Current and Emerging Therapies for the Management of Diabetic Retinopathy

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ABSTRACT
Diabetes Mellitus (DM) has many complications, in which Diabetic Retinopathy (DR) is the major one. Blindness among working age people was due to DR. Retinal angiogenesis and retinal vascular permeability is the pathogenesis behind vision loss. Polyol pathway, protein kinase C (PKC) activation, renin angiotensin-aldosterone system (RAAS), oxidative stress etc are the pathophysiological pathways which are discussed in this review for better understanding. PKC inhibitors, anti-inflammatory agents, RAAS blockers, anti-vascular endothelial growth factor (VEGF) agents, antioxidants and fibrates which are the used for the better treatment for DR is also elaborated in this review.

INTRODUCTION
DM is characterized by high levels of blood glucose which is the disorder of carbohydrate metabolism (King et al., 1998). Globally, 387 million people had diabetes in 2014 and its prevalence will increase to 592 million individuals by 2035 as per International Diabetes Federation (Diabetes Federation., 2014). According to World Health Organization (WHO) diabetes is defined as a chronic disease in which enough insulin was not produced by the pancreas or the body does not take enough insulin. DR was caused by a sustained increase in glucose level and consequences in minor vascular retinal vessels (Porta and Bandello, 2002). DR may be characterized by the hypoxia (abnormal blood vessel growth) in the retina (Rechtman et al., 2007). DR is not only chronic disease, but also it is a sight threatening disease of retinal vasculature (NICECKS., 2010).

The pathogenesis behind this blindness may increase retinal vascular permeability and retinal angiogenesis. These changes are due to hypoxia and chronic hyperglycemia. If the diagnosis was done with proper timing and retinal laser treatment, blindness can be reduced in 90% patients. For avoiding DR and slowing down its progression, prevention of DM and good metabolic control is more important (ETDRS, 1991).

There are two different types of DR. Polyol pathway, non-enzymatic glycation, PKC, inflammatory, hemodynamic changes, growth factor, oxidative stress and renin angiotensin pathways are pathological pathways which leads to DR. DR can be also prevented by controlling blood sugar levels and blood pressure. Various approaches to treat DR are PKC inhibitors, RAAS inhibitors, Anti-VEGF inhibitors, Fibrates, antioxidants and anti-inflammatory agents as well. As conventional therapy has limitations for DR treatment there are certain therapies that are emerging for the treatment that includes laser therapy, vitrectomy and intra-vitreal injections of anti VEGF agents, corticosteroids and certain other pharmacological agents as well.
In DR, combination therapy was used rather than monotherapy that intra-vitreal injection of one or two drugs has given to the patient who has undergone vitrectomy surgery for proliferative diabetic retinopathy (PDR). So there is a stronger support for combination therapies than monotherapy. This paper reviews about DR mechanisms, new emerging therapies and various approaches for the management of the disease.

**Pathogenesis of Diabetic Retinopathy**

DR may cause visual acuity (VA) because it is a microvascular complication of diabetes, which leads to vision loss. Increased blood sugar can damage retinal blood vessels. Swelling of retinal tissue and clouding of vision was due to leakage of blood and other fluids. Cotton wool spots, capillary closure, arteriovenous shunts, neovascularisation, retinal haemorrhage, retinal exudates/oedema, lipid exudates and macular edema are the clinical symptoms of DR. Vascular permeability was also increased which leads to retinal thickening and loss of visual acuity. DR was managed by controlling hyperglycemia, hypertension and dyslipidemia. EDTRS classified DR as follows:

**Non-proliferative retinopathy (NPDR)**

It is more extensive than background retinopathy. Blood flow becomes restricted, but did not show any new blood vessel growth.

**Mild NPDR**

Micro-aneyrums (secular enlargement of the venous end of a retinal capillary)

**Moderate NPDR**: Between mild NPDR and severe NPDR

**Severe NPDR**

Severe intra-retinal haemorrhages and micro-aneyrums

**Proliferative retinopathy (PDR)**

Growth factors are the chemicals which are released when blood vessels of retina damages, this leads to growth of tiny blood vessels (proliferate) from the damaged blood vessels.

The major reason for DR complication is hyperglycemia. Metabolic dysfunction increased by high glucose level and other signalling pathways activation leads to DR progression. At present, DR represented by glycemic control which is the most effective medical treatment (Hudson, 1996; Aiello, 2003; Porta and Allione, 2004; Wang et al., 2009). There are Studies which showed that blood sugar level control is more important (Schaumberg et al., 2005; Kilpatrick et al., 2006). It was found that more recent pathogenesis behind diabetes complications are poly (ADP-ribose) polymerase (PARP), reactive oxygen and inflammatory cascade mechanisms are involved in the (Stratton et al., 2006). Rather than oxidative stress and PARP activation increased aldose reductase activity is a major cause in the pathogenesis of diabetes (Obrosova et al., 2005). There are many biochemical pathways involved in the DR progression. They may include: polyol pathway, non enzymatic glycation, PKC activation, hemodynamic changes, RAAS system, subclinical inflammation, leukostasis, oxidative stress and growth factors. Schematic diagram of pathogenesis of DR was shown in Fig1:

**Fig 1: Pathogenesis of DR.**

**Polyl pathway**

Certain amount of glucose is metabolized in cellular metabolism by polyol pathway. Glucose flux is increased by this pathway in diabetes patients. Polyol pathway is controlled by the two steps. In the polio pathway, aldose reductase helps to reduce sorbitol from glucose using NADPH, and then sorbitol dehydrogenase is an enzyme that metabolizes sorbitol to fructose, which uses NAD+ as a cofactor (Dagher et al., 2004). If an excess of sorbitol in retinal vascular cells cause osmotic damage leads to DR. In order to predict individual susceptibility in retinopathy, aldose reductase gene polymorphisms may be helpful. Even though aldose reductase inhibitors (ARIs) have yielded incompatible results in DR of experimental animals polyol pathway has become a dread target (Hammes et al., 1991).

**Non-enzymatic protein glycation**

AGEs are important pathogenic mediators which reduce sugars, by non-enzymatic reaction. Diabetic patients have AGEs in their retinal vessel, same as in serum and retinopathy. Cells get affected by AGEs by three mechanisms: (a) adducts which is present on altered serum proteins, (b) glucose metabolism product endogenous adducts, and (c) ECM-immobilised structural modification of proteins. Amadori product is formed as a result of early glycation and oxidation. AGEs is generated by protein and lipid glycation. AGE formation and activation of AGE receptors represent important as per early experimental works. In DR, inhibition of these pathways with interconnected pathogenic mechanisms presents a valid avenue for therapeutic exploitation.
PKC Activation

It helps in cell signalling. Hyperglycemia leads to increase in the de novo synthesis of di-acylglycerol (DAG), which causes major changes in endothelial permeability, hemodynamic changes, extracellular matrix protein synthesis, intracellular changes and VEGF production (Koya and King., 1998; Clarke and Dodson., 2007). The PKC \( \beta \)/2 isoform expression contributes to the loss of capillary pericytes. Inhibition of PKC only reduces the loss of vision, not for preventing DR (Simonson 1988).

Hemodynamic changes

The mechanism for DR progression has increased blood flow in the retina and loss of auto regulation. It has documented that the diabetic patients have a high incidence of hypertension (Kohner., 1993; Mancia., 2005). Hypertension contributes to DR progression by two mechanisms. First, the endothelial dysfunction occurs by mechanical stretch and shear stress on the endothelial cells (Berka., 2006). Second, regulation of blood pressure in the endocrine system was involved in the pathogenesis of DR (Funatsu et al., 2002).

RAAS

RAAS involved in the maintain body fluid balance and regulates blood pressure. During PDR, the expression of the receptors, signalling molecules of the RAAS and angiotensin receptors increases in the retina (Funatsu et al., 2002; Sjolie et al., 2008). The DR Canesartan Trials (DIRECT) and RASS both reported with the reduction of retinopathy progression (Van Hecke et al., 2005; Chaturvedi 2008; Mauer et al., 2009).

Subclinical inflammation and leukostasis

Retinal inflammation causes increased intraocular blood pressure eNOS, new blood vessels formation and VEGF leads to haemorrhages in the retina which causes increased permeability and leukostasis. (Lutty et al., 1997). Inflammation is due to increase in the serum concentration of cytokines, adhesion molecules and activation of immune cells (Schoroder et al., 1991; Spijkereman et al., 2007; Klein et al., 2009).

In DR pathogenesis leukostasis leads to capillary occlusion and ROS associated apoptosis (Halliwell and Gutteridge., 1990).

Oxidative stress

Oxidative stress is lack of proportion between ROS production and ROS neutralization by antioxidants. The cellular components are damaged by oxidative stress and leads to the pathogenesis of many diseases. ROS are detoxified in normal physiological conditions (Mates et al., 1999). Increased oxidative species causes DR progression (Enden et al., 1995).

Growth factors

Growth factors which contribute DR development includes basic fibroblast growth factor (bFGF) (Armstrong et al., 1998), insulin-like growth factor-1 (IGF-1) (Hueber et al., 1996; Haurigot et al., 2009), angiopoietin-1 and -2 (Patel et al., 2005; Berka et al., 2006; Rangasamy et al., 2011), stromal-derived factor-1 (Coxon et al., 2010), epidermal growth factor (EGF) (Lev-Ran et al., 1990), transforming growth factor-beta 2 (TGF-\( \beta \)/2) (Min et al., 2006), platelet-derived growth factors (PDGFs) (Praidou et al., 2009), and erythropoietin (Eckardt, 2009). Among these growth factors VEGF plays an important role in DR pathogenesis.

The DR leads to two visual complications, (i.e.,) diabetic macular edema (DME) and PDR. Standard treatments for DME and PDR are glycemic control and photocoagulation. In recent years, there are certain measures to avoid the risk for blindness which includes medical managements and ocular managements. An adjunctive pharmacologic therapy by anti-VEGF agents and triamcinolone acetonide shows better treatment for both PDR and DME. There are some new factors involved in the pathogenesis of DR, emerge to the new therapies.

Currently approved therapies

The therapies that are currently available for the management of DR. Laser treatment, vitrectomy surgery, anti-VEGF agents and corticosteroids are the therapies that are available presently in the market for the treatment of DR.

Laser Treatment

Laser treatment depends on the disease severity. Laser photocoagulation was more effective for the treatment of DR. There are two types of laser treatment.

Scatter or pan retinal photocoagulation

Small amount of laser has been needed to treat DR. Laser should not be applied to the central part of the retina.

Focal laser photocoagulation

Laser photocoagulation leads the hypoxic condition in retina to anorexia.

Vitrectomy surgery

Complications of DR may be the interactions between the vitreous and retinal surface. Here vitreous gel is removed from the centre of eye. Local or general anaesthesia are used to stop bleeding from vitreous. In order to carryout vitrectomy, it needs overnight hospital stay. Eyes may take weeks to get recovered after treatment. Inflammation and infection is reduced by applying eye drops. If both eyes require vitrectomy, after the first eye has recovered second eye will be treated again (Harbour et al., 1996; Smiddy and Flynn., 1999; DRCRNWC., 2010).
Anti VEGF Treatment

Anti-VEGF agents were helped in the retinal vascular permeability improvement, causes blood-retinal barrier breakdown, and finally results in retinal edema (Aiello et al., 1997). VEGF level is increased in DR. There are known 5 isoforms of VEGF. At present, pegaptanib (Macugen; Pfizer, Inc., New York, USA), (Cunningham et al., 2005; Gonza’lez et al., 2009), ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, California, USA) (Chun et al., 2006; Rosenfeld et al., 2006; Erfurth et al., 2014; Comyn et al., 2014), bevacizumab (Yanyali et al., 2007; Roh et al., 2008; Fang et al., 2008;) (Avastin®; Genentech, Inc.), and VEGF Trap-Eye (Do et al., 2009; -108) (Regeneron Pharmaceuticals, Inc., Tarrytown, New York, USA).

Corticosteroids

Corticosteroids are used for various intraocular neovascular and edematous diseases, which includes certain diseases such as DME, PDR, neovascular glaucoma and chronic prephthisical ocular hypo tony (Paccola et al., 2008).

Emerging therapies

Treating DR was done by initiation of some of the biochemical mechanisms, the drugs which includes are aldose reductase inhibitors, PKC inhibitors, anti-inflammatory drugs, fenofibrate, somatostatin analogs, RAAS blockers, anti-oxidants and certain combination therapies.

Aldose reductase inhibitor

Newly developed inhibitors addressed more efficient action than older but in clinical testing which showed failure in the better management of DR (Sun et al., 2006).

PKC Inhibitors

When vascular endothelial cells were exposed to oxidative stress PKC activity also has been increased, which leads to the development diabetic micro vascular complications. Endothelial cell permeability, blood flow and angiogenesis are regulated by PKC (Taher et al., 1993; Huang et al., 1997).

Table 1: List of drugs and therapies that are currently available in the market for DR treatment.

<table>
<thead>
<tr>
<th>Drug/Therapy</th>
<th>Mechanism of action</th>
<th>Grade</th>
<th>Number of patients examined</th>
<th>Study Type</th>
<th>Outcomes</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser</td>
<td>Destruction of retina and supply oxygen, reduction in VEGF expression</td>
<td>PDR and NPDR</td>
<td>60</td>
<td>Intervventional</td>
<td>Incidence of vision loss after 1 yr.</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Vitrectomy surgery</td>
<td>Surgical removal of vitreous gel</td>
<td>PDR</td>
<td>347</td>
<td>Randomized</td>
<td>Persistent haemorrhage were evaluated</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDR</td>
<td>70</td>
<td>Randomized</td>
<td>Intraoperative bleedings and intraoperative retinal breaks was measured.</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Anti-VEGF agents</td>
<td>Pegaptanib (Inhibits the VEGF from binding and activating the VEGFR2 receptor)</td>
<td>PDR</td>
<td>30</td>
<td>Non-Randomized</td>
<td>To further establish the efficacy of intra-vitreal injections in the regression of retinal neovascularisation secondary as compared to laser.</td>
<td>Phase 4</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab (It binds and inhibits the all isoforms of human VEGF activity)</td>
<td>Severe NPDR</td>
<td>40</td>
<td>Non-Randomized</td>
<td>Evaluated Visual Acuity, neovascularisation leakage points and florescent angiography</td>
<td>Phase 2 &amp; Phase 3</td>
</tr>
<tr>
<td></td>
<td>Ranibizumab (Inhibits VEGF A and activating the VEGF 2 receptor)</td>
<td>PDR</td>
<td>20</td>
<td>Randomized</td>
<td>The improvement or worsening of vision was measured</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Aflibercept (Have VEGF binding sites)</td>
<td>PDR</td>
<td>20</td>
<td>Randomized</td>
<td>Incidence and severity was measured</td>
<td>Phase 2 &amp; Phase 3</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>IVTA (Down regulating matrix metalloproteinase activation)</td>
<td>PDR</td>
<td>60</td>
<td>Randomized</td>
<td>Visual acuity, no of treatments, duration of efficacy was measured</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Fluocinolone acetonide (Inhibition of VEGF and anti-inflammatory properties)</td>
<td>DR &amp; DME</td>
<td>40</td>
<td>Randomized</td>
<td>Between group difference in mean visual acuity change</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone (PKC activation)</td>
<td>PDR</td>
<td>100</td>
<td>Randomized</td>
<td>Reoperation was needed</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>
Table 2: Emerging therapies for the better management of DR.

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldose reductase</td>
<td>Aspirin</td>
<td>Reduce VEGF expression</td>
<td>(Sun et al., 2006)</td>
</tr>
<tr>
<td>PKC inhibitors</td>
<td>Ruboxistaurin mesylate</td>
<td>Inhibitor of PKC-1 and 2 receptors</td>
<td>The PKC-DRS group., 2005</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>selective inhibitor of glycation that leads to inhibition of VEGF and PEDF</td>
<td>Thakur et al., 2011</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Etanercept, Fidarestat</td>
<td>Intercellular adhesion molecule1 (ICAM1) expression can be reduced</td>
<td>Tsilimbaris et al., 2007, Kato et al., 2009</td>
</tr>
<tr>
<td></td>
<td>Infliximab</td>
<td>Block the inflammatory molecule tumour necrosis factor α (TNFα).</td>
<td>Sifakis et al., 2010</td>
</tr>
<tr>
<td></td>
<td>ESBA105</td>
<td>Anti TNFα</td>
<td>Ottiger et al., 2009</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Fenofibrate</td>
<td>VEGF inhibition, reduction of cytokines levels, PKC activation</td>
<td>Cheung and Wong., 2008</td>
</tr>
<tr>
<td>Somatostatin analogs</td>
<td>Octreotide</td>
<td>PKC activation</td>
<td>Grant et al., 2000</td>
</tr>
<tr>
<td>RAAS inhibitors</td>
<td>Valsartan</td>
<td>Angiotensin I (AT1) receptor antagonist</td>
<td>Satofuka et al., 2009</td>
</tr>
<tr>
<td></td>
<td>Lisinopril</td>
<td>Angiotensin-converting enzyme blocks rennin-angiotensin system</td>
<td>The EUCLID Study Group, 1997</td>
</tr>
<tr>
<td></td>
<td>Candesartan</td>
<td>Angiotensin receptor blocker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Losartan</td>
<td>ACE inhibition</td>
<td></td>
</tr>
<tr>
<td>Anti-oxidants</td>
<td>Ascorbic Acid</td>
<td>Stimulates the retinal GSH reductase and SOD activities inhibition</td>
<td>Chen., 2009</td>
</tr>
<tr>
<td></td>
<td>Curcumin</td>
<td>Inhibition of VEGFs production</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitamin E</td>
<td>Prevention of lipid per oxidation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipoic Acid</td>
<td>Reduction of VEGF expression</td>
<td>Clinicaltrials. Gov., 2016</td>
</tr>
<tr>
<td></td>
<td>Resveratrol</td>
<td>Reduction of retinal oxidative stress</td>
<td>Kim et al., 2012</td>
</tr>
<tr>
<td>Combination therapies</td>
<td>Triamcinolone Acetoneide</td>
<td>Intra-vitreal injection + Laser</td>
<td>Gilles et al., 2011</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab + Triamcinolone</td>
<td>Intra-vitreal injection</td>
<td>Paccola et al., 2008; Shamura et al., 2008;</td>
</tr>
<tr>
<td></td>
<td>Ranibizumab + Triamcinolone Acetoneide</td>
<td>Intra-vitreal injection + Laser</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>Intra-vitreal injection + Laser</td>
<td>Huang et al., 2009; Cho et al., 2009</td>
</tr>
<tr>
<td></td>
<td>Pegaptanib</td>
<td>Intra-vitreal injection + Laser</td>
<td>Clinical trials Gov., 2015</td>
</tr>
<tr>
<td></td>
<td>Aflibercept</td>
<td>Intra-vitreal injection + Laser</td>
<td>Clinical trials Gov., 2015</td>
</tr>
<tr>
<td></td>
<td>Ranibizumab</td>
<td>Intra-vitreal injection + Laser</td>
<td>Brown et al., 2006</td>
</tr>
</tbody>
</table>

Anti-Inflammatory Agents

Intraocular inflammation is the second mechanism for the DR development. For this reason non steroidal anti-inflammatory (NSAIDS) agents were used for prostaglandins production inhibition (Sifakis et al., 2005; Tsilimbaris et al., 2007).

Fibrates

Fibrates are lipid-lowering drugs which have been used often in dyslipidemia treatment. Reduction in total cholesterol, LDL, glycerides and increase in HDL levels are due to activation of alpha receptor (Keech et al., 2007; Dodson 2009).

Somatostatin analogues

Somatostatin is also known as a growth hormone inhibitor. It exists in two forms, one form has 14 amino acids and other has 28 amino acids. It shows that somatostatin prevents PDR progression, haemorrhage and it was used in laser and vitrectomy surgery in DR (McCombe et al., 1991; Grant et al., 2000; Boehm et al., 2001; Davis et al., 2001)

RAAS blockers

RAAS is involved in DR pathogenesis. Studies reported that increased levels of rennin, pro renin, and angiotopetin 2 (Ang 2) in the vitreous in patients with DR. As RAS blocker therapy may improve the condition of DR patients (Satofuka et al., 2009).

Antioxidants

Increase in oxidative stress due to hyperglycemia leads to high glucose level and other metabolic abnormalities. This results in the ROS overproduction. When there is no balance between their production and destruction it results in oxidative stress. The ROS formation was mediated by both enzymatic and non-enzymatic mechanisms. These are the some of the important antioxidants that are currently being studied (Bursell et al., 1999; Garcia-Medina et al., 2011; 139-141).

Cryotherapy (Freezing)

It may help in DR treatment. Laser can be performed after blood in vitreous layer settles down. In some cases retinal blood vessels may shrink and retina is bonded back of the eye.

Combination Therapies

Combination therapy has yielded better results than intra-vitreal monotherapy. The RESTORE study (SchmidtErfurth et al., 2014) showed a greater improvement in patients treated with both intra-vitreal and laser than in patients treated with monotherapy.
Similarly, several studies reported an increased likelihood of an improvement in BCVA from baseline in patients treated with IVTA and laser versus only laser at 2 years. On the other hand, the READ2 study reported no significant difference in visual outcomes in the combination therapy group (Nguyen et al., 2010), although combination treatment provided an improvement in BCVA and a greater decrease in macular edema with fewer injections.

Future Therapies

The future DR treatment relies not only on the development of medications targeting molecules to the DR pathogenesis, but also on the development of novel delivery techniques. In order to maximize the effect of the treatment and minimize systemic adverse effects, targeted delivery of medication to the retina was ideal. Data’s are emerging that medicine which is administered as eye drops are able to reach the retina than any other formulation with better therapeutic concentrations. Future development for therapies for DR treatments includes hepatocyte growth factor, matrix metalloproteinase-9 (MMP9), monocyte chemo tactic protein1 (MCP1), kallikrein, Ang2, and NFkB. Inhibition of hepatocyte growth factor and MMP9 may prevent DR or cause regression of PDR. Retinal neovascularisation was suppressed by NFkB inhibition (Yoshida et al., 1999). Retinal vascular permeability improvement was associated with Ang2 (Rangasamy et al., 2011), Kallikrein activation (Feener., 2010) and Hepatocyte growth factor (Nishimura et al., 1998). Increased level of MMP9 has been found in vitreous and retina of patients with diabetes (Jin et al., 2001).

DR and PDR regression can be prevented by these two molecules. As the exact mechanisms involved in the pathogenesis of DR are elucidated more therapeutic targets will emerge, and the armamentarium of treatment options for DR will expand greatly.

CONCLUSION

DR is which may lead to legal blindness and it is a major public health problem. Early detection through screening, educating the population and timely intervention may decrease the complications in the course of disease. As laser therapy is not that much effective, pharmacological treatments may provide alternative strategy for DR. Both intra-vitreal corticosteroids and intra-vitreal anti-VEGF agents are widely used in clinical settings. Diabetic vitrectomy increased life quality by improving vision. Early treatment for vitrectomy showed cost-effective intervention. FenoFibrate treated patients showed reduction in retinal laser therapy. The role of combination therapies is yet to be determined. Finally it was shown that DR can be treated in earlier stages.

The ideal medication for the treatment of DR is fast acting, long lasting and above all, safe. As the development of DR is a multi factorial process, involving inflammation and ischemia, future therapies, especially combination therapies, targeting different pathways may lead to more favourable outcomes.

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REFERENCES

Clinical trials Gov. Prospective, randomized, open Label, phase II study to assess efficacy and safety of Macugen® (Pegaptanib 0.3 mg intravitreal injections) plus panretinal photocoagulation (PRP) and PRP (Monotherapy) in the treatment with high risk proliferative diabetic retinopathy. https://clinicaltrials.gov/ct2/show/NCT01281098. Last updated: March 18, 2015.


Diabetes - type 2: NICECKS. July 2010 (UK access only)


Hudson C. The clinical features and classification of diabetic retinopathy. Ophthalmic physiol opt 1996; 16(suppl. 2):S43–8


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