

The Treatment of Diabetic Retinopathy

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Abstract: *Retinopathy is a major cause of morbidity in patients with type 1 and 2 diabetes. The incidence of blindness, for example, is much higher in patients with diabetes than in the general population. This is a systematic review of reports, articles and guidelines published in web regarding the treatment and management of diabetic retinopathy. The indications and timing for photocoagulation and vitrectomy achieved consensus across all guidelines. Intraocular steroids and anti-VEGF agents have consistently generated interest as having the greatest potential in treatment of diabetic macular edema and proliferative disease. Recommendations for the use of intraocular corticosteroids in treatment of DME achieved consensus across the guidelines. All studies acknowledged that intravitreal corticosteroids including triamcinolone (IVTA) was widely used in managing DME that was refractory to focal/grid laser.*

Keywords: diabetic retinopathy, treatment, medication, guidelines

1. Introduction

Retinopathy is a major cause of morbidity in patients with type 1 and 2 diabetes. The incidence of blindness, for example, is much higher in patients with diabetes than in the general population. Furthermore, diabetic retinopathy (DR) is the most common cause of blindness in middle-aged subjects, accounting for at least 12,000 new cases in the United States each year (1). Visual loss from DR may be secondary to macular edema (retinal thickening and edema involving the macula), hemorrhage from new vessels, retinal detachment, or neovascular glaucoma. The pathogenesis of DR is multifactorial but is primarily caused by the metabolic effects of chronic hyperglycemia, which result in vascular changes and subsequent retinal injury and ischemia. More advanced retinal disease, including proliferative vascular changes and neovascularization in the setting of retinal ischemia, may be mediated by other mechanisms such as the action of vasoactive substances released during the inflammatory process. Diabetic retinopathy (DR) is divided into two major forms: nonproliferative and proliferative, named for the absence or presence of abnormal new blood vessels emanating from the retina. DR can be further classified by severity. These stratifications have been useful for analysis of treatment efficacy in the literature and general indicators for treatment strategies. However, each patient with DR has a unique combination of findings, symptoms, and rate of progression, which necessarily requires an individualized approach to treatment in the effort to preserve vision. Chronic hyperglycemia — Chronic hyperglycemia is thought to be the primary cause of diabetic retinopathy (DR) (2). Additional risk factors include a lesser degree of glycemic control, the type of diabetes (historically, type 1 more than 2), and the presence of associated conditions such as hypertension, smoking, nephropathy, dyslipidemia, and pregnancy (2,3). In some populations, such as minority youth with type 2 diabetes, the prevalence of diabetic retinopathy is higher in patients with type 2 than type 1 diabetes (4). Although these risk factors are strongly predictive of the development and severity of retinopathy in populations, and controlling some of these risk factors is important for the prevention of retinopathy, it is difficult to predict the development of retinopathy in a particular individual. As an example, many patients are under the

impression that they will not develop retinopathy if they maintain good glycemic control. While lower glycated hemoglobin (A1C) levels are associated with a decreased risk of retinopathy development and progression, good glycemic control does not guarantee that retinopathy will not develop or preclude regular screening for diabetic retinopathy (5). This is a systematic review of reports, articles and guidelines published in web regarding the treatment and management of diabetic retinopathy.

2. Materials & Methods

A structured search was conducted to identify existing DR guidelines for patients with Type 1 and 2 diabetes. This was performed by searching electronic databases: MEDLINE, CINAHL, PubMed, Web of Science, Scopus and the Cochrane library. The following websites were also searched: WHO, the National Health and Medical Research Council (NHMRC), International Agency for Prevention of Blindness (Vision 2020), International Council of Ophthalmology, NICE, National Screening Committee (NSC), ClinicalTrials.gov, National Guideline Clearing house and Google Scholar. Titles, abstracts and articles were searched for the terms 'diabetic retinopathy', 'screening', 'management' and 'clinical guidelines'.

3. Results and Discussion

Glycemic Control. Early epidemiologic studies have shown showed a consistent relationship between glycated hemoglobin (HbA1c) levels and the incidence of DR (6,8).

Blood Pressure Control. Epidemiologic studies have not found blood pressure to be a consistent risk factor for DR incidence and progression (9,10).

Lipid-Lowering Therapy. Observational studies suggest that dyslipidemia increases the risk of DR, particularly DME (11-14).

• Laser Photocoagulation & Vitrectomy

The indications and timing for photocoagulation and vitrectomy achieved consensus across all guidelines. Laser

photocoagulation was consistently observed as the standard practice for treating DR. The NHMRC, AAO, WHO, SIGN, International Society for Pediatric and Adolescent Diabetes and RCO all specified the timing and type of photocoagulation. Laser photocoagulation was indicated in patients with Type 1 and Type 2 DM with new vessels elsewhere in the presence of vitreous hemorrhage, or with new vessels on the optic disc with or without vitreous hemorrhage. Patients with severe or very-severe NPDR were to be considered for pan-retinal photocoagulation.

- Similarly, there was consensus regarding the timing of vitrectomy. Study that demonstrated statistically significant recovery of visual acuity in patients with Type 1 DM (15-17). Vitrectomy was indicated across all guidelines recommending vitrectomy in the setting of advanced DR including severe PDR with nonresolving vitreous hemorrhage or fibrosis, retinal detachment or areas of retinal traction that threatened the macula.

Intraocular steroids and anti-VEGF agents have consistently generated interest as having the greatest potential in treatment of diabetic macular edema and proliferative disease (18-20).

VEGF has long been considered an important mediator of neovascularization, and retinal vascular permeability, and therefore a likely therapeutic target for the treatment of proliferative DR and macular edema. Randomized clinical trials have demonstrated that the suppression of VEGF is particularly beneficial in the context of vision-threatening macular edema. Presently, three anti-VEGF medications are available for use: pegaptanib, ranibizumab and bevacizumab.

Bevacizumab is a full length humanized anti-VEGF antibody that inhibits all forms of VEGF-A and improves reduction of central macular thickness letters compared with patients assigned to macular laser treatment alone (23-25). Similarly, ranibizumab is a recombinant antibody fragment derived from humanized anti-VEGF antibody that inhibits all isoforms of VEGF-A.

Despite the promising clinical benefits of anti-VEGF agents, uncertainty into long-term potential side effects including infection, retinal detachment, vitreous hemorrhage and systemic ischemic events remains. Therefore, given the absence of longer-term safety data in patients with DM, evaluating the risks and benefits for the individual patient is advised.

- Corticosteroids inhibit inflammatory responses. They inhibit processes associated with inflammation such as edema, fibrin deposition, capillary dilation, deposition of collagen, leukocyte migration, and fibroblast and capillary proliferation.

Recommendations for the use of intraocular corticosteroids in treatment of DME achieved consensus across the guidelines. All studies acknowledged that intravitreal corticosteroids including triamcinolone (IVTA) was widely used in managing DME that was refractory to focal/grid laser. Thus, current evidence supports the use of IVTA in patients with refractory DME (26,27). However, the

individualized treatment considering the risk of adverse outcomes is imperative.

4. Conclusion

Tight control of blood glucose levels and hypertension remains the key element for preventing or arresting diabetic retinopathy. However, two drugs (fenofibrate and candesartan), originally not designed for treatment of diabetic retinopathy, have become new adjuncts in its management. The information drawn from clinical trials indicates that in normotensive diabetic patients, candesartan reduces the incidence of diabetic retinopathy in those with type 1 diabetes and favors diabetic retinopathy regression only in type 2 diabetic patients with mild retinopathy. By contrast, fenofibrate, which has only been tested in type 2 diabetes, has no effect on the incidence of diabetic retinopathy. However, it reduces the progression of existing diabetic retinopathy, thus lessening the need for laser treatment in both DME and PDR, and this beneficial effect is unrelated to changes in serum lipids. Therefore, it would be reasonable to recommend candesartan for type 1 diabetic patients (with or without hypertension) at high risk to develop diabetic retinopathy and for type 2 diabetic patients with mild retinopathy, whereas fenofibrate seems to be a good option for type 2 diabetic patients (with or without dyslipemia) with a wide range of diabetic retinopathy stages (from mild to severe nonproliferative diabetic retinopathy). In addition, the benefit on diabetic retinopathy shown by fenofibrate and candesartan should be considered an extra value when treating dyslipemia and hypertension in diabetic patients. Nevertheless, the mechanisms by which candesartan and, in particular, fenofibrate exert their reported benefits need to be elucidated before these drugs can be launched (alone or in combination) as new tools in the management of diabetic retinopathy. Another question needing specific research is whether such treatments could be administered topically and directly into the eye in order to increase the benefits in diabetic retinopathy.

In advanced stages of diabetic retinopathy, intravitreal delivery of anti-VEGF agents are currently used by many ophthalmologists despite the lack of phase 3 studies supporting their effectiveness and safety. This is due to the successful results obtained in wet AMD and the promising preliminary data in diabetic retinopathy. Intravitreal injection permits antiangiogenic drugs to effectively reach the retina and theoretically overcomes the problem of the systemic blockade of angiogenesis. However, this is an invasive procedure that can have complications such as endophthalmitis and retinal detachment and could even have deleterious effects for the remaining healthy retina. This is especially important in diabetic patients for whom long-term administration is expected. Apart from local side effects, anti-VEGF agents could also produce systemic complications because of their capacity to pass into systemic circulation. The effectiveness and safety of intravitreal anti-VEGF agents are being evaluated in several clinical trials. Meanwhile, in order to minimize systemic adverse effects, it seems reasonable to avoid long-term treatment with anti-VEGF agents for patients with hypertension, proteinuria, renal failure, cardiovascular disease, and foot lesions with wound healing impairment.

A future scenario will involve using a combination of anti-VEGF agents and laser photocoagulation or combining antiangiogenic agents aimed at different steps of angiogenic cascade. This would probably be more successful than single-molecule-specific approaches, would permit a decrease in the frequency of dosing, and would reduce adverse effects. Although it is premature at this stage to advocate such maneuvers, these aspects are certainly worth pursuing in future studies because they may suggest attractive new strategies for improving the treatment of diabetic retinopathy. However, it should be emphasized that, at present, the milestones in diabetic retinopathy treatment are the optimization of blood glucose levels, lowering of blood pressure, and regular fundoscopic screening. In summary fenofibrate, candesartan, and anti-VEGF agents are now in the armamentarium for diabetic retinopathy treatment. Ophthalmologists and physicians treating diabetic patients should be aware of the potential usefulness of these drugs and work together not only in future research but also in establishing clinical guidelines that will include these newer medical treatments for diabetic retinopathy. Only such coordinated action, as well as competent strategies targeting prevention, will be effective in reducing the burden and improving the clinical outcome of this devastating complication of diabetes.

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