



Recent Advancements in the Treatment of Diabetic Retinopathy

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ABSTRACT: Diabetic Retinopathy (DR) remains the most widely recognized challenge of the micro vascular problems of diabetes, despite recent advancements in the treatment of DR worldwide. The drugs that block the actions of vascular endothelial growth factor (VEGF) and corticosteroids, have shifted the goal of DR treatment from stabilization of vision to improvement. Although aggressive treatment improves vision in most patients, but many still do not achieve reading and driving vision. For over 30 years laser was the mainstay for the treatment of diabetic macular edema (DME), but several important management questions and treatment deficiencies remain unanswered with the laser therapy. This review summarizes updates on diagnosis, imaging, systemic factors, and glycemic control, vitreolysis, surgery, limitations and current treatment options such as neurovascular unit, which includes ranibizumab, aflibercept, bevacizumab, dexamethasone, fluocinolone acetonide and important clinical treatments in the management of DR. © 2020 iGlobal Research and Publishing Foundation. All rights reserved.

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INTRODUCTION

The worldwide prevalence of diabetes mellitus is predicted to increase adequately in the coming years. The approximate increment is 382 million in 2013 to 592 million in 2035.[1,2] Diabetic patients suffer several life-restricting problems, which may include micro vascular-related retinopathy, nephropathy, macrovascular related retinopathy, and ischemic heart disease. Diabetic Retinopathy (DR) is the most widely recognized micro vascular problems of diabetes. [3] DR presently influences around 100 million people globally and is ready to turn into an ever-increasing health problem. DR related visual impairment and blindness raised by 64% & 27% as seen in the year between 1990 and 2010. [4] In spite of earlier searches in the diagnosis and treatment of diabetic retinopathy, this problem remains a dedicated challenge to patients and physicians. Moreover, the majority of the population globally does not have access to specialized care and affordable drugs. A dreadful challenge to the healthcare system is represented by the treatment, prevention, and diagnosis of DR. This review aims to provide diagnosis, imaging, limitations, and important clinical updates in the management of DR.

AN UPDATE ON DIAGNOSIS AND IMAGING

The root cause of DR is complex and the primary contributor is intense capillary non-perfusion and retinal ischemia. The communication molecules insulin-like growth factor-1, platelet-derived growth factor, angiopoietin and Vascular Endothelial Growth Factor (VEGF) plays a vital role in the consequent advancement of microangiopathy. [5] Evidence from the recent clinical data recommends that neurodegeneration is an early event within the pathological process of DR.6,7 Imaging modalities particularly Optical Coherence Tomography (OCT) and Fluorescein Angiography (FA), currently plays an important role in the identification and management of complications of DR, especially for Diabetic Macular Edema (DME) and subtle NV. Modern procedure of OCT, together with Optical Coherence Tomography Angiography (OCTA) expands by utilizing variation in phases and speed of the light signal from vascular structure. [6-8] OCTA can resolve vascular subtleties not attainable by the ordinary FA, for instance, the superficial capillary plexus. [9]

Systemic factors and Glycemic control

The United Kingdom prospective diabetes study and the Diabetes Control and Complications Trial (DCCT) validates that glycemic control decreases micro vascular problems for type 1 and type 2 diabetes. [10] An ongoing 30 years follow up of DCCT and the epidemiology of diabetes interventions and complication study reveals the importance of HaemoglobinA1c (HbA1c) control, coming out with a 50% risk reduction of retinopathy progression in intensive glycemic control patients, in spite a consequent increase (and alternative decrease in standard control patients) to a mean HbA1c value of 8%. [11,12]

Vitreolysis and Surgery

The vitreoretinal medical procedure is the standard treatment of many visual inconveniences of DR. Macular Edema from vitreous traction or epiretinal membranes can be experienced by diabetic patients and both of these can be treated surgically. [13]

Laser

The study of diabetic retinopathy gives an explanation of the reduction in some vision loss in patients with high risk Proliferative Diabetic Retinopathy (PDR) followed by immediate treatment with Pre Retinal Photocoagulation (PRP). [14] The Early Treatment Diabetic Retinopathy Study (ETDRS) indicates a 50% reduction in vision loss in patients having Clinically Significant Diabetic Macular Edema (CSDME) who have undergone instant focal laser photocoagulation. [15]

Limitations and Current Treatment Options

Laser photocoagulation intravitreal injections of anti-VEGF and steroidal agents are the intra ocular surgery procedure for diabetic eye illness. Modern therapeutic paradigms targets for treatment of advanced diseases, by developing PDR or DME. In the current scenario phase 3 clinical trials have indicated the prevalence of intravitreal anti-VEGF injections to laser monotherapy in lowering vision loss and bettering the rates of vision gaining eye with DME. [16-18] Aflibercept, Bevacizumab, and Ranibizumab are frequently been utilized as anti-VEGF agents which have shown an efficiency in correcting vision by 1 and 2 years of treatment of DME [19-20] Anti-VEGF medical care is very efficient in relapsing retinal neovascularization in eyes with PDR. [21]

Neurovascular Unit

Enhanced retinal imaging with early cell changes in the diabetic retina has prompted a conceptualization that DR can be seen as a disorder of the retinal neurovascular unit. It alludes to the practical coupling and interdependency of

neurons, glia and vascular which integrate to direct ordinary retinal function. [22]

Ranibizumab

The Anti-VEGF agents have revolutionized the management of DR. Under the trials of ranibizumab for diabetic Macular Edema (Ride and Rise) two doses 0.5mg and 0.3mg has been investigated for the monthly use for the treatment of DME. [23] First-line agents to treat central-involving DME are intravitreal VEGF inhibitors.

Aflibercept

One of the world's most widely used agent Aflibercept is a fusion of the Human Ig GFc region and the extracellular VEGF receptor ligand-binding region combines to VEGF-A, VEGF-B, Placental growth factor-I (PLGF-1) & (PLGF-2). [24] FDA approves it for the treatment of DME & DR.

Bevacizumab

Bevacizumab (Avastin, Genetch) comprise of a full-length humanized murine monoclonal antibody that binds to VEGF-A. [25] FDA has not approved it for the treatment of DME and DR. the efficacy of bevacizumab versus focal laser for DME has been examined by the intravitreal bevacizumab or laser therapy in the management of DME.

Dexamethasone & Fluocinolone acetonide

In spite of the predominance of anti-VEGF agents, there is yet a role to carry out for intravitreal corticosteroids. Steroids firstly inhibit leukostasis and then improve the barrier function of tight junctions and in last modify the release of local inflammatory factors, which may include VEGF. [26]

CONCLUSION

Corticosteroids are initials to take an area as second-line medical aid for patients insensitive to anti-VEGF agent and focal optical device. This is mainly relevant for pseudophakic patients who exceed a steroid IOP challenge. The continued outcome of these current studies on pharmacological agents is that early diagnosis of DME in NPDR or PDR, as is crucial to stop and sometimes converse retinopathy. Despite significant growth has been made in the diagnosis of DR and its development, the initial strategy DR should be ardent. Anti-VEGF specialists have treated into primary line operators for the diagnosis of DME. It has been proved that intravitreal VEGF inhibitors are effective in DR regression. VEGF inhibitors give the effective result for the treatment cure vision in individuals with DR. Future planning should target on alternative therapeutic agents or an invasive delivery method. During the rising stages of DR, an important role is played by neurodegeneration, also intravitreal anti-VEGF injections have

shown an aggressive approach. At this point of time topical therapies, for instance endogenous neuroprotective substances holds an exciting promise. [27]. We have witnessed dramatic improvements in the treatment of DR with the introduction of potent pharmacotherapy over the past decade. As we better understand the capabilities of available drugs and integrate them with treatments such as laser and surgery, and add new pharmacologic drugs to our treatment paradigms when they receive FDA approval, the future treatment for DR appears increasingly promising.

FUTURE DIRECTIONS

Concept of protective mechanism: Although a significant research effort has been conducted/ supervised to recognize the pathogenic pathways, adding to the beginning and progression of DR, a developing paradigm is the significance if endogenous systems that secure against DR. [28,29] This concept is actively being supported by the Joslin medalist study of 50 year, in which about 1000 individuals had taken part with Type 1 Diabetes with a time period of 50 years or more and approximately 40% of these patients were treated with diabetes before glycemic control, still they had no or mild DR. [30] Many protective factors opted in the DR, which may include Pigment Epithelium Derived Factor (PEDF), Somatostatin, NFE2-related factor 2 (Nrf2) have been identified. [31-33]

New therapeutic angles in diabetic retinopathy: While the past decade has shown vital enhancements within the treatment choices for DR, extra therapies are required urgently. Current treatments are coordinated solely towards progressive phases of DR, usually when invariable harm has resulted, in this manner medication that are protective or address early pathology are desirable. Anti-VEGF therapy is just half way compelling against DME and the recognizable proof of additional, VEGF free pathogenic particles, in this condition could prompt new medications that have better protected vision. [34] TNF- α and lipoprotein-associated phospholipase A2(LP-PLAA2) are the additional molecular targets, identified for pharmacological inhibitors. [35-36]

Precision Medicine: Patients with diabetes inhibit long variations during their treatment of retinopathy. It includes the pace of progressions as well as clinical manifestations. For example, some patients show a high tendency to treat DME while few may move towards PDR. Some individuals give better result for anti-VEGF therapy, while some shows moderate or poor response, this may lead to the variable result of the treatment. [37] A robust development pipeline of new DME drugs in phase I and II testing is available. Their potential uses vary from disease modulation in patients with early DR, to monotherapy or combination therapy for patients and can be a better treatment option for patients with DR in near future.

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CONFLICTS OF INTEREST

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