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Short Communication

Updates on Pharmacotherapy of Diabetic Retinopathy

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Received: April 29, 2022; **Published:** May 27, 2022

"Pandemy" of diabetes mellitus is recorded worldwide [1]. It's hard to overstate just how big of a problem diabetes is and is projected to be in the future. The incidence and prevalence of diabetes and diabetic retinopathy, as the most common microvascular complication of diabetes, is exponentially growing due to increased life expectancy in many parts of the world. Diabetic retinopathy (DR) is a visually disabling disease affecting the retina and representing a major cause of vision loss and even blindness [2], which currently is characterized as a neurovasculopathy. The forecast for the year 2040 indicates that the number of patients with diabetic retinopathy will reach 224 million [3].

These raising numbers of persons suffered from DR highlight not only medical issues including public health problem [2], but also an economic burden, representing a medico-social challenge, to meet which it is extremely important to identify a disease as soon as possible and successfully treat it.

A new era in ocular pharmacotherapy starts nearly 20 years ago from the discovery of anti-VEGF (Vascular endothelial growth factor) agents as an ophthalmic drugs for intraocular use. Currently several antiangiogenic agents (bevacizumab (Avastin, Roche), ranibizumab (Lucentis, Novartis) and aflibercept or VEGF Trap-Eye (EYLEA, Bayer)) are being widely and successfully used for the treatment of eye diseases like neovascular age-related macular degeneration (AMD), retinal vein occlusion (RVO), diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR) [4]. Ophthalmology has witnessed an explosion in the number of intravitreal injections delivered to patients over the past years. Patients with DME and/or PDR require continued treatment by anti-VEGF drugs, which itself represents a multidimensional challenge with medical and economic components, including also the therapy expenses [5]. The medical component is still multistructured containing issues related with primary non-responders, tachyphylaxis, and ocular (relatively invasive procedure and chemical compound related) and systemic (cardiovascular events, nephrotoxicity) safety concerns. The last is especially actual for the patients suffered from diabetic retinopathy taken into account that these patients may present with a different spectrum of underlying diseases and potentially higher risk profiles. Aforementioned indicates a need for search of patient-friendly and health care-friendly millennium- minded highly effective versatile therapy.

The key obstacles in the development of suitable therapeutics for diabetic retinopathy lies in its complex pathophysiology therefore left a room for further improvements in the progress and applications of new drugs. Scientific understanding of DR continues to develop, but there are still gaps in understanding of the mechanisms underlying of its development.

Recent studies have implicated neurovascular unit (NVU) formed by different neuron cells (horizontal cells, bipolar cells ganglion cells, amacrine cells), glial cells (microglia, astrocytes, Müller cells) and vascular cells (pericytes, endothelial cells) in both physiologi-

cal and pathological eye conditions attracting attention as a potential druggable target in DR [6,7]. At the same time available findings suggest that the cardinal position belongs to primary neurodegeneration manifesting before microvascular abnormalities [6-8]. These findings are valuable with respect to the identification of new drugs with a high therapeutic potential. Several therapeutic agents aimed to reduce the rate of disease progression are being investigated, including drugs with antioxidative properties, anti-inflammatory properties, neurotrophic factors, inhibitors of the complement cascade, neuroprotective agents [6,7]. Great interest lies in repurposing existing, approved drugs for the treatment of DR. From this point of view fenofibrate primarily used as a hypolipidemic agent is a good candidate, which have shown efficacy in multiple clinical studies reconfirmed by recent experimental research [9-12].

Currently available preclinical and clinical evidence underscores additional cholesterol independent or pleiotropic effects, contributing to prevention or retardation of DR. These vasoprotective and neuroprotective impact is realized through antioxidative, anti-inflammatory and anti-apoptotic effects [6]. Two large randomized clinical trials, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) [13] study and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [14] study have evaluated efficacy of fenofibrate, in preventing or arresting the progression of DR in patients with diabetes. Findings from FIELD study based on data of 4895 patients, and incorporating a substudy of 1012 patients, who received fenofibrate 200mg daily, indicate decreased need of laser treatment in 31% of DME and 30% of PDR cases respectively. It is postulated that therapeutic effect of drug was not related to lipid lowering properties [13]. In the multicenter eye- subgroup of ACCORD study (2856 patients) with 4-year follow-up of patients with DR was documented a 40% decrease in retinopathy progression [14]. In both studies it was evidenced a significant positive effect of therapy on DR progression, with a relative reduction of 30-40% over 4 - 5 years, and no impact as a preventive measure.

The new randomized trial with 910 participants evaluating the effect of fenofibrate in 160mg dosage compared with placebo for prevention of DR worsening through 4 years of follow-up in eyes with mild to moderately severe non-proliferative DR and no clinically important DME at baseline is ongoing with expected completion in April 2027 (ClinicalTrials.gov Identifier: NCT04661358). Hopefully, this study will add more to the body of knowledge on manageability of DR demonstrating a new strategy to prevent vision threatening complications of diabetes. Future pharmaceutical studies are required on increased drug retinal bioavailability through improved solubility and nanoparticles as nanocarriers [15].

Summarizing, there are multiple therapeutic challenges due to the multifactorial and complex nature of DR.

With the progress of diabetic retinopathy understanding, ophthalmopharmacotherapy is emerging a new era of focus. Systemically delivered agents with multimodal action and multitarget approach have an added advantage of treating of such bilateral disease, as a DR, and at the same time to prevent other diabetic microangiopathies. Future research will be directed to development of oral agent with an increased bioavailability to become an attractive therapeutic target. The continued assessment and refinement of management algorithms, along with advances in therapeutic modalities, have the potential to enhance both visual acuity outcomes and quality of life in patients with DR.

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Volume 13 Issue 6 June 2022