (13% relative risk; $P = 0.20$). However, a significant increase in diabetic retinopathy regression was observed (34%, $P = 0.009$), this effect being more evident in patients with mild retinopathy (12). Thus, although the prespecified primary end point was not reached in the DIRECT program, data analysis suggests an overall beneficial effect of candesartan in diabetic retinopathy.

The DIRECT results should be compared with the Action in Diabetes and Vascular Disease (ADVANCE) study, which included 11,140 type 2 diabetic patients (51). In this study, patients randomized to intensive glucose control with glicazide (modified release), as well as other drugs required to achieve A1C $\leq$6.5% and an ACE inhibitor–diuretic combination (perindopril-indapamide), presented the same 4-year incidence or progression of diabetic retinopathy as the placebo group. These results suggest the possibility that candesartan but not ACE inhibitors might have beneficial effects in diabetic retinopathy. However, it should be noted that unlike DIRECT, ADVANCE did not use standardized retinal photography and there was a lower rate of progression of diabetic retinopathy, thus limiting the power of the study to detect any moderate effects of intervention on microvascular eye disease.

INTRAVITREAL ANTI-VEGF AGENTS

VEGF has been identified as having a major role in the genesis of diabetic retinopathy, with increased levels in animals with experimental diabetes and in the vitreous of patients with diabetic retinopathy. Intravitreal VEGF administration in experimental animals duplicates many features of diabetic retinopathy. Thus, agents that attenuate VEGF action are very attractive because they are able to reduce permeability and neovascularization, the hallmarks of DME and PDR, respectively (4,52).

In general, systemically administered drugs reach the retinochoroidal tissue via blood circulation. However, because the BRB limits the influx of drugs into the retina, large amounts of the drug must be administered to maintain therapeutic concentrations. Regarding anti-VEGF agents, this would lead to systemic inhibition of angiogenesis, which could compromise critical vascular response to ischemic events in diabetic patients with cardiovascular, cerebrovascular, or peripheral vascular disease. Moreover, hypertension and proteinuria (two surrogate markers of systemic VEGF inhibition) as well as the impairment of wound healing are other potential consequences of blocking VEGF and would be particularly worrying to the diabetic population (14). By contrast, the local administration of anti-VEGF agents into the eye by means of intravitreal injections would avoid systemic adverse effects. However, this is invasive and a skilled specialist is required. In addition, in order to maintain effective levels, frequently repeated injections would be necessary, thus increasing local complications such as endophthalmitis, vitreous hemorrhage, retinal detachment, and traumatic cataract. Furthermore, although the eye is thought of as a closed and self-contained system, anti-VEGF drugs injected into the vitreous cavity pass into systemic circulation to varying degrees and could potentially cause the systemic adverse effects mentioned previously (14,52). At present four anti-VEGF agents are available: pegaptamib sodium (macugen; Pfizer), ranibizumab (lucentis; Genentech/Novartis), bevacizumab (avastin; Genentech), and aflibercept (Regeneron Pharmaceuticals/sanofi-aventis).

Pegaptanib is a PEGylated (i.e., conjugated to polyethylene glycol) neutralizing RNA aptamer with an extremely high affinity for isoform 165 of VEGF ($VEGF_{165}$), which is the isoform that participates in pathological but not physiological neovascularization (53). Aptamers are modified nucleotides composed of single-stranded nucleic acids that adopt a specific three-dimensional conformation, allowing them to bind with high specificity and affinity to molecular targets in a manner similar to that of monoclonal antibodies. An important feature of aptamers is that they do not exhibit immunogenicity. Pegaptamib was approved by the U.S. Food and Drug Administration (FDA) for treatment of exudative (wet or neovascular) age-related macular disease (AMD) in December 2004.

Ranibimizumab is a full-length monoclonal antibody directed against VEGF. In contrast to pegaptamib, ranimizumab inhibits the biological activity of all isoforms of human VEGF and could be immunogenic. The FDA approved ranibizumab for wet AMD in June 2006.

Bevacizumab is an anti-VEGF agent similar to ranibizumab and was approved by the FDA in February 2004 for the treatment of disseminated colorectal cancer but not licensed for intraocular use. Nevertheless, intravitreal injection of bevacizumab has become a current off-label treatment by ophthalmologists for neovascular AMD because although it seems to be as effective as pegaptamib or ranimizumab, it is much cheaper.

Aflibercept, also known as a VEGF Trap-Eye because of its ability to block all six VEGF proteins (VEGF-A to VEGF-E as well as placental growth factor), is a fusion protein comprised of segments of the extracellular domains of human VEGF receptors 1 (VEGFR1) and 2 (VEGFR2) fused to the constant region (Fc) of human IgG. Afilbercept is currently being used in clinical trials for both exudative AMD and DME. Aflibercept has a higher binding affinity than other anti-VEGF agents. This higher binding affinity translates into greater activity at lower biological levels and, consequently, a longer duration of action.

The results of prospective clinical trials using pegaptanib and ranibizumab in patients with AMD have been very impressive and have led to the design of specific trials for DME and PDR. At present, only a prospective double-blind multicenter dose-ranging controlled trial has been reported in diabetic patients (54). In this study 172 patients with DME were included, and the patients randomized to receive repeated intravitreal pegaptamib showed better visual outcomes ($P = 0.03$), were more likely to show a reduction in retinal thickness ($P = 0.02$), and needed less additional focal laser ($P = 0.04$) at follow-up (36 weeks) than patients who received intravitreal sham injections. Retrospective data analysis of the eyes of 16 patients with PDR also showed regression of neovascularization (55).

Uncontrolled studies using ranibizumab and bevacizumab have also found a rapid regression of retinal neovascularization, improvement of visual acuity, and decrease of retinal thickness in DME, even in nonresponders to conventional treatment (14,56). However, the response to treatment of DME by VEGF blockade is

not prolonged and is subject to significant variability. This is in distinct contrast to the rapid response of those with both iris and retinal neovascularization in PDR and of those with choroidal neovascularization in wet AMD (57). Interestingly, when the outcomes of intravitreal bevacizumab treatment of DME were compared with those of intravitreal cortisone (triamcinolone acetonide), better outcomes in terms of reduction of foveal thickness and visual results were found with triamcinolone (58). The extent to which VEGF blockade is beneficial for DME is currently being investigated in prospective clinical trials. Apart from their potential as isolated treatments for PDR and DME, intravitreal anti-VEGF agents, in particular bevacizumab, have been shown to be useful in increasing the short-term response to panretinal photocoagulation in high-risk PDR and also seem to be efficacious and safe as an adjuvant treatment to vitrectomy in severe PDR or vitreous hemorrhage (56). This is because intravitreal anti-VEGF agents reduce active neovascularization and vitreous hemorrhage, thus allowing a safe and efficient panretinal photocoagulation or pars plana vitrectomy to be performed while minimizing the risk of complications. Aflibercept has been recently tested in an exploratory study performed in five patients with DME (59). In this study, using a single intravitreal injection, Trap-Eye was well tolerated and preliminary evidence of bioactivity was detected. Taken together, these promising results present a new scenario in the management of diabetic retinopathy. Nevertheless, larger studies investigating not only the effectiveness but also the systemic adverse effects of these agents in the diabetic population are still needed.

It is possible that a drug with more extensive and nonspecific anti-VEGF activity, such as pan-VEGF inhibitors (ranibizumab, bevacizumab, and aflibercept), could be more effective than a drug such as pegaptamib that selectively targets $VEGF_{165}$. In this regard, pegaptamib is substantially less effective than ranibizumab in AMD treatment. By contrast, given that $VEGF_{165}$ plays an essential role in pathological but not physiological neovascularization, pegaptanib could be the best option for avoiding systemic adverse effects in diabetic patients. In addition, long-term intravitreous injections of pan-VEGF inhibitors could lead to retinal neurodegeneration and an increased risk of circulation disturbances in the choriocapillaris (60). However, the theoretical advantage of selective blocking of $VEGF_{165}$ by pegaptamib in terms of both systemic and local side effects remains to be demonstrated in head-to-head clinical trials.

CONCLUDING REMARKS AND FUTURE RESEARCH

Tight control of blood glucose levels and hypertension remains the key element for preventing or arresting diabetic retinopathy. However, two drugs (fenofibrate and candesartan), originally not designed for treatment of diabetic retinopathy, have become new adjuncts in its management. The information drawn from clinical trials indicates that in normotensive diabetic patients, candesartan reduces the incidence of diabetic retinopathy in those with type 1 diabetes and favors diabetic retinopathy regression only in type 2 diabetic patients with mild retinopathy. By contrast, fenofibrate, which has only been tested in type 2 diabetes, has no effect on the incidence of diabetic retinopathy. However, it reduces the progression of existing diabetic retinopathy, thus lessening the need for laser treatment in both DME and PDR, and this beneficial effect is unrelated to changes in serum lipids. Therefore, it would be reasonable to recommend candesartan for type 1 diabetic patients (with or without hypertension) at high risk to develop diabetic retinopathy and for type 2 diabetic patients with mild retinopathy, whereas fenofibrate seems to be a good option for type 2 diabetic patients (with or without dyslipemia) with a wide range of diabetic retinopathy stages (from mild to severe nonproliferative diabetic retinopathy). In addition, the benefit on diabetic retinopathy shown by fenofibrate and candesartan should be considered an extra value when treating dyslipemia and hypertension in diabetic patients. Nevertheless, the mechanisms by which candesartan and, in particular, fenofibrate exert their reported benefits need to be elucidated before these drugs can be launched (alone or in combination) as new tools in the management of diabetic retinopathy. Another question needing specific research is whether such treatments could be administered topically and directly into the eye in order to increase the benefits in diabetic retinopathy.

In advanced stages of diabetic retinopathy, intravitreal delivery of anti-VEGF agents are currently used by many ophthalmologists despite the lack of phase 3 studies supporting their effectiveness and safety. This is due to the successful results obtained in wet AMD and the promising preliminary data in diabetic retinopathy. Intravitreal injection permits antiangiogenic drugs to effectively reach the retina and theoretically overcomes the problem of the systemic blockade of angiogenesis. However, this is an invasive procedure that can have complications such as endophthalmitis and retinal detachment and could even have deleterious effects for the remaining healthy retina. This is especially important in diabetic patients for whom long-term administration is expected. Apart from local side effects, anti-VEGF agents could also produce systemic complications because of their capacity to pass into systemic circulation. The effectiveness and safety of intravitreal anti-VEGF agents are being evaluated in several clinical trials. Meanwhile, in order to minimize systemic adverse effects, it seems reasonable to avoid long-term treatment with anti-VEGF agents for patients with hypertension, proteinuria, renal failure, cardiovascular disease, and foot lesions with wound healing impairment.

A future scenario will involve using a combination of anti-VEGF agents and laser photocoagulation or combining antiangiogenic agents aimed at different steps of angiogenic cascade. This would probably be more successful than single-molecule–specific approaches, would permit a decrease in the frequency of dosing, and would reduce adverse effects. Although it is premature at this stage to advocate such maneuvers, these aspects are certainly worth pursuing in future studies because they may suggest attractive new strategies for improving the treatment of diabetic retinopathy. However, it should be emphasized that, at present, the milestones in diabetic retinopathy treatment are the optimization of blood glucose levels, lowering of blood pressure, and regular fundoscopic screening.

In summary fenofibrate, candesartan, and anti-VEGF agents are now in the armamentarium for diabetic retinopathy treatment. Ophthalmologists and physicians treating diabetic patients should be aware of the potential usefulness of these drugs and work together not only in future research but also in establishing clinical guidelines that will include these newer medical treatments for diabetic retinopathy. Only such coordinated action, as well as competent strategies targeting prevention, will be effective in reducing

the burden and improving the clinical outcome of this devastating complication of diabetes.

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