Editorial

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The omnipresence of vascular endothelial growth factor in retinal diseases

More than seven decades ago, Michaelson[1] proposed that a diffusible and soluble factor X was responsible for retinal vascular growth during development and pathological states such as ischemic retinopathies. Many decades later, vascular endothelial growth factor (VEGF) was found to be Michaelson's elusive factor X. VEGF has multiple biologic properties including angiogenesis, increasing vascular permeability, neuroprotection, and inflammation.[2] Pharmacological inhibition of VEGF has revolutionized the treatment of blinding diseases such as diabetic macular edema (DME), proliferative diabetic retinopathy (PDR), retinopathy of prematurity (ROP), and exudative age-related macular degeneration (AMD).

ROP is one of the leading causes of childhood blindness. Taiwanese researchers have been at the forefront of research on ROP and VEGF inhibition.[3-6] In this issue of the Journal, Sen *et al*. reported their results of 60 eyes with Zone 1 ROP that underwent treatment. Of these 60 eyes, 40 achieved a favorable anatomic outcome. Almost half of these 40 eyes received VEGF inhibitors as adjuncts to vitrectomy or laser photocoagulation, underscoring the important role that VEGF plays in ROP. These results are in line with the Taiwanese experience.[3,5] Since intravitreal VEGF inhibitors lead to the suppression of serum VEGF levels, it is important to know the systemic implications of this finding.[6] It is reassuring that Fan *et al*.[4] showed that the neurodevelopmental outcomes of bevacizumab-treated children did not differ from those who did not receive bevacizumab.

Neovascular AMD is one of the main causes of visual loss in the elderly. Anti-VEGF drugs have revolutionized the management of this condition. In this issue of the Journal, Yang *et al*. report on 73 eyes with exudative AMD that had a follow-up of at least 4 years. Following a loading dose of three consecutive monthly injections of ranibizumab, the patients were followed on a modified treat and extend protocol. The injection interval was extended or shortened by 1-month interval. Eyes with persistent neovascular activity were eligible for rescue treatment with aflibercept. In this group of patients, the visual gains were maintained at 4 years, particularly those patients with a worse baseline visual acuity and older age. Yet not all patients with neovascular AMD respond equally to anti-VEGF drugs. In this issue of the Journal, Rodriguez *et al*. analyzed the response to ranibizumab according to polymorphisms in the CFH, HTRA1, and ARMS2 genes. They found that in their Colombian population, the response to treatment with ranibizumab differed according to the CFH genotype but not to ARMS2 and HTRA1 polymorphisms. Several polymorphisms in different genes, including the CFH, ARMS2, HTRA1, PEDF, VEGF, tumor necrosis factor-alpha, and interleukin-8 genes, have been associated with AMD in the Taiwanese population.[7-12] To the best of my knowledge, there is currently no information on how genetics affects the response to anti-VEGF therapy in neovascular AMD in the Taiwanese population. This may represent an interesting avenue of research for Taiwanese researchers.

Over 150 years ago, Noyes[13] published his clinical observations of "*retinitis by*

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glycosuria". It is noteworthy that Noyes stated that, "*I am aware that disease of the retina has been found complicating diabetes mellitus, but cases of this kind are by no means common.*" Unfortunately, the global incidence and prevalence of diabetes mellitus (DM) have reached epidemic proportions.[14] Taiwan is not an exception. According to the International Diabetes Federation, there were almost 2 million Taiwanese diabetic patients in 2017. There may be some light at the end of the tunnel as the incidence of DM peaked in 2012 at a rate of 9.04/1000 persons. By 2014, the incidence rate had dropped to 8.82/1000 persons.[15] All of these individuals will be at risk of developing diabetic retinopathy (DR) and DME.

The revolution in molecular biology has elucidated some of the underlying pathologic mechanisms in both DR and DME. VEGF plays an important role in the pathogenesis of both DR and DME.[16,17] Nevertheless despite an intensive anti-VEGF treatment, approximately a third to two-thirds of patients with DME exhibit persistent DME at 6 months.[18,19] Current alternatives for eyes that have a suboptimal response to anti-VEGF agents include intravitreal corticosteroids and pars plana vitrectomy (PPV). In this issue of the Journal, Chawan-Saad *et al*. and Flikier *et al*. thoroughly review these topics.

Chawan-Saad *et al*. analyzed the advantages and disadvantages of intravitreal corticosteroids when compared to intravitreal anti-VEGF drugs. Intravitreal corticosteroids are generally used as a second-line treatment for DME because of their less favorable safety profile. Nevertheless, certain patients may benefit from primary treatment with a corticosteroid intravitreal implant. These patients include those who have difficulty in maintaining a monthly appointment, particularly those with pseudophakic eyes, previously vitrectomized eyes, and eyes with long-standing DME.

Flikier *et al*. remind us that eyes with DME and vitreomacular traction clearly benefit from PPV as the primary treatment. In contrast, eyes with DME without tractional elements probably do not benefit from PPV. However, these views were based on eyes that had previously failed macular laser photocoagulation and had had persistent DME for a long time before being considered for PPV. Eyes with a shorter disease course may have better outcomes with PPV as the primary treatment and not as the salvage treatment.[20]

In this issue of the Journal, Wu *et al*. remind us that prior to the invention of the laser, most diabetic patients would become blind from PDR if they lived long enough. The introduction of panretinal photocoagulation (PRP) in routine clinical practice was a huge breakthrough that significantly decreased the rates of blindness in diabetic patients. However, PRP is not without adverse events. These include loss of peripheral visual fields, loss of color vision, loss of night vision, loss of contrast sensitivity, and exacerbation of DME. It is not surprising that interest in less destructive alternative treatments has been explored. Randomized clinical trials have shown the effectiveness of VEGF inhibitors in the treatment of PDR. The main drawback of anti-VEGF monotherapy for PDR is that these drugs need to be administered periodically for some time because of the chronic nature of the disease and the relatively short half-life of the VEGF inhibitors. Patients with PDR notoriously miss appointments and become hospitalized. Interruption of treatment can be catastrophic and lead to irreversible blindness. Combination treatment of PRP plus an anti-VEGF drug may be the treatment of choice for PDR.

In summary, the discovery of VEGF and the introduction of anti-VEGF agents in routine clinical practice have greatly improved the treatment outcomes of several blinding retinal disorders. The future looks bright, but several hurdles need to be overcome before we can truly once again exclaim "*I am aware that disease of the retina has been found complicating diabetes mellitus, but cases of this kind are by no means common*."[13]

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Conflicts of interest

The author declares that there are no conflicts of interests of this paper.

Lihteh Wu[1,2]

[1]Macula, Vitreous and Retina Associates of Costa Rica, San José, Costa Rica, [2]Illinois Eye and Ear infirmary, University of Illinois, Chicago, IL, USA

Address for correspondence:
Dr. Lihteh Wu,
Macula, Vitreous and Retina Associates of Costa Rica, Primer Piso, Torre Mercedes, Paseo Colón, San José, Costa Rica.
E-mail: lw65@cornell.edu

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