Treating Early and Advanced Stage of Diabetic Retinopathy

Subjects: Ophthalmology

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A brief overview about the advances in the experimental field on the treatment of early stages of diabetic retinopathy (ESDR), as well as the main gaps to be filled will be given. In addition, a critical view on the current clinical practice for treating advanced stages of diabetic retinopathy (ASDR) will be provided.

diabetic retinopathy | diabetic macular edema | treatment | retinal neuroprotection | eye drops | in-travitreal injections

1. General Goals

Achieving glycemic control is a clear and well-founded form of treatment to prevent Diabetic retinopathy (DR) or arrest its progression [1][2][3]. Tight versus less tight glycemic control in the type 1 diabetic population of the Diabetes Control and Complications Trial (DCCT) reduced the risk of new retinopathy by 76% and of the progression of existing retinopathy by 54% [1]. Intensive vs. conventional glycemic management was associated with a 39% reduction in the risk of laser photocoagulation in the type 2 diabetic population of the UK Prospective Diabetes Study (UKPDS) [2].

Several randomized controlled trials (RCTs) have demonstrated the benefit of blood pressure (BP) control as a major modifiable factor for either incidence or progression of DR [4][5][6][7][8]. The UKPDS showed that after nine years of follow-up, the group under BP control had a 34% reduction in the risk of deterioration of DR, i.e., by two steps in the ETDRS scale (p = 0.0004), and a 47% reduction in the risk (p = 0.004) of deterioration in visual acuity, i.e., by three lines on the ETDRS chart [9]. Ambulatory blood pressure monitoring (ABPM) may provide better estimates of an individual's average blood pressure and makes it possible to differentiate among several phenotypes [10]. Several of these phenotypes, including elevated mean 24-h BP, elevated night-time BP and non-dipping BP pattern, have been associated with increased cardiovascular risk [10][11][12][13]. However, no data regarding blood pressure phenotypes and the risk of DR have been reported.

Despite the influence of metabolic control and blood pressure on the development and progression of DR, there is clinical evidence that substantial variation exists. In fact, clinicians are aware that a subset of patients with poor control of glycemia and/or uncontrolled blood pressure does not develop DR. On the other hand, there are patients with good control of both blood glucose levels and hypertension that will develop DR. In fact, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group

showed that hemoglobin A1c (HbA1c) values explained up to 11% of the risk of DR, and that the unexplained 89% of variation in risk was due to elements of the diabetic milieu not captured by the mean HbA1c value [14].

At present there is no evidence that the prevention of hypoglycemic episodes influences the natural history of DR, and specific clinical studies aiming at addressing this important question are needed. This is particularly relevant from the general assumption that DR is a complex neurovascular disease in which neurodegeneration plays an essential role. The vulnerability of neurons faced with sustained and recurrent hypoglycemia is unquestionable, and therefore, hypoglycemia might lead to retinal neuron death.

Glycemic variability may also be involved in the weaknesses of HbA1c in predicting the development and progression of DR; studies showing that the reduction of glycemic variability can prevent DR or arrest its progression are needed [15][16][17]. Finally, changes in the epigenome may contribute to the phenomenon of “metabolic memory”, which explains the long-term effects of metabolic statuses obtained several years ago [18].

Dyslipidemia seems to have less influence than hyperglycemia or hypertension on the development and progression of proliferative DR or DME [19][20]. However, a growing body of evidence suggests that nontraditional lipid measures such as apolipoproteins A and B are stronger risk markers of DR than total cholesterol and triglyceride levels [21][22].

Heritability of DR has been estimated to be around 27% for DR and 52% for PDR. Among the large number of putative genes and genetic variants reported in the literature, ALR2, VEGF and RAGE exhibit consistent associations with DR. However, a huge effort to validate these results in multiple populations is needed before the researchers can use these genes as biomarkers to indicate high risk [23]. In addition, specific gene variants in ICAM1, PPARGC1A and MTHFR have been associated with different NDPR phenotypes [24]. These results support the concept that different pathogenic mechanisms are involved in the different risks of progression of NDPR phenotypes. However, further confirmation in larger cohorts is needed.

2. Systemic Treatments

There is evidence based on clinical trials that fenofibrate, a peroxisome proliferator-activated receptor alpha (PPARα) currently used as a hypolipidemic agent, slows the progression of DR and reduces the need for laser photocoagulation and vitrectomy surgery [25][26][27]. However, the progression of DR was not the primary outcome of these clinical trials, and the scientific community has not accepted fenofibrate as an established treatment for arresting the progression of DR. To fill this scientific gap, a large randomized clinical trial is ongoing in the US (ClinicalTrials.gov Identifier: NCT04661358). It should be noted that the multifaceted non-lipidic actions of fenofibrate seem more important in reducing the progression of DR than the lipidic-mediated mechanisms [28].

Calcium dobesilate (CaD) is a safe drug that has been approved for many years for the treatment of DR in a large number of countries. However, it has not been broadly used in clinical practice. Two randomized placebo-controlled trials demonstrated the effectiveness of CaD in preventing the progression of early-stage DR [29][30], but its

effectiveness in AEDR remains to be determined. As occurs with fenofibrate, CaD targets multiple pathogenic pathways involved in DR [31]. However, further research to better understand the mechanisms of action and more targeted clinical trials are needed.

Some clinical trials have highlighted renin-angiotensin system (RAS) blockade as a promising systemic treatment for DR [32]. However, there is no robust clinical evidence on this issue. In fact, two large clinical trials, the Diabetic Retinopathy Candesartan Trials (DIRECT) program [33][34] and the Action in Diabetes and Vascular Disease (ADVANCE) study [35], failed to demonstrate any beneficial effect, taking into account the primary endpoints. Therefore, the classic concept that lowering blood pressure is the most important strategy, regardless of the choice of drug, has re-emerged with renewed rigor.

3. Targeting Neurovascular Unit (NVU)

NVU comprise diverse neural cell types (i.e., amacrine cells, ganglion cells, horizontal and bipolar cells), glia (astrocytes and Müller cells), professional immune cells (microglia and perivascular macrophages) and vascular cells (endothelial cells and pericytes) [36]. In recent years, several experimental approaches attempting to prevent diabetes-induced NVU impairment have been reported, but long-term clinical trials to support this therapeutic strategy in the context of DR are needed.

Route of administration is an issue in ESDR, because vision is generally preserved and repeated intravitreal injections represent an aggressive and unacceptable treatment. The systemic administration of drugs to block the main pathogenic pathways involved in DR has two main problems. First, the blood–retinal barrier impedes their reaching the retina at pharmacological concentrations; and second, systemic administration could lead to adverse effects and pharmacologic interference with other drugs used for the treatment of diabetes and its co-morbidities. Eye drops containing small molecules have been shown to be effective in treating early-stage DR in experimental models [37]; such compounds can reach the retina by the trans-scleral route [38][39][40]. In addition, topical administration limits the action of such compounds in the eye and minimizes the associated systemic effects.

Several proteins with neurotrophic activity that are required for retinal homeostasis are synthesized by the retina. However, in the diabetic retina, a downregulation exists of these neurotrophic factors. As such, a therapeutic strategy based on their replacement seems reasonable. In fact, treatments using eye drops seeking to replace these natural neuroprotective factors, such as pigment epithelial growth factor (PEDF), somatostatin and glucagon-like peptide 1 (GLP-1), or to avoid their degradation, such as DPP-IV inhibitors to enhance GLP-1, have been effective in experimental models [38][39][41][42][43]. Apart from neuroprotection, PEDF, GLP-1 and DPP-IV inhibitors significantly abrogate vascular leakage and, therefore, can be envisaged as promising treatments which should be tested in the clinical arena.

4. Advances for Treating advanced-Stage DR (ASDR)

4.1. General Measures

Tight control of blood glucose levels and blood pressure is recommended in ASDR, but the beneficial effects are less evident than when these general measures are implemented at the beginning of the disease or when ESDR appears.

The therapeutic goal of tight metabolic control should be balanced against the risk of hypoglycaemia, especially in older people, in whom aggressive glycaemic control does not further reduce retinopathy risk, and might even be associated with increased mortality [44]. In addition, an initial worsening of DR has been reported as a consequence of the rapid improvement of hyperglycemia in both type 1 and type 2 diabetes [45][46][47][48]. The most important risk factors for early worsening were shown to be a higher hemoglobin A1c level at baseline, a large reduction of HbA1c (>2%) and the severity of DR at baseline [49][50][51]. Recently, systematic reviews confirmed this concept and suggested that early worsening of DR could be particularly relevant when HbA1c is reduced to >1.5% after 3 months or to >2% after 6 months [52].

4.2. Critical Overview of Current Treatment

The treatment for ASDR is based on laser photocoagulation and intravitreal injections of anti-angiogenic factors or corticosteroids. Fenofibrate seems to be a reasonable treatment to arrest progression to sight-threatening DR but, as previously mentioned, a specific clinical trial supporting this indication is still lacking. Vitreo-retinal surgery is a complex and expensive treatment that is reserved for the ultimately blinding complications of DR [53].

4.2.1. Laser Treatment

Laser photocoagulation is generally indicated in PDR or in clinically significant DME and prevents further deterioration of vision if applied sufficiently early in the progression of the disease [54]. However, laser treatment does not usually restore lost vision and is associated with potentially severe adverse effects such as impaired adaptation to changes in light levels, some loss of visual acuity, loss of peripheral vision, changes in colour vision and exacerbation of macular edema.

4.2.2. Anti-Angiogenic Treatment

Intravitreal anti-VEGF agents are currently used as a first-line treatment for clinically significant DME [55]. Although both proinflammatory cytokines and VEGF play a crucial role in the pathogenesis of DME, the blockade of VEGF, rather than an anti-inflammatory approach, is primarily used [56]. Clinical trials have provided robust evidence that the intravitreous administration of anti-VEGF agents is better than laser therapy both at preserving and improving the vision of patients with DME [55][56][57]. However, around 50% of DME patients do not adequately respond to anti-VEGF therapy [58]. These findings support the concept that other mechanistic pathways may operate independently or in conjunction with VEGF in the pathogenesis of ASDR. In this regard, in the seminal study by Aiello et al. [59], 36% of the patients with PDR did not show increased VEGF levels in the vitreous fluid. Therefore, it was not surprising that a high rate patients showed an inadequate response to anti-VEGF treatment. In this subgroup of non-responders, proinflammatory cytokines/chemochines and other angiogenic factors unrelated to

VEGF (platelet-derived growth factor, basic fibroblast growth factor, hepatocyte growth factor, angiopoietin-2) probably play a more relevant pathogenic role.

Aflibercept produces a more extensive angiogenic blockade than anti-VEGF agents and may provide superior outcomes in certain patients compared with treatments that inhibit only VEGF (i.e., bevacizumab and ranibizumab) [60]. Aflibercept is a soluble decoy receptor that binds vascular endothelial growth factor-A (VEGF-A), VEGF-B and placental growth factor (PIGF) with a greater affinity than the body's native receptors. Therefore, VEGF binds to aflibercept instead of its original receptors, thereby reducing the activity of VEGF [61].

A potential serious complication of pan-VEGF inhibition is the neurodegeneration of the remaining healthy retina [62][63][64]. This can occur because VEGF is a powerful neurotrophic factor, raising questions about the potential use of neuroprotective agents to prevent this adverse effect. Specific studies seeking to address this important question are warranted.

The angiopoietin (Ang)/Tie2 signalling axis, a key regulator of angiogenesis, has emerged as a potential therapeutic strategy, and several clinical trials have demonstrated the efficacy of pharmacologic and biologic mediators of the Ang/Tie2 pathway [65]. The VEGF pathway is important for inducing endothelial cell sprouting and primary network formation, whereas the Ang/Tie2 pathway regulates blood vessel remodelling and maturation in the later stages of the angiogenic process [66]. The simultaneous inhibition of angiopoietin-2 and VEGF-A with faracimab have been shown to be superior to anti-VEGF alone at week 24 in treatment-naive patients with DME [67].

4.2.3. Corticosteroids

Intravitreal corticosteroids are mainly used due to their anti-inflammatory mechanisms. Intravitreal use limits the action to the eye and makes it possible to reach pharmacological concentrations. However, the complication rate (in the eye) of intravitreal corticosteroid injections is high, e.g., glaucoma and cataract formation [68]. For this reason, the use of intravitreal corticosteroids is generally restricted to patients affected by persistent or refractory DME, especially in pseudophakic eyes [69]. Apart from abrogating the effects of proinflammatory cytokines, corticosteroids are able to exert neuroprotection, as has been proven in experimental and clinical studies. Furthermore, they also have antiangiogenic action. These multifaceted effects have led to increased interest in these classic drugs, and sustained release formulations or implants that reduce the frequency of intravitreal injections are now available [68].

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