Review Article

Diabetic Retinopathy: An Overview of Treatments

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Abstract

Diabetic retinopathy (DR), substantially impacts the quality of life of diabetic patients, it remains, in developed countries, the leading cause of vision loss in working-age adults (20–65 years). Currently, about 90 million diabetics suffer from DR. DR is a silent complication that in its early stages is asymptomatic. However, over time, chronic hyperglycemia can lead to sensitive retinal damage, leading to fluid accumulation and retinal haemorrhage (HM), resulting in cloudy or blurred vision. It can, therefore, lead to severe visual impairment or even blindness if left untreated. It can be classified into nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). NPDR is featured with intraretinal microvasculature changes and can be further divided into mild, moderate, and severe stages that may associate with diabetic macular oedema (DME). PDR involves the formation and growth of new blood vessels (retinal neovascularisation) under low oxygen conditions. Early identification and treatment are key priorities for reducing the morbidity of diabetic eye disease. In the early stages of DR, a tight control of glycemia, blood pressure, plasma lipids, and regular monitoring can help prevent its progression to more advanced stages. In advanced stages, the main treatments of DR include intraocular injections of anti-vascular endothelial growth factor (VEGF) antibodies, laser treatments, and vitrectomy. The aim of this review is to provide a comprehensive overview of the published literature pertaining to the latest progress in the treatment of DR.

Keywords: Antivascular endothelial growth factor, diabetic retinopathy, laser photocoagulation, proliferative diabetic retinopathy, vitrectomy

Introduction

Diabetic retinopathy (DR), substantially impacts the quality of life of diabetic patients, it remains, in developed countries, the leading cause of vision loss in working-age adults (20–65 years).[1,2] Currently, about 90 million diabetics suffer from DR, including 17 million diabetics with proliferative diabetic retinopathy (PDR), 21 million with diabetic macular edema (DME), and 28 million patients with DR that pose a serious threat to vision, and this prevalence of DR is expected to double by 2025 in the absence of better preventive therapeutic strategies.[2-4]

In almost all type 1 diabetics (T1D), the course of diabetes in the first two decades after the onset of diabetes can be complicated by DR, and about two-thirds of patients with type 2 diabetes (T2D) can also have some form of disease.[1] DR is a silent complication that, in its early stages is asymptomatic. However, over time, chronic hyperglycemia can lead to sensitive retinal damage, leading to fluid accumulation and retinal HMs, resulting in cloudy or blurred vision. It can, therefore, lead to severe visual impairment or even blindness if left untreated.[5] It can be classified into nonproliferative DR (NPDR) and PDR.[6,7] NPDR is featured with intraretinal microvasculature changes,[8] and can be further divided into mild, moderate, and severe stages that may associate with DME.[9] PDR involves the formation and growth of new blood vessels (retinal neovascularisation) under low oxygen conditions.[8] Thus, the fragility of the newly formed blood vessels without timely treatment can lead to vision loss. The presence of microaneurysms (MAs), soft/hard exudates (EXs), and haemorrhages (HMs) in the fundus image

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are pathognomonic signs of DR, as shown by several clinical studies.[10]

Early identification and treatment are the key priorities for reducing the morbidity of diabetic eye disease. Nevertheless, when appropriate treatments were applied, at least 90% of new cases of DR return to normal retinal structure, as well as normal functional restoration.[11] Although significant therapeutic progress has been made over the past decade and a variety of DR treatments are currently available, none of them are yet curative.[5] The need for an adequate screening programme for retinal surveillance for timely determination of the retinal condition and perhaps the level of damage has been reiterated. Moreover, new modalities of salvation treatment have arisen, and these have served as a source of hope even for patients with advanced DR, where it is calculated that 95% of them could continue with their vision once well treated before the retina is severely damaged.[12]

In the early stages of DR, a tight control of glycemia, blood pressure, plasma lipids and regular monitoring can help prevent its progression to more advanced stages. In advanced stages, the main treatments of DR include intraocular injection of antivascular endothelial growth factor (VEGF) antibodies, laser treatment, and vitrectomy.[13,14] In recent studies, the advantage of using these intraocular pharmacotherapies in treating the progression of PDR and DME has been shown, particularly applying anti-inflammatory (corticosteroids) and antiangiogenic agents (VEGF inhibitors).[15]

Although the results are encouraging, several adverse effects of the treatment were reported, and the treatment does not respond in some of the patients.[5]

The aim of this systematic review is to provide a comprehensive overview of the published literature pertaining to the treatment of DR.

Pathogenesis of Diabetic Eye Disease

Microangiopathy and capillary occlusion underlie the pathogenesis of DR, which is related to prolonged episodes of hyperglycemia.[16] Together, these lead to microvascular leakage and breakdown of the blood – the retinal barrier, resulting in retinal HM, EXs, and oedema, as well as the development of macular oedema. An increase in the level of VEGF is probably one of the major angiogenic factors implicated in the pathogenesis of DR.[17] In addition, some evidence clearly show that neurodegeneration is an early event in the pathogenesis of DR that could be linked to the development of microvascular abnormalities. The hallmarks of diabetes-induced neuroglial degeneration, which include reactive gliosis, diminished retinal neuronal function, and neural-cell apoptosis, have been observed to occur before overt microangiopathy in experimental models of DR and in the retina of diabetic donors.[18-20]

Paraclinical Examinations of DR

Optical coherence tomography

Optical coherence tomography (OCT) is an optical analogue of ultrasound imaging using low-coherence interferometry to give cross-sectional images of the retina. It makes it possible to quantify retinal thickening, confirm the diagnosis of macular edema and monitor it.[21]

Others paraclinical examinations of DR

They may also assist in the diagnosis of retinal lesions including biomicroscopy of the fundus with GOLDMAN 3 mirror and 90/78 dioptre lenses; retinography which in the form of photographs, makes it possible to obtain an image of the back of the eye or retina; fluorescein angiography is the baseline exam for the management of DR; Ultrasound of the posterior segment is indicated in case of intravitreous HM to detect detachment, tearing, or traction of the retina, or in case of the non-visible fundus.[22]

Systemic Factor Control and Treatment of DR

DR treatment depends on its stage or type. It should be remembered that this complication can be classified as nonproliferative and proliferative or macula edema.

Nonproliferative (background) DR

The recommendation for mild to moderate NPDR is a screening programme well implemented for the control of blood glucose systemic levels via intensive insulin therapy that significantly reduces the risk for retinopathy prevalence and progression of the disease.[23] In addition to the systemic insulin therapy's effect on glycemic and circulating insulin levels, it has been shown a local impact on ocular tissue as well, including restoration of retinal insulin receptor signalling cascade and rod photoreceptor function.[24,25]

Three large randomised clinical trials have demonstrated the beneficial effects of systemic blood glucose control on retinopathy. The Diabetes Control and Complications Trial,[26] the United Kingdom Prospective Diabetes Study (UKPDS),[27] and the action to control cardiovascular risk in diabetes (ACCORD) Eye Study Group,[27] all these studies have shown that tight glycemic control prevented the development of DR and decreased the progression of existing DR.

With regard to controlling blood pressure, high blood pressure is another well-known systemic risk factor for DR that may require specific management. Several studies[23] found that controlling blood pressure significantly reduced visual loss, leading to decreased progression of DR, and Candesartan has been shown to reduce the incidence of DR by 25% in T1D and 34% in T2D patients compared to Placebo. However, others studies showed that tight control of hypertension did not significantly reduce the incidence of DR.[21] Indeed, although there are contradictions about the advantage of antihypertensive therapy alone in the management of DR, the

control of blood glucose combined with that of blood pressure has clearly shown its evidence by significantly delaying the onset and slowing the progression of DR.[28,29]

Serum lipid levels, specifically dyslipidemia and elevated low-density lipoprotein (LDL) have also gained recent attention for their potential impact on vision loss in diabetic patients. They have been shown to be significantly associated with retinal hard EX formation.[25] Many studies[28,30,31] have shown a correlation between triglyceride levels and diabetic eye disease, although its impact on retinopathy specifically is debated. Some studies have shown that Fenofibrate (200 mg/day) added to simvastatin therapy in T2D slowed down the progression of DR in 4 years.[27]

Proliferative diabetic retinopathy

Laser photocoagulation

Pan-retinal photocoagulation (PRP) for PDR was first proposed in the 1960s. It can be PRP or focal laser photocoagulation. PRP is a gold standard technology for treating very serious NPDR, PDR, and DME.[32] The strongest evidence comes from two related studies which show that early PRP therapy reduces the risk of high-risk proliferative DR compared with delayed treatment, although the incidence of severe vision loss is low in both the early and delayed treatment groups (2.6% vs. 3.7%).[33] Supplementing pharmacotherapy with laser therapy both as focal and grid application for macular oedema and as PRP application for proliferative disease may provide a more durable response, which have been demonstrated by some clinical trials.[34-36] PRP laser therapy has been identified as the primary treatment for PDR, but there are also noteworthy side effects, including deterioration of the original macular oedema, peripheral retinal function, and damage to night vision function.[37]

Subthreshold laser (STL) is a latest laser model, which involves the grid-like application of non-photocoagulation laser spots to "photostimulate" external retinal tissues, mainly the retinal pigment epithelium (RPE), increasing the production of metabolites that inhibit neovascularisation and reduce the activity of vascular permeability or regulate the decrease in the production of mediators that increase vascular permeability and neovascularisation. In STLs, all benefits of continuous wave (CW) lasers can be achieved without adverse side effects. There are now several laser manufacturers supplying threshold laser systems such as the Micropulse laser™ (Iridex Corp.; Quantel Medical), Endpoint Management™ (Topcon), Microsecond Pulse (Navilas OD OS), and 2RT® (Ellex), they can all be applied to the fovea safely without visible damage.[38-57] Another innovation in retinal laser therapy is a photocoagulation system based on a back-of-the-eye camera integrated with retinal eye-tracking technology (NAVILAS). This technique allows the ophthalmologist to take an image of the retina of a patient with DR or DME, digitally surrounding the area requiring treatment, and have the device automatically deliver laser spots to the specified area.[58-60]

Recently, the PETER PAN study reported that retina visualisation technologies have also affected PDR treatment options and may have the potential to make targeted retinal photocoagulation a viable treatment option. This new technology, especially the Optos camera (Optos, Dunfermline, UK), allows a clinician to visualise the retina up to 200 internal degrees (sometimes without pupillary dilation), perform fluorescein angiography and autofluorescence to map STL burns on the retina. Targeted retinal photocoagulation could be used in conjunction with visible peripheral retinal ischaemia on Optos angiography. An optomap is a high-resolution ultra-widefield image of the retina, a high-definition photograph of eyes. Compared to traditional retinal imaging, Optos can capture up to 65% more of the retina. Optos devices are safe and may continue to become more prominent in the treatment of retinal lesions.[61]

With the emergence of new drugs that help effectively control macular oedema and retinal neovascularisation, the use of laser therapy for DR are diminishing. However, it still forms the mainstay of managing severe NPDR, PDR, and DME, because of the limited period of action of these new antiangiogenic agents.[62]

Anti-VEGF agents for PDR

VEGF is known for its important role in the genesis of DR.[63] Currently, the anti-VEGF molecules whose role in the management of DR is being studied are pegaptanib (Macugen), ranibizumab (Lucentis), bevacizumab (Avastin), and aflibercept intravitreal (Eylea). Among these anti-VEGF agents available, bevacizumab, in addition to being the most economical, has also shown good results when currently used as an off-label drug.[62]

Several studies found that intravitreal bevacizumab is also beneficial in PDR patients, although a study suggests that the procedure may increase the risk of traction retinal detachment (TRD) in fibrous eye growth. A prospective study assessed 40 eyes with PDR and found that the visual acuity (VA) of the eyes treated with PRP alone deteriorated significantly over a 3-month period ($P = 0.041$), while the VA of the eye receiving PRP combined with bevacizumab underwent no significant changes in VA. Bevacizumab has also been shown to be effective in PDR patients with vitreous haemorrhage (VH). Most patients with retinal neovascularization (NV) who received the drug showed abating at week 36. The results of other studies seem to suggest that taking bevacizumab a few days before surgery may have a substantial advantage in PDR patients. Whether physicians decide to use PRP or anti-VEGF therapy in PDR may depend on the presence or nonexistence of DME. In the presence of DME, anti-VEGF therapy may be preferable because it can treat both DME and PDR, provided that the patient receives monthly injections. In addition, care needs to be taken when using anti-VEGF drugs in patients with apparent fibrovascular membranes, as these drugs may aggravate TRD.[64-66]

Results from the Diabetic Retinopathy Clinical Research Network (DRCR) S Protocol S trial concluded that ranibizumab treatment for RDP also offered several advantages over PRP

for 2 years. It is an effective alternative to PRP for PDR treatment. The ranibizumab group showed superior gain in VA over the course of 2 years, decreased peripheral visual field loss, and few vitrectomies. In addition, ranibizumab-treated eyes were less likely to develop central-involved DME causing vision impairment of 20/32 or worse. With good therapeutic adherence, applying the anti-VEGF treatment algorithm DRCR.net for PDR can provide excellent clinical results for 2 years.[67]

The protocol AB randomised clinical trial is a surgical study evaluating rapid vitrectomy versus anti-VEGF therapy for VH due to PDR. This clinical trial was designed to compare these two initial treatment options. PDR patients with VH who received monthly 2 mg aflibercept intravitreal injections were compared to similar patients who had pars plana vitrectomy with PRP within 2 weeks of randomisation. This study has concluded that both aflibercept and vitrectomy with PRP are viable first-line options for the treatment of VH from PDR.[68]

Vitrectomy for PDR

At present, vitrectomies still play a key role in some treatments for DR.[36] It is an important means for the treatment of long-standing VH, tractional retinal detachment, and combined tractional and rhegmatogenous retinal detachment.

The Diabetic Retinopathy Vitrectomy Study has shown a benefit of earlier surgery in patients with T1D and in those with active neovascularisation.[11,26]

Over the past 40 years, many reports have clearly demonstrated the beneficial effects of vitrectomy in these cases. To date, however, there is no clear study to support this conclusion. Most studies have shown benefits in using preoperative anti-VEGF therapy to reduce the likelihood of intraoperative and postoperative HMs. In addition, reduced surgical time and improved postoperative VA trends have been confirmed in smaller case series. In addition, DR and DME vitrectomy are widely used in low-insured patients in areas of the world with limited economic resources, even in relatively affluent countries.[36] In a prospective, randomised, controlled study (Diabetic Retinopathic Vitrectomy Study, DRVS), the benefits of vitrectomy were confirmed and the optimal point in time was determined. Patients who underwent an early vitrectomy had significantly better vision than those who underwent surgery a year later.[69]

Corticosteroids for DR

The majority of studies involving corticosteroid therapy in DR has been predominantly focused on the effect of triamcinolone acetonide, dexamethasone and fluocinolone acetonide in the treatment of DR.[70-72] Considering that chronic inflammation contributes to the pathophysiology of DR, for this purpose, several new therapeutic targets have been identified for this disease targeting the liberating processes of cytokines and chemokines. The new therapeutic targets are the direct and indirect antagonism of interleukins, proteases, chemokines, tumour necrosis factor (TNF), angiopoietin-2, and kallikrein. Another compound involved in many systemic inflammatory diseases as well as DR is TNF. Angiopoietin-2 is another effective mediator of increased vascular permeability in DR. Corticosteroids are effective anti-inflammatory and antiangiogenic agents, which support the rationale for their use in the management of PDR. Side effects have been reported, namely, cataract formation, glaucoma, and infection.[63]

The corticosteroid drugs can be administered through topical route generally employed in the form of eye drops, systemic delivery via oral or intravenous routes, periocular delivery or transscleral delivery includes subconjunctival, subtenon, retrobulbar, peribulbar and posterior juxtascleral injections, which are less invasive than intraocular routes and intraocular delivery includes the intravitreal and suprachoroidal routes.[73]

The Diabetic Retinopathy Clinical Research Network (DRCR) and other clinical studies evaluated the role of intravitreal triamcinolone acetonide as adjunctive treatment to panretinal photocoagulation (PRP) for patients with PDR and DME in two different studies and have demonstrated the effectiveness of combination in preventing exacerbations of macular oedema with improvement in VA and macular thickness in patients having PDR and DME.[74-78] The DRCR first study compared two doses of intravitreal triamcinolone acetonide as monotherapy to focal/grid laser photocoagulation in 840 eyes with DME. The study has demonstrated that the 4 mg intravitreal triamcinolone acetonide group had better VA at 4 months; however, at 16 months, two years and three years, the laser group had better VA than either intravitreal triamcinolone acetonide groups. The laser group had fewer incidences of glaucoma and cataract.[79-81]

The second randomised controlled trial by the DRCR network compared focal/grid laser alone to 4 mg of intravitreal triamcinolone plus laser. Two additional arms utilised intravitreal ranibizumab. Similar to the previous study, the triamcinolone plus laser showed superiority compared to laser alone in terms of VA at 24 weeks follow-up. However, at 1 and 2 years, the treatments appeared equivalent in terms of VA outcome, but with increased rates of cataract and elevated intraocular pressure in the triamcinolone plus laser group. In the subgroup analysis of patients who were pseudophakic at baseline, the triamcinolone plus laser group appeared superior to the laser alone treatment and equivalent to the treatment arms using ranibizumab.[82,83]

Gillies *et al*.,[84] in another study reported the 2 years results of a randomised controlled trial of intravitreal triamcinolone plus laser versus laser treatment only for DME which showed that treatment with intravitreal triamcinolone acetonide plus macular laser resulted in a doubling of improvement in vision compared with laser only over 2 years in eyes with DME, but associated with cataract and raised intraocular pressure.

However, another study showed no beneficial effect of combined intravitreal triamcinolone acetonide plus PRP and macular photocoagulation in coexisting high-risk PDR and

DME in terms of VA and macular thickness compared with standard treatment.[85]

Beneficial effects of higher doses of aspirin (990 mg) in patients with early DR have been reported by the dipyridamole aspirin microangiopathy of diabetes (DAMAD) study, in contrast to the poor results obtained in advanced DR patients using 650 mg of aspirin, reported by the DR early treatment study (ETDRS). A prospective study made in 2020 showed the beneficial effects of sulindac on DR development and progression. More recently, preclinical studies with specific cyclooxygenase 2 (COX-2) inhibitors have shown beneficial effects translated in reduced vascular leakage, capillary cell apoptosis, and vessel degeneration. The topical administration of a COX-2 inhibitor in preclinical studies has been found to reduce DR symptoms similarly to systemic administration. While clinical use, when administered systemically, is discouraged due to the increased risk of heart attack and stroke.[86,87]

Others drugs

Some drugs often used for other pathologies have been tested as an anti-inflammatory against DR. Preclinical studies showed that oxides of nitrogen (NOX) blockers were able to reduce vascular leakage and neovascularisation, as well as oxidative stress and inflammation, by inhibiting nuclear factor-kappa B (NF-kB) activation and the production of chemokine (C-C motif) ligand 2 (CCL2).[88-90] Second-line oral antidiabetic drug dipeptidyl peptidase 4 (DPP-4) inhibitors (also known as gliptins) have shown anti-inflammatory properties and prevent blood retinal-barrier (BRB) breakdown in preclinical models of diabetes.[5,46] In addition to inhibitors (DPP-4), glucagon-like peptide 1 receptor agonists (GLP1RAs), have also proven similar benefits in experimental models, including protection against inflammation secondary to hyperglycemia, oxidative stress, BRB breakdown, angiogenesis and, neurodegeneration, being at least in part mediated by the AKT pathway.[91-93] Liraglutide, which is a GLP1RA, has also shown vasoprotective effects, as described in a recent study in diabetic rats.[50] Nicotinamide adenine dinucleotide phosphate (NAD (P) H) oxidase (NOX) inhibitors, including diphenyleneiodonium and apocynin, have demonstrated preventive effects against DR progression, which may be due to decreased reactive oxygen species (ROS) and VEGF levels, although independent NOX effects have also been reported.[51] Recently, several studies have focused on the possibility that nutraceutical agents may complement pharmacological therapy with the aim of preventing or delaying the evolution of DR. Some natural molecules, including a variety of polyphenols (resveratrol, curcumin, quercetin, pterostilbene, epicatechin, epigallocatechin gallate, etc.) and anthocyanins, sesamine (a lignan isolated from sesame seeds and sesame oil), bromelain (a cysteine protease found in pineapple juice and stems), as well as alpha-lipoic acid (a vitamin-like chemical present in liver, kidney, and some vegetables), and lutein (a carotenoid present in green vegetables), etc., Strong anti-inflammatory and antioxidant properties, including their ability to protect against hypoxia and angiogenesis, have been highlighted by several recent reviews. These properties have been associated with interference with adhesion, angiogenesis, and inflammation molecules/mediators such as intercellular adhesion molecule 1(ICAM-1), VEGF, and tumour necrosis factor a (TNF-a) and signalling namely via NF-kB, nuclear factor erythroid-related factor 2- Kelch-like ECH associating protein 1(NRF2-Keap1), and toll-like receptors (TLRs).[94-99] These molecules could be an attractive nutraceutical alternative to pharmacological approaches. Intravitreal administration of mesenchymal stem cell-derived (MSC-derived) exosomes is able to reduce retinal ischaemia and neovascularisation in a murine model of oxygen-induced retinopathy (OIR),[100] and reduce apoptosis and inflammatory responses through the reduction of monocyte chemoattractant protein-1 (MCP-1) in the retina of a mouse model of retinal laser injury.[101] MSC-derived EVs also show protective properties against DR in the retina of STZ-induced diabetic animals, being able to prevent retinal degeneration by increasing miRNA-222 expression,[102] and to reduce hyperglycemia-induced retinal inflammation, decreasing the levels of inflammatory markers, namely IL-1β, IL-18, and caspase-1 through miR-126 overexpression.[103] However, not only mesenchymal stem cell-derived extracellular vesicles (MSC-derived EVs) present protective effects. Exosomes from retinal astrocyte cells were able to prevent retinal vessel leakage and inhibit neovascularisation in a laser-induced choroidal neovascularisation model, which have been shown by Hajrasouliha *et al*. These initial findings encourage further research and the development of novel EVs-based therapies for the treatment of DR.[104-108]

Conclusions

A multidisciplinary approach can help significantly reduce the risk for vision loss from diabetes and associated eye diseases, such as DR. Primary prevention of DR and its progression through control of risk factors such as hyperglycemia and dyslipidemia are probably the prime aim of all clinicians. Current pharmacotherapies, particularly anti-VEGF agents and corticosteroids, now form the mainstay of treatment in the majority of cases where they serve as an important adjunct to laser. Since these need to be used via an intravitreal route, certain risks are involved and research is focusing on drugs which may be administered orally. Various agents such as aspirin, vitamin E, vitamin C, aldose reductase inhibitors, and protein kinase C inhibitors, which were expected to be promising theoretically, have not shown adequate outcomes. More clinical research is needed to complement the preclinical evidences for the use of nutraceuticals as an alternative to pharmacological approaches. The surgical outcome after diabetic vitrectomy has continued to steadily improve with advances in vitreoretinal surgical instrumentation and technique. The indications, efficacy, and safety of latest medical and surgical treatments, however, require further evaluation. One thing that is now certain is that in view of the multiple and complex pathways involved in the formation of DR, no single standard treatment strategy

is sufficient and multiple modes of treatment are needed as a part of the algorithm for DR management.

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Conflicts of interest

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