REVIEW ARTICLE

Update on the treatment of diabetic retinopathy

CME

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Objectives To describe the classification, clinical features, and evaluation of diabetic retinopathy and to review its conventional as well as most updated management.

Data sources Literature search of Medline up to October 2006.

Study selection Key words for the literature search were 'diabetic', 'retinopathy', 'treatment', 'laser photocoagulation', 'vitrectomy', 'corticosteroid', 'protein kinase C inhibitor', and 'VEGF inhibitor'.

Data extraction Original articles, review papers, and book chapters were reviewed.

Data synthesis Diabetic retinopathy remains one of the leading causes of blindness worldwide. The duration of diabetes and severity of hyperglycaemia are the major risk factors. It progresses from non-proliferative diabetic retinopathy to proliferative diabetic retinopathy through various stages, and the accurate diagnosis of its stage is important. Strict metabolic control and tight blood pressure control can significantly reduce the risk of developing retinopathy and its progression, but are difficult to achieve in clinical practice. Laser photocoagulation and vitrectomy are effective in preventing severe visual loss from sight-threatening diabetic retinopathy and its complications, but both modalities have potential side-effects. Results from clinical trials for protein kinase C inhibitors, intravitreal steroid injections, anti–vascular endothelial growth factor agents, angiotensin converting enzyme inhibitors, and growth hormone inhibitors are promising. Evidence from past clinical trials does not support a role for anti-platelet agents, aldose reductase inhibitors, and advanced glycation end-products inhibitors.

Conclusion Strict metabolic control, tight blood pressure control, laser photocoagulation, and vitrectomy remain the conventional management of diabetic retinopathy. Further clinical trials exploring the role of protein kinase C inhibitors, intravitreal steroid, anti–vascular endothelial growth factor agents, angiotensin converting enzyme inhibitors, growth hormone, and other potential therapies for diabetic retinopathy are actively ongoing. In the near future, results from these clinical trials may lead to the introduction of additional treatments and a corresponding reduction in the frequency of visual loss due to diabetic retinopathy.

Key words
Diabetic retinopathy; Laser coagulation; Treatment outcome; Triamcinolone acetonide; Vitrectomy

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Introduction

Diabetic retinopathy (DR) is the commonest microvascular complication of diabetes, and remains one of the leading causes of blindness worldwide.[1] During the first two decades of disease, nearly all patients with type 1 diabetes and over 60% with type 2 diabetes develop retinopathy. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% of younger-onset patients (type 1 diabetes) and 1.6% of older-onset patients (type 2 diabetes) were blind.[1] Duration of diabetes and severity of hyperglycaemia are the major risk factors for DR. Others include age, type of diabetes, clotting factors, and renal disease.[2]

Classification and natural history

Diabetic retinopathy is generally classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR), both of which are further graded into different

levels. Diabetic macular oedema (DMO) can occur at any stage. Accurate diagnosis of the stage of the disease is critical because the varying risk of progression to PDR and the more serious high-risk PDR depends on the specific NPDR level (Table 1[3-5]).

The earliest stage of DR (or NPDR) is characterised by retinal vascular abnormalities including microaneurysms (saccular out-pouchings from the capillary wall), intraretinal haemorrhages, and cotton-wool spots (nerve fibre layer infarctions). As the disease progresses, the gradual closure of retinal vessels results in retinal ischaemia, giving rise to signs including venous abnormalities (beading, loops), intraretinal microvascular abnormalities, and increasing retinal haemorrhage and exudation.[3] Non-proliferative diabetic retinopathy is graded as mild, moderate, severe, and very severe according to the presence and extent of the above lesions (Table 1).

The more advanced stage of DR (or PDR) involves the formation of new blood vessels, induced by the retinal ischaemia, which spreads out either from the disc (neovascularisation of the disc, NVD) or from elsewhere in the retina (neovascularisation elsewhere, NVE). New vessels extending into the vitreous can cause vitreous haemorrhage, and tractional retinal detachments (associated with accompanying contractile fibrous tissue). Ghost cell glaucoma resulting from vitreous haemorrhage can occur. Small full-thickness retinal holes may be seen near the proliferation; these sometimes lead to combined rhegmatogenous and tractional retinal detachment.[6] Late in the course of the disease, neovascular glaucoma can result from new vessels growing on the iris and anterior chamber angle structures.[3] The extent and location of neovascularisation determines the level of PDR (Table 1).

Diabetic macular oedema involves the breakdown of the blood-retinal barrier, with increased vascular permeability resulting in central retinal thickening (oedema) and lipid deposits (hard exudates).[3] This is termed clinically significant macular oedema (CSMO), when it is present close to the central macula (definition in Table 1). Both CSMO and PDR are the predominant causes of visual loss in DR.

Evaluation of diabetic retinopathy

The initial stages of DR are frequently asymptomatic, thus regular comprehensive eye evaluation to detect early treatable stages is very important. Currently, type 1 diabetic patients aged 10 years or older are encouraged to have eye examinations within 3 to 5 years of diabetes onset, while those with type 2 disease should receive comprehensive eye examinations shortly after being diagnosed.[1] Thereafter, diabetic patients without DR should have annual eye examinations to detect its emergence. For patients with moderate-to-severe NPDR, more frequent eye examinations are necessary to determine when to initiate treatment (as listed in Table 1).

A comprehensive eye evaluation should begin with a thorough history and eye examination, as shown in Table 2.[7] Clinical fundus examination with dilated indirect ophthalmoscopy coupled with biomicroscopy, and seven-standard field stereoscopic 30° fundus photography are both standard methods for examining DR. Stereo fundus photography is more sensitive at detecting retinopathy than clinical fundus examination, but the latter is superior for detecting retinal thickening in macular oedema and for early neovascularisation. Fundus photography also requires both a trained photographer and a trained reader. The use of film and digital non-mydriatic images may eventually permit undilated photographic retinopathy screening, but these techniques have not been fully evaluated.[1]

Fluorescein angiography is not a routine examination for diabetic patients, and is not required to diagnose CSMO or PDR, both of which are clinical diagnoses.

治療糖尿病視網膜病變的最新情況

目的 描述糖尿病視網膜病變的分類、臨床特徵和評估，並檢討各種傳統和最新的治療方法。

資料來源 在醫學資料庫「Medline」搜尋直至2006年10月的文獻。

研究選取 用以搜索文獻的關鍵詞為「diabetic」（糖尿病的）、「retinopathy」（視網膜病變）、「treatment」（治療）、「laser photocoagulation」（激光凝固療法）、「vitrectomy」（玻璃體切除術）、「corticosteroid」（皮質類固醇）、「protein kinase C inhibitor」（蛋白質激活酶C抑制劑）和「VEGF inhibitor」（血管內皮細胞生長因子）。

資料選取 論著、綜述和書籍的有關章節。

資料綜合 糖尿病視網膜病變仍然是全球引致失明其中一個主因，主要的風險因素是患糖尿病時間的長短和血糖過高的嚴重程度。糖尿病視網膜病變會分階段由非增生性惡化為增生性，因此準確診斷出病情屬哪個階段十分重要。嚴格控制代謝率和血壓能明顯減低發展成視網膜病變和惡化的風險，但臨床上很難控制。激光凝固療法和玻璃體切除術能有效防止因糖尿病視網膜病變及其併發症導致的嚴重視力缺損，但兩種方法都有潛在副作用。臨床試驗使用蛋白質激活酶C抑制劑、玻璃體內類固醇注射、抗血管內皮細胞生長因子藥物、血冠緊張素轉換酶抑制劑和賀爾蒙生長抑制劑，效果令人滿意。過去的臨床試驗並不支持以抗血小板藥、醛糖還原酶抑制劑和蛋白質高度糖化終產物抑制劑作治療藥物。

結論 嚴格控制代謝率和血壓、激光凝固療法和玻璃體切除術仍是糖尿病視網膜病變的慣常治療方法，而醫學界正積極嘗試蛋白質激活酶C抑制劑、玻璃體內類固醇、抗血管內皮細胞生長因子藥物、血冠緊張素轉換酶抑制劑、賀爾蒙生長抑制劑和其他潛在的糖尿病視網膜病變的治療方式。在未來一段短時間，這些臨床實驗的結果或會帶來新的治療方法，從而減低糖尿病視網膜病變導致失明的比率。

TABLE 1. Clinical stages of diabetic retinopathy and management recommendations* [3-5]

Level of diabetic retinopathy	Clinical findings	Rate of progression		
		PDR 1 yr	HR PDR 1 yr	HR PDR 5 yrs
No NPDR	-	-	-	-
Mild NPDR	At least one microaneurysm Mild level of microaneurysms and retinal haemorrhage	5%	-	15%
Moderate NPDR	Moderate level of microaneurysms and retinal haemorrhage Mild levels of cotton wool spots, venous beading, and IRMA	12-27%	1.2-8.1%	33%
Severe NPDR	Any one of the features: (1) Severe intraretinal haemorrhages and microaneurysms in all four quadrants (2) Venous beading in two or more quadrants (3) Moderate IRMA in at least one quadrant	52%	14.6%	60-75%
Very severe NPDR	Any two of the features: (1) Severe intraretinal haemorrhages and microaneurysms in all four quadrants (2) Venous beading in two or more quadrants (3) Moderate IRMA in at least one quadrant	75%	45%	75%
PDR < HR	NVD or NVE, less severe than HR PDR	NA	NA	75%
HR PDR	Any one of the features: (1) NVD ≥1/3-1/2 disc area (2) NVD and vitreous or preretinal haemorrhage (3) NVE ≥1/2 disc area and preretinal or vitreous haemorrhage	Severe visual loss (VA ≤5/200) develops in 25-40% within 2 years		
Severe PDR/VH	Posterior fundus obscured by preretinal or vitreous haemorrhage or centre of macula detached	NA	NA	NA

* Abbreviations: CSMO denotes clinically significant macular oedema; FA fluorescein angiography; HR high-risk; IRMA intraretinal microvascular abnormalities; MO macular oedema; NA not applicable; NPDR non-proliferative diabetic retinopathy; NVD neovascularisation of the disc; NVE neovascularisation elsewhere; PDR proliferative diabetic retinopathy; PPV pars plana vitrectomy; PRP panretinal photocoagulation; US ultrasonography; VA visual acuity; and VH vitreous haemorrhage

† CSMO is defined as: (1) thickening of the retina located ≤500 μm from the centre of the macula, or (2) hard exudates ≤500 μm from the centre of the macula, if associated with thickening of adjacent retina, or (3) a zone of retinal thickening, 1 disc area or larger in size located ≤1 disc diameter from the centre of the macula

‡ Deferral of photocoagulation for a brief period of medical treatment for cases of hypertension or fluid retention associated with heart failure, renal failure, pregnancy or any other causes that may aggravate diabetic macular oedema may be considered. Also deferral of CSMO treatment is an option when centre of the macula is not involved, visual acuity is excellent, close follow-up is possible, and the patient understands the risks

§ Early PRP may be indicated in the presence of rapidly advancing retinal disease, history of poor patient follow-up, in patients with type 2 diabetes mellitus or type 1 diabetes mellitus of long duration, or if concurrent medical status suggests rapid progression of diabetic retinopathy

‖ Because PRP may exacerbate diabetic macular oedema, macular oedema approaching CSMO may be treated first if PRP is indicated

¶ Treatment of CSMO should be performed as part of first treatment session along with initial PRP

However, it is useful in guiding the treatment of CSMO, identifying macular capillary non-perfusion, and investigating unexplained visual loss. Ultrasonography is a valuable test for evaluating DR with opaque media, particularly to determine the presence of retinal detachment.[2] Optical coherence tomography (OCT) is a new modality to evaluate DR, which provides images by projecting a pair of near-infrared light beams into the eye. The resulting interference pattern from these beams is dependent of the thickness and reflectivity of the retinal structures that is detected by the measuring system. The images produced appear to be cross-sections of the retina and allow retinal thickness to be measured.[8] This technology can be used to quantify retinal thickness, monitor partial resolution of macular oedema, and identify vitreomacular traction in selected patients with DMO (caused by a taut posterior hyaloid face).[2]

Treatment of diabetic retinopathy

Decades of clinical research have provide excellent data on the treatment strategies for DR; these are based on randomised controlled interventional trials (Table 3).[9-16]

Control of systemic factors

Glycaemic control

At present, the most effective medical treatment for DR is glycaemic control. Two important trials, the Diabetes Control and Complications Trial (DCCT)[9] and the United Kingdom Prospective Diabetes Study (UKPDS)[10] conclusively demonstrated that intensive glycaemic control significantly reduces the risk of DR development and progression in both type 1 and type 2 diabetes, though not preventing retinopathy completely (Table 3). Interest-

Involvement of macular oedema (MO)	Evaluation by FA	Ocular treatment		Follow-up (months)
		Panretinal laser	Focal/grid laser	
-	No	No	No	12
No MO	No	No	No	12
MO	Occasional	No	No	4-6
CSMO†	Yes	No	Yes‡	2-4
No MO	No	No	No	6-8
MO	Occasional	No	No	4-6
CSMO	Yes	No	Yes‡	2-4
No MO	No	Consider§	No	3-4
MO	Occasional	Consider§	Occasional‖	2-3
CSMO	Yes	Consider§	Yes	2-3
No MO	No	Consider§	No	3-4
MO	Occasional	Consider§	Occasional‖	2-3
CSMO	Yes	Consider§	Yes	2-3
No MO	No	Consider§	No	2-3
MO	Occasional	Consider§	Likely‖	2-3
CSMO	Yes	Consider§	Yes	2-3
No MO	No	Yes	No	2-3
MO	Occasional	Yes	Likely‖	2-3
CSMO	Yes	Yes	Yes¶	2-3
-	FA/US as indicated	PRP/focal/PPV/endolaser		-

ingly, early worsening of retinopathy (cause unknown) was observed during the first year of treatment in some patients in the intensive therapy group, but in the long term it progressed more slowly than in those treated conventionally.[17] The current recommendations for glycaemic control aim for a preprandial plasma glucose level of 5.0-7.2 mmol/L, a postprandial level of <10.0 mmol/L, and an HbA1c level of <7%.[8] There does not appear to be a level below which there is not a reduction of microvascular complications. However, there are risks to intensive glycaemic control, including two-to-three fold increase in severe hypoglycaemia, and weight gain.[2]

Tight blood pressure control

Hypertension might contribute to worsening of DR by increasing endothelial shear stress and the release of vascular endothelial growth factor (VEGF) that follows stretching of the vessel walls, leading to altered retinal autoregulation and increased perfusion pressure.[18] Both the UKPDS[11] and Appropriate Blood Pressure Control in Diabetes (ABCD[12]) trials showed a highly significant beneficial effect of tight blood pressure (BP) control on the progression of retinopathy and visual loss (Table 3). Unlike tight glycaemic control, there were no clear adverse reactions to tight BP control.[8] Current recommendation for BP control for diabetic adults is aimed to <130/85 mm Hg.[19]

Lipid control

Elevated serum lipid levels are positively associated with retinal hard exudates in DR. Hard exudates, in turn, are associated with visual impairment and subretinal fibrosis from macular oedema.[20] A recent small prospective trial of patients with macular oedema and dyslipidaemia found a statistically significant reduction in hard exudates versus controls after initiation of atorvastatin, but visual acuity (VA) was not affected.[21] Another study found that simvastatin inhibited progression of retinopathy in diabetic patients with dyslipidaemia.[22] Further clinical trials are currently underway examining the effects of statins.[23]

Laser photocoagulation

Timely laser photocoagulation remains the principal therapy for sight-threatening DR. Laser photocoagulation techniques can be classified as panretinal, focal, or grid.

The Diabetic Retinopathy Study (DRS[13]) and the Early Treatment Diabetic Retinopathy Study (ETDRS[14]) are the two major trials providing strongest support for

TABLE 2. Comprehensive clinical eye evaluation with particular relevance to patients with diabetes[7]

Element of evaluation	Examples of particular relevance to patients with diabetes
History	Type of diabetes, age at onset and duration of diabetes, degree of glycaemic control, concurrent complications (neuropathy, nephropathy, retinopathy, cardiovascular disease), associated systemic findings (hypertension, lipid levels, pregnancy status, onset of puberty, obesity), compliance with general medical follow-up, extent of patient involvement in and understanding of disease process
Best corrected visual acuity	Quantitates level of high-contrast, high-frequency visual function Decline can indicate onset of visually significant macular oedema, vitreous haemorrhage, cataract, macular traction detachment
Ocular alignment and motility	Evaluates function of oculo-motor cranial nerves Abnormalities can indicate cranial nerve palsies (III, IV, and VI) associated with diabetic neuropathy
Pupil reactivity and function	Evaluates pupil-motor pathway and structural integrity of the iris Abnormalities can indicate neuropathy, iris neovasularisation, or afferent papillary defect
Visual fields	Evaluates possible defects in peripheral vision. Confrontational fields provide a qualitative assessment, and perimetry a quantitative assessment Abnormalities can indicate vitreous/preretinal haemorrhage, retinal detachment, or vascular occlusion
Intra-ocular pressure	Measurement of intra-ocular pressure. Applanation tonometry is preferred Abnormalities can indicate possible neovascular or open angle glaucoma
Slitlamp examination	
Cornea	Assessment of ocular surface Abnormalities can indicate epithelial abnormalities, defects, or infection
Iris	Assess iris and when indicated gonioscopy for possible angle closure or angle neovascularisation Abnormalities can indicate neovascular glaucoma
Lens	Assess lens nucleus, cortex, and posterior capsule Abnormalities can indicate cataract
Vitreous	Assess clarity and character of vitreous gel Abnormalities can indicate vitreous haemorrhage (red cells), retinal tear or detachment (pigment cells), or possible vitreoretinal traction (posterior vitreous detachment)
Fundus examination	
Dilated fundus examination Slitlamp biomicroscopy and binocular indirect ophthalmoloscopy	Assess presence, location, and extent of retinal-vitreal disease Abnormalities include retinal thickening, hard exudates, retinal haemorrhages and microaneurysms, intraretinal microvascular abnormalities, venous beading, neovascularisation of the disc or neovascularisaton elsewhere, vitreous or preretinal haemorrhage, retinal traction, nonperfusion, retinal tears or holes, and tractional or rhegmatogenous retinal detachment

the therapeutic benefit of photocoagulation. These trials demonstrated that panretinal photocoagulation (PRP) effectively reduces by at least 50% the risk of severe vision loss (VA ≤5/200), and that focal or grid laser reduced the risk of moderate vision loss (doubling of the visual angle) from CSMO, by at least 50% (Table 3). In general, PRP is indicated in high-risk PDR and neovascular glaucoma; the rationale being to ablate ischaemic areas of the peripheral retina and thereby reduce induction of angiogenic growth factors.[19] Focal and grid laser photocoagulation is indicated for CSMO; the goal being to limit vascular leakage through a series of focal laser burns at leaking microaneurysms or grid laser burns in regions of diffuse breakdown of the blood-retinal barrier.[19] In some patients with less than high-risk PDR or with severe or very severe NPDR, PRP may be indicated under certain circumstances. The latter include: presence of rapidly advancing retinal disease, history of poor patient follow-up, type 1 or 2 diabetes mellitus of long duration, a strong family history of diabetes mellitus, or concurrent medical status suggesting rapid progression of DR.[7] Typical management recommendations are shown in Table 1.

Focal or grid laser photocoagulation may result in an initial decrease in central vision. Rarely, they may induce subretinal fibrosis with choroidal neovascularisation. On the other hand, peripheral visual field constrictions with poor dark adaptation are the side-effects of extensive PRP. In the presence of neovascularisation, vitreous haemorrhage may occur during the course of treatment.[2]

New modalities of subthreshold diode micropulse photocoagulation, inducing invisible burns targeted at the retinal pigmented epithelium and sparing the neurosensory layer have been proposed as minimally invasive strategies with fewer side-effects, but claims of benefit are limited to uncontrolled reports.[24]

Vitrectomy

For severe complications of PDR (most commonly tractional retinal detachment), vitrectomy remains the treatment of choice. Macular oedema induced by the contraction of taut, persistently attached posterior hyaloid not responding to focal or grid laser photocoagulation, is another indication.[2] The Diabetic Retinopathy Vitrectomy

TABLE 3. Summary of multicentred randomised controlled trials on diabetic retinopathy (DR)[*] [9-16]

Trial[†]	Agent	Length (years)	Sample size	Major conclusion
DCCT[9]	Glycaemic control	6.5 (3-9)	1441 (T1DM)	Intensive glycaemic control[‡] can achieve (when compared with conventional control): • 76% risk reduction in onset of new retinopathy • 54% risk reduction in existing DR worsening • 56% reduction in necessity of photocoagulation
UKPDS[10]	Glycaemic control	11	3867 (T2DM)	Intensive glycaemic control can achieve (when compared with conventional control): • 21% risk reduction in existing DR worsening • 29% risk reduction in necessity of photocoagulation
UKPDS[11]	BP control; ACEI	9	1148 (T2DM)	Tight BP control[§] can achieve (when compared with less tight control) • 34% risk reduction in 2-step worsening of DR • 47% risk reduction in doubling of visual angle Beneficial effect from BP control on DR progression was independent of whether using ACEI or beta blocker
ABCD[12]	BP control; ACEI	5	480 (T2DM, normo-tensive)	• A significantly lower progression of retinopathy in intensive BP control group versus moderate control group (34% vs 46%) • No statistically significant difference in using ACEI or calcium channel blocker as the primary antihypertensive medication
DRS[13]	Photocoagulation	5	1758	• PRP reduced the risk of severe visual loss (VA ≤5/200) by 50% in eye with PDR • PRP has moderate risk of decrease in VA (usually only 1 line) and visual field • Treatment benefit outweighs risks for eyes with high-risk PDR
ETDRS[14]	Photocoagulation; aspirin	5	3711 (T1 and T2 DM)	• Focal and grid photocoagulation reduced the risk of moderate visual loss (doubling of the visual angle) from CSMO by 50% or more and increased the chance of a small improvement in VA • Both early PRP with or without focal photocoagulation and deferral were followed by low rates of severe visual loss (5-year rates in deferral subgroups were 2-10%; in early photocoagulation groups, these rates were 2-6%) [not only from CSMO] • Focal and grid photocoagulation should be considered for eyes with CSMO • PRP is not indicated for mild-to-moderate NPDR but should be considered as retinopathy approaches the high-risk stage and usually should not be delayed when the high-risk stage is present • Benefit of early PRP is more pronounced for patient with type 2 DM or with type 1 DM of long duration • Aspirin had no effect on progression of retinopathy, frequency of vitreous haemorrhage, or cataract development
DRVS[15]	Vitrectomy	4	370	• Early vitrectomy was beneficial for patients with VA ≥20/400 plus one of the following: 1. Severe neovascularisation and fibrous proliferation 2. Fibrous proliferation and moderate vitreous haemorrhage 3. Moderate neovascularisation, severe fibrous proliferation, and moderate vitreous haemorrhage • Among such patients, 44% with early vitrectomy and 28% with deferral treatment had VA ≥20/40 at 4 years' follow-up • The advantage of attaining good vision was most pronounced in type 1 DM (36% vs 12% for early vitrectomy vs deferral of vitrectomy respectively) and was not statistically significant for type 2 DM
EUCLID[16]	ACEI (lisinopril)	2	354 (T1DM)	Lisinopril reduced DR progression by 50% and development of PDR by 80% over 2 years in normotensive patients with type 1 DM

[*] Abbreviations: ACEI denotes angiotensin-converting enzyme inhibitor; BP blood pressure; CSMO clinically significant macular oedema; DM diabetes mellitus; DR diabetic retinopathy; NPDR non-proliferative diabetic retinopathy; PDR proliferative diabetic retinopathy; PRP panretinal photocoagulation; and VA visual acuity

[†] Trial abbreviations: DCCT denotes Diabetes Control and Complications Trial; UKPDS United Kingdom Prospective Diabetes Study; ABCD Appropriate Blood Pressure Control in Diabetes; DRS Diabetic Retinopathy Study; ETDRS Early Treatment Diabetic Retinopathy Study; DRVS Diabetic Retinopathy Vitrectomy Study; EUCLID EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes Mellitus

[‡] Definition of intensive glycaemic control: preprandial blood glucose concentrations between 3.9 and 6.7 mmol/L, postprandial concentrations of <10 mmol/L, a weekly 3-a.m. measurement >3.6 mmol/L, and haemoglobin A1c, measured monthly, below the normal level (<6.05%)

[§] Definition of tight BP control: <150/85 mm Hg

Study (DRVS),[15] was an important trial evaluating the role of vitrectomy in the management of advanced DR. It found that compared to deferred vitrectomy (after 1 year), early vitrectomy (within first 6 months) conferred more benefit for patients with VA ≥20/400 plus one of the following: (1) severe neovascularisation and fibrous proliferation, (2) fibrous proliferation and moderate vitreous haemorrhage, (3) moderate neovascularisation with severe fibrous proliferation and moderate vitreous haemorrhage. Among such patients, 44% with early vitrectomy and 28% with deferral treatment had VA ≥20/40 after 4 years follow-up[15] (Table 3). The benefits were more pronounced in type 1 diabetes, but not statistically significant in type 2 diabetes. However,

BOX. Indications for vitrectomy following severe complications of diabetic retinopathy[25]

Media opacities

A. Nonclearing haemorrhage
   1. Vitreous
   2. Subhyaloid, premacular haemorrhage
   3. Anterior segment neovascularisation with posterior segment opacity
B. Cataract preventing treatment of severe proliferative diabetic retinopathy (lensectomy)

Vitreoretinal traction

A. Progressive fibrovascular proliferation
B. Tractional retinal detachment involving the macula
C. Combined traction and rhegmatogenous retinal detachment
D. Macular oedema associated with taut, persistently attached posterior hyaloid

Post-vitrectomy complications

A. Vitreous haemorrhage/ghost cell glaucoma
B. Retinal detachment—tractional or rhegmatogenous
C. Anterior hyaloidal fibrovascular proliferation
D. Fibrinoid syndrome
E. Epiretinal membrane (nonvascularised)

the DRVS results should be interpreted in the light of subsequent advances in vitreoretinal surgery (endolaser photocoagulation, certain bimanual techniques, and use of perfluorocarbon liquid). Thus, early vitrectomy for type 2 diabetes patients with severe non-clearing vitreous haemorrhage should probably be considered, particularly if active neovascularisation is present.[2] Indications for vitrectomy have considerably widened in the past few years as it has become a safer and more effective treatment option (Box).[25]

The main objectives of vitrectomy are to remove media opacities, completely relieve all tractional adhesions, and manage recurrent complications from previous vitrectomy.[25]

In a review of literature, 55 to 89% of participants undergoing vitrectomy achieved some improvement or stabilisation of VA.[26] The most frequent short-term postoperative complication of vitrectomy is recurrent vitreous haemorrhage, while the premature development of cataract is the most common long-term complication. Rubeosis iridis with secondary glaucoma, endophthalmitis, retinal tear, and detachment are other important complications.[25]

Future directions: potential pharmacological therapies

Due to the limitations of current treatment, new pharmacological therapies are being developed. The latter target underlying biochemical mechanisms that cause DR through involvement of: protein kinase C (PKC) activation, oxidative stress, the angiogenesis pathway, and the glycation and sorbital pathway. These treatments aim to prevent diabetes-induced damage to the retinal microvasculature.

Protein kinase C inhibitors

Hyperglycaemia-induced de-novo synthesis of diacylglycerol leads to selective activation of PKC isozymes, especially PKC-β. This results in basement membrane thickening and changes in vessel permeability and/or blood flow.[5] Two PKC inhibitors are in development to reduce microvascular complications in diabetic patients.

Ruboxistaurin (LY333531) is a specific inhibitor of PKC-β, which ameliorates vascular complications of diabetes in animal models,[20] and diabetes-induced retinal blood flow abnormalities in patients, demonstrating its ability to reach the human retina in bioeffective concentration.[27] The initial results of the PKC-β Inhibitor Diabetic Retinopathy Study (PKC-DRS) demonstrated that ruboxistaurin had no significant effect on the progression of retinopathy, but there was a trend towards benefit in terms of preservation of vision.[28] Recently, the results from the PKC-β Inhibitor Diabetic Retinopathy Study 2 (PKC-DRS2) showed that the drug reduces the occurrence of sustained moderate visual loss by 40% in patients with moderately severe to very severe NPDR, while increasing the likelihood of visual improvement 2-fold. Ruboxistaurin treatment also reduces progression of CSMO to within 100 microns of the centre of the macula, progression of overall DMO severity, and the need for initial focal photocoagulation.[29] Ruboxistaurin is the first oral pharmacologic agent shown to reduce visual loss in diabetic patients over an extended period. Use of this novel therapeutic approach in concert with optimal metabolic control and current ophthalmic therapies may be able to achieve improved preservation of vision in DR.[29]

The second PKC inhibitor, PKC412, was found to be generally tolerable at the doses tested in a phase I trial.[30] Another phase I/II placebo-controlled, dose-ranging study showed that orally administered PKC412 at doses of 100 mg/day or higher may significantly reduce macular oedema and improve VA in diabetic subjects.[31]

Intravitreal injection of triamcinolone acetonide

The intravitreal injection of a slow-release steroid, triamcinolone acetonide, which suppresses inflammation, reduces extravasion from leaking blood vessels and inhibits fibrovascular proliferation, has emerged as a promising therapy for DMO refractory to conventional laser photocoagulation.[32] Many clinical trials had been conducted to evaluate the efficacy of intravitreal injection of triamcinolone acetonide (IVTA) therapy for DMO, and the results are summarised in Table 4.[33-55]

The most convincing evidence for the effect of IVTA in the treatment of DMO comes from a recent randomised trial by Gillies et al.[33] They performed a prospective, double-masked, placebo-controlled, randomised clinical trial on 69 eyes of 43 patients, with 34 eyes randomised to IVTA (4 mg) and 35 to receive placebo. Two-year results demonstrated that 19 (56%) of the former eyes gained five or more letters in best-corrected VA compared with 9 (26%) of eyes treated with placebo. In the treatment group, foveal thickness had decreased by 59 μm more than that in the placebo group. A similar result was reported from another randomised controlled study involving 6 months follow-up on 40 eyes of 38 patients,[34] in which 28 (70%) of the eyes were randomised to treatment with 20 mg IVTA and 12 (30%) to placebo injection. The gain in VA at 3-month and 6-month follow-ups was significantly higher in the treatment group.[34] In another prospective randomised interventional trial of 63 eyes, efficacy of IVTA versus macular laser grid (MLG) photocoagulation, versus both (IVTA+MLG) in the treatment of cystoid macular oedema was evaluated.[45] In this study, 48 of 63 eyes had cystoid macular oedema due to DR. It was shown that IVTA improved VA and reduced central macular thickness more than MLG, and nor did combination therapy offer any further advantage.

Using a dosage of about 20 mg IVTA, the increase in VA was most marked during the first 3 to 6 months after injection, and was evident for about 6 to 9 months.[40] Using a dosage of 4 mg, the duration of the effect (as measured by a reduction in macular thickness by OCT) was less than 6 months.[38] These results lead to clinical trials comparing the efficacy of different IVTA doses (Table 4),[46-48] which confirmed that, in general the duration of the effect increased with increasing dosage. Since the beneficial effects of IVTA are transient, with recurrence of macular oedema, in a proportion of eyes repeated injection may be necessary. Jonas et al[52] described the response of four eyes with diffuse CSMO whose VAs improved after an initial and repeated IVTA injection of 20 mg. However, the same group later described a larger series of 22 eyes in 19 patients who received two to three injections of 20 mg and demonstrated that VA improvements were not significantly different between injections.[50] Another study also reported that VA improved after repeated 4 mg injections, but at all time points it was significantly worse than that after the initial injection.[49]

The role of IVTA as adjunctive treatment to PRP for PDR is also being evaluated. Evidently IVTA enabled PRP to be applied without worsening of macular oedema and progression of retinopathy in a young patient with florid PDR.[56] Another single case study reported marked regression of optic nerve head neovascularisation after IVTA.[57] Zacks and Johnson[55] described the effectiveness of combined IVTA and PRP in preventing exacerbations of macular oedema in patients having PDR and CSMO. A recent interventional case series also demonstrated beneficial effect of IVTA on PRP in such patients, by reducing neovascularisation and macular thickening.[54] In a study of 35 eyes with both high-risk PDR and CSMO when the effect of combined IVTA and PRP were compared to combined MLG and PRP, 34% of eyes in IVTA group had final vision of 20/40 or better versus 11% in the laser group; 84% of IVTA eyes had complete resolution of macular oedema versus 46% of laser eyes.[53] Thus it was concluded that in management of patients with both PDR and CSMO, the addition of IVTA to PRP seems promising and warrants further study.[53]

Two of the most common side-effects of IVTA are: (1) steroid-induced elevation of intra-ocular pressure (IOP), and (2) steroid-induced cataract. In the randomised controlled trial by Gillies et al,[33] the IOP increased more than 5 mm Hg or more in 23 (68%) of 34 treated eyes versus 3 (10%) of 30 untreated eyes. Glaucoma medication was required in 15 (44%) of 34 treated versus 1 (3%) of 30 untreated eyes. Two eyes in the IVTA group required trabeculectomy. Cataract surgery was performed in 15 (54%) of the 28 treated phakic eyes versus 0 (0%) of 21 untreated eyes. There was one case of infectious endophthalmitis in the treatment group.[33]

Anti–vascular endothelial growth factor agents

Vascular endothelial growth factor is produced in response to hypoxia from capillary loss and/or microaneurysm formation. It is a key mediator of angiogenesis and blood-retina barrier breakdown in the ischaemic retina.[20] Thus, inhibition of VEGF activity may play a pivotal role in the prevention of PDR. Currently, there are three main anti-VEGF agents under investigation: (1) pegaptanib sodium (Macugen; Eyetech Pharmaceuticals Inc, New York and Pfizer Inc, New York, US); (2) ranibizumab (Lucentis; Genentech Inc, South San Francisco, CA, US) and (3) bevacizumab (Avastin; Genentech, South San Francisco, California, US). Clinical study results for anti-VEGF therapies in DR are summarised in Table 5.[58-61]

Pegaptanib is a modified 28-base pegylated RNA aptamer that binds VEGF165 and the longer VEGF isoforms.[62] A phase II clinical trial of pegaptanib in patients with DMO followed up for 36 weeks, resulted in better VA outcomes, reduced central retinal thickness, and reduced resort to additional photocoagulation therapy when compared with sham injections (Table 5).[58] A retrospective analysis of the same study on patients with retinal neovascularisation at baseline, demonstrated reduced leakage, and regression of the neovascularisation after intravitreal pegaptanib administration (Table 5).[59] A phase III clinical trial is currently ongoing.[62]

Ranibizumab is a recombinant humanised monoclonal antibody fragment with specificity for all isoforms of human VEFG.[62] A pilot study in patients with CSMO showed that therapy with this drug has the potential to maintain or improve VA and reduce retinal thickness (Table 5).[60]

TABLE 4. Summary of clinical trials of intravitreal triamcinolone therapy in diabetic macular oedema (DMO) and proliferative diabetic retinopathy (PDR)* [33-55]

Purpose of study	Author (year)	Study design	Disease	Length (mean follow-up time)
Efficacy of IVTA	Gillies et al[33] (2006)	Randomised controlled trial	DMO	2 years
Efficacy of IVTA	Jonas et al[34] (2006)	Randomised controlled trial	Diffuse DMO	3 and 6 months
Efficacy of IVTA	Avci et al[35] (2006)	Prospective interventional case series	Diffuse DMO	7.8 months
Efficacy of IVTA	Desatnik et al[36] (2006)	Retrospective case series	Refractory DMO	6-13 months
Efficacy of IVTA	Sutter et al[37] (2004)	Randomised controlled trial	DMO	3 months
Efficacy of IVTA	Massin et al[38] (2004)	Interventional case series	DMO	3 months
Efficacy of IVTA	Micelli Ferrari et al[39] (2004)	Interventional case series	Refractory DMO	4 months
Efficacy of IVTA	Jonas et al[40] (2004)	Interventional case series	Diffuse DMO	13.2 months
Efficacy of IVTA	Jonas et al[41] (2004)	Prospective comparative clinical interventional study	DMO	7.4 months
Efficacy of IVTA	Ciardella et al[42] (2004)	Retrospective interventional non-comparative case series	Refractory DMO	11.7 months
Efficacy of IVTA	Jonas et al[43] (2003)	Interventional case series	CSMO	6.64 months
Efficacy of IVTA	Martidis et al[44] (2002)	Prospective interventional case series	Refractory CSMO	6.31 months
Comparison of efficacy of IVTA with MLG photocoagulation	Avitabile et al[45] (2005)	Prospective randomised interventional trial	DMO	9 months
Efficacy of different doses of IVTA	Lam et al[46] (2006)	Randomised interventional study	CSMO	6 months
Efficacy of different doses of IVTA	Audren et al[47] (2006)	Randomised interventional study	Refractory DMO	6 months
Efficacy of different doses of IVTA	Spandau et al[48] (2005)	Randomised interventional study	DMO	6.6 months
Efficacy of repeated IVTA	Chan et al[49] (2006)	Retrospective observational case series	CSMO	N/A
Efficacy of repeated IVTA	Jonas et al[50] (2006)	Retrospective interventional comparative study	Diffuse DMO	N/A
Efficacy of repeated IVTA	Ramezani et al[51] (2006)	Prospective interventional case series	Refractory DMO	N/A
Efficacy of repeated IVTA	Jonas et al[52] (2005)	Interventional case series	Diffuse DMO	N/A
Efficacy of combination of IVTA with PRP	Zein et al[53] (2006)	Prospective interventional case series	PDR + CSMO	9.6 months
Efficacy of combination of IVTA with PRP	Bandello et al[54] (2006)	Prospective interventional case series	PDR	12 months
Efficacy of combination of IVTA with PRP	Zacks and Johnson[55] (2005)	Retrospective case series	PDR + CSMO	3-6 months

* CFT denotes central foveal thickness; CSMO clinically significant macular oedema; IOP intra-ocular pressure; IVTA intravitreal injection of triamcinolone acetonide; MLG macular laser grid; N/A not applicable; PDR proliferative diabetic retinopathy; PRP panretinal photocoagulation; and VA visual acuity

Sample size (No. of eyes)	Dosage of IVTA	Results
69	4 mg	• 56% treated with IVTA gained 5 or more letters in best-corrected VA compared with 26% treated with placebo • Foveal thickness had decreased by 59 μm more in the IVTA group than in the placebo group
40	20 mg	• At 6 months follow-up, 48% and 39% eyes gained 2 and 3 lines in best-corrected VA, respectively in the study group, versus 0% eyes and 0% eyes in the control group
59	4 mg	• Macular oedema was resolved and decreased during follow-up in 63% and 37% of IVTA-treated eyes respectively • Recurrence of macular oedema in 49% of eyes at 6 months and 71% at 9 months after injection
31	4 mg	• IVTA for DMO is effective in reducing foveal thickness and improving VA in short term • VA returned to pre-injection values on longer follow-up, but modest decrease in foveal thickness persisted
69	4 mg	• 55% treated with IVTA gained 5 or more letters in best-corrected VA compared with 16% treated with placebo • Macular oedema was reduced in 75% of eyes treated with IVTA versus 16% of eyes with placebo • Mean central retinal thickness reduces by 152 μm
30	4 mg	• Significant reduction in macular thickness in IVTA group compared with control group • The difference between central macular thickness of IVTA group and control group was not significant at 6 months because of the recurrence of macular oedema • VA in both IVTA group and control group was not significantly different
6	N/A	• Significant improvement in VA and reduction in macular thickness after IVTA
38	20 mg, 25 mg	• VA and IOP began to increase significantly within first week, reaching a plateau-like maximum at 1-7 months, returning to baseline values 8-9 months post-injection
50	20 mg	• 92% treated with IVTA had an increase in VA during follow-up
30	4 mg	• Significant improvement in VA and reduction in macular thickness within 6 months after IVTA • Progressive reduction in the number and size of the hard exudates was noted after IVTA in all patients
26	25 mg	• 81% of eyes treated with IVTA with follow-up period >1 month had significant VA improvement • Significant decrease in fluorescein leakage was noted after IVTA
16	4 mg	• Mean improvement in VA measured 2.4, 2.4, and 1.3 snellen lines at 1-, 3-, and 6-month follow-up respectively • Central macular thickness decreased by 55%, 57.5%, and 38% respectively
48	4 mg	• IVTA improves VA and reduces central macular thickness more than MLG photocoagulation • Combination therapy of IVTA + MLG dose not offer further advantage when compared with IVTA alone
63	8 mg, 6 mg, 4 mg	• Higher dose of IVTA prolonged the duration of visual benefit and result in more sustained reduction in macular oedema
32	4 mg, 2 mg	• Difference in central macular thickness was not statistically significant between both groups • The between-group differences in the gain in VA and in IOP were not significant
27	13 mg, 5 mg, 2 mg	• Maximal increase in VA was significantly correlated with the dosage of IVTA • Duration of effect of IVTA increased significantly with dosage of IVTA • Increase in IOP was not statistically significant between doses
10	4 mg (2 injections)	• VA and CFT were not significantly different before initial and repeated injection • Transient improvements of VA and CFT after each injection • After repeated injection, VA and CFT were significantly worse at all time points, compared with the initial injection
22	20 mg (2-3 injections)	• IVTA may repeatedly lead to an improvement in VA and a rise of IOP • VA improvement and IOP rise did not differ significantly between various injections • Duration of the effect after each injection is approximately 6-8 months
12	4 mg (2 injections)	• VA and central macular thickness changes were not significantly different between 1st and 2nd injection • IVTA-related ocular hypertension was more persistent after reinjection
4	20 mg	• VA improved after an initial and repeated IVTA injection of 20 mg
35	4 mg	• 34% of eyes in IVTA group had final vision of 20/40 or better versus 11% in the laser group • 84% of IVTA eyes had complete resolution of macular oedema versus 46% of laser eyes
9	4 mg	• Both leakage due to retinal new vessels and macular thickening were significantly reduced in the combined treatment group comparing with control group • VA improved in combined treatment group, but decreased in control group
5	4 mg	• All cases showed improvement in the amount of macular oedema, despite the application of PRP, as well as complete regression of neovascularisation

TABLE 5. Summary of the clinical study results for currently available and emerging anti–vascular endothelial growth factor (anti-VEGF) therapies in diabetic retinopathy[58-61]

Agent	Study design	Target	Sample size	Dosage	Comparison group	Result*	Significant adverse events
Pegaptanib[58,59] (Macugen)	Phase II randomised, double-masked, multicentre, dose-ranging controlled trial	VEGF165 and large isoforms	172	0.3 mg, 1 mg, 3 mg	Sham	• 34% gained at least 2 lines and 18% at least 3 lines by month 9 (with dosage of 0.3 mg) • Mean central retinal thickness decreased by 68 μm (with dosage of 0.3 mg) • 62% of subjects with retinal NVD at baseline showed either regression of NVD on fundus photographs or regression or absence of fluorescein leakage from NVD (or both) at week 36	Endophthalmitis (0.8%)
Ranibizumab[60] (Lucentis)	Single-centre, open-label, dose-escalating pilot study	All VEGF-A isoforms	10	0.3 mg, 0.5 mg	Not applicable	• 50% gained at least 2 lines and 40% at least 3 lines by month 3 • Mean central retinal thickness decreased by 45.3 (with dosage of 0.3 mg) and 197.8 μm (with dosage of 0.5 mg)	Mild-to-moderate ocular inflammation (50%)
Bevacizumab[61] (Avastin)	Interventional retrospective case series	All VEGF-A isoforms	45	6.2 μg - 1.25 mg	Not applicable	• 100% of subjects with retinal NVD had complete (or at least partial) reduction in fluorescein leakage from NVD within 1 week after injection • 73 and 82% of subjects had complete resolution of angiographic leakage of NVD and that of NVI respectively • Reduction in leakage as early as 24 hrs after injection • Recurrence of fluorescein leakage varied; as early as 2 weeks in one case	None

* NVD denotes neovascularisation of the disc; and NVI neovascularisation of the iris

Bevacizumab is a full-length humanised monoclonal antibody against VEGF related to the parent molecule of ranibizumab, which binds to all isoforms of human VEGF and its biologically active by-products.[62] A recent retrospective case series of 45 eyes (in 32 patients) with retinal and/or iris neovascularisation secondary to diabetes, showed that intravitreal injection is well tolerated and associated with a rapid regression of retinal and iris neovascularisation (Table 5).[61] Similar cases of rapid, complete regression of NVE and NVD after intravitreal injection of bevacizumab had also been reported.[63,64] Furthermore, in two patients with PDR, Spaide and Fisher[65] demonstrated rapid resolution of vitreous haemorrhage and regression of retinal neovascularisation within 1 month. However, bevacizumab's role in such treatment will likely be limited by the short duration of its effect and early recurrence of neovascularisation (Table 5).[62] Nevertheless, even a transient effect may be beneficial in a variety of clinical settings, such as when media opacity prevents the placement of PRP. Similarly, in cases of severe PDR with concurrent macular oedema, injection of bevacizumab given with PRP may minimise the latter's propensity to exacerbation of macular oedema.[61] Finally, intravitreal bevacizumab, with its antiangiogenic properties, has also been used successfully as a pre-vitrectomy adjunct (to suppress fibrovascular proliferation) for the repair of retinal detachment in eyes with severe active PDR.[66]

Angiotensin converting enzyme inhibitors/ angiotensin II receptor blockers

The renin-angiotensin system is expressed in the eye, whilst angiotensin converting enzyme (ACE) is produced locally by vascular endothelial cells and retinal pigment epithelial cells.[67] Moreover, angiotensin II has been shown to stimulate retinal angiogenesis, possibly via potentiation of VEGF activity.[67] The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus Study (EUCLID[16]) found that lisinopril reduced the risk of DR progression and the development of PDR in normotensive type 1 diabetic patients. However, both UKPDS and ABCD trials failed to show a benefit ACE inhibitor treatment in DR patients (Table 3). The Diabetic Retinopathy Candesartan Trials (DIRECT), evaluating the effects of candesartan (an angiotensin II receptor blocker) on DR in types 1 and 2 diabetic subjects, is currently ongoing.[67]

Growth hormone inhibitors

The importance of growth hormone (GH) as a possible growth factor in PDR is supported by clinical observation of progression of retinopathy during puberty and the fact that serious retinopathy is seldom seen in GH-deficient dwarfs.[68]

Thus, somatostatin analogue might inhibit an-

giogenesis directly through somatostatin receptors present on endothelial cells, and also indirectly through the inhibition of postreceptor signaling events of peptide growth factors such as insulin-like growth factor 1 and VEGF.[69] In a small-scale randomised controlled study of 23 patients with severe NPDR or early PDR, octreotide (a long-acting somatostatin analogue) reduced the requirement for laser photocoagulation compared with conventional treatment.[68] The incidence of ocular disease progression was only 27% in patients treated with octreotide in addition to conventional treatment compared with 42% in patients receiving conventional treatment alone. A large-scale, muticentre, randomised placebo-controlled clinical trial of octreotide is currently underway in patients with severe NPDR and early PDR.[69]

Antioxidants

Hyperglycaemia is associated with increases in oxidative stress, and reactive oxygen species are thought responsible for microvascular damage. Antioxidants such as vitamin E may prevent some of the vascular dysfunction associated with diabetes, as shown in animal studies.[70] A recent clinical study demonstrated that short-term, high-dose oral vitamin E therapy normalised retinal and renal haemodynamics in diabetic patients despite no change in glycaemic control.[71] Whether these changes will eventually result in suppression of DR awaits a randomised control trial.

Cyclooxygenase-2 inhibitors

Cyclooxygenase (COX)-2 is an enzyme causing angiogenesis in response to inflammation. It was shown to be expressed on diabetic retinas.[20] A clinical trial to evaluate the effects of the COX-2 inhibitor, celecoxib, on PDR is ongoing.[20]

Other potential therapies

Platelet inhibitors

Experimental results suggested high-dose aspirin may be useful in DR treatment. However, the ETDRS[14] conclusively showed that aspirin has no effect on the progression of severe DR. However, it does not increase the risk of bleeding from new vessels in patients with PDR (Table 3). Hence, PDR is not a contra-indication to anti-platelet treatment for prevention of ischaemic cardiovascular events.

Aldose reductase inhibitors

High levels of glucose result in a net increase in the activity of the enzyme aldose reductase and a buildup of intracellular sorbitol concentrations, resulting in osmotic damage to vascular cells.[19] Clinical trials of aldose reductase inhibitors (ARIs) for the treatment of DR have been conducted, but the results were disappointing.[5]

Advanced glycation end-products inhibitor

High serum glucose can lead to non-enzymatic binding of glucose to protein side-chains, resulting in the formation of one or more nonfunctional, advanced glycation end-products (AGE).[20] Excessive formation of AGEs has been linked to the development of diabetic microvascular complications. Aminoguanidine, an AGE formation inhibitor, which has proved promising in the prevention of DR in animal models was studied in a clinical trial that had to be prematurely terminated due to safety considerations.[72]

Other agents

Potential therapies for DR, such as interferon-alpha 2a,[73] acetazolamide,[74] intravitreal injection of tissue plasminogen activator,[20] and pigment epithelium-derived factor[20] are also being developed, but evidence regarding these agents is still limited.

Conclusion

Extensive clinical researches had provided guidelines on the treatment of DR. Strict metabolic control and tight BP control can significantly reduce the risk of retinopathy progression, but are difficult to achieve in clinical practice. Laser photocoagulation and vitrectomy are effective in preventing severe visual loss in the presence of sight-threatening DR and its complications, but both modalities have potential side-effects. Evidence from past clinical trials does not support a role for anti-platelet agents, ARIs and AGE inhibitors. The results from clinical trials with PKC inhibitors, intravitreal steroid, anti-VEGF agents, ACE inhibitors, and GH inhibitors are promising and further clinical trials are actively ongoing. In the near future, results from these trials may lead to the introduction of additional pharmacological agents for the treatment and reduction of visual loss of DR.

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