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Survey of Ophthalmology

Major review

The other CNVM: A review of myopic choroidal neovascularization treatment in the age of anti-vascular endothelial growth factor agents

Feisal A. Adatia, MD[a,b,*], *Micah Luong, MD*[b], *Monique Munro, MD*[b], *Adnan Tufail, MD*[c]

[a] *Mitchell Eye Centre, Calgary, Alberta, Canada*
[b] *Division of Ophthalmology, University of Calgary, Calgary, Alberta, Canada*
[c] *Moorfields Eye Hospital, London, United Kingdom*

ARTICLE INFO

Article history:
Received 7 June 2013
Received in revised form
14 October 2014
Accepted 31 October 2014
Available online 5 November 2014

Keywords:
bevacizumab
choroidal neovascular membrane
macular degeneration
pathological myopia
PEDG
photodynamic therapy
ranibizumab
vascular endothelial growth factor

ABSTRACT

Choroidal neovascular membranes (CNVM) associated with pathological myopia (PM) can result in significant vision loss and legal blindness. These membranes usually occur subfoveally and are a major complication of PM, developing in approximately 5–10% of such eyes. PM is the second most common cause of choroidal neovascularization after age-related macular degeneration (AMD), and accounts for nearly 60% of CNVM cases in patients younger than age 50. Vascular endothelial growth factor-A has been implicated as the major angiogenic stimulus responsible for choroidal neovascularization secondary to AMD and several major studies have proved the benefits of anti-VEGF treatment for AMD-related CNVM. Benefits have also been observed in a number of prospective and retrospective studies evaluating PM CNVM. Despite the small differences in molecular properties of ranibizumab and bevacizumab, both drugs showed similar therapeutic effects for CNVM associated with PM. Many studies also highlighted that patient age, previous photodynamic therapy treatment, axial length, and visual acuity prior to treatment may affect treatment prognosis. Although there is a paucity of large randomized controlled trials, this systematic review highlights the large numbers of individual trials that demonstrate a significant improvement in VA. The inferior long-term results of alternative therapies, combined with an excellent safety profile from anti-VEGF treatment, make anti-VEGF the current recommended first-line therapy.

Although 25% of the general population is myopic, only 2% suffer from pathological myopia (PM), defined as myopia with complications of the posterior segment.[17,26] In urban Asia, such as Singapore, Hong Kong, and Taiwan, the prevalence of myopia in high school graduates is 80–90%, of which 10–20% are highly myopic and 8.4% have PM. The prevalence of

The authors have no proprietary interest in this study or its findings.

* Corresponding author: Feisal A. Adatia, MD, 100 5340-1 St SW, Calgary, Alberta T2H 0C8, Canada.
E-mail address: fadatia@gmail.com (F.A. Adatia).

0039-6257/$ – see front matter
http://dx.doi.org/10.1016/j.survophthal.2014.10.002

myopia continues to increase over time in all parts of the world and may result in significant visual loss.[17,19,48,62] The National Eye Institute in 1976 found myopia to be the fifth most frequent cause of impaired vision, the eighth most frequent cause of severe visual impairment, and the seventh most frequent cause of legal blindness.[17,29] A study by the National Society for Prevention of Blindness also found that myopia was the seventh most common cause of blindness in those aged 20 years and over.[49]

1. Pathophysiology of myopic CNVM

Choroidal neovascular membranes (CNVM) can occur from any perturbation of the retinal pigment epithelium (RPE)–Bruch membrane complex, including PM, age-related macular degeneration (AMD), angioid streaks, multifocal choroiditis with panuveitis, presumed ocular histoplasmosis syndrome, and trauma.[26,27] In myopic patients, lacquer cracks and patchy atrophy within one disk diameter of the fovea are important predisposing findings for CNVM, found in 29.4% and 20% of myopic CNVM eyes, respectively.[53] Choroidal neovascularization can cause vision loss from the exudation of intraretinal or subretinal fluid, hemorrhage, or fibrosis.[38] Choroidal neovascular membranes usually occur subfoveally and are a major complication of PM, developing in approximately 5–10% of such eyes.[26,27,53] In fact, PM is the second most common cause of choroidal neovascularization after AMD, and accounts for nearly 60% of CNVM cases in patients younger than age 50.[15,16,86] In a retrospective review of 325 highly myopic eyes, the incidence of CNVM was higher among fellow eyes of patients with CNVM (34.8%) than among patients without pre-existing CNVM (6.1%). Thus, if one eye is affected, there is a greater than one-third chance the fellow eye will be affected within approximately 8 years in these young patients.[53] This can lead to significant visual loss in people that are otherwise young and healthy, with visual acuity (VA) decreasing up to 20/200 ($\leq$0.1 logMar) or less in 88.9% at 5 years, and 96.3% of eyes at 10 years, after the onset of CNVM, if left untreated. The effect of this disease on this young demographic is a significant societal loss, as these individuals are in their most productive years.[64,66] On an individual level, this visual loss may affect their career expectations and financial status—important considerations for patients who may be supporting themselves and their families.[45]

2. Treatments and outcomes

2.1. *Thermal laser*

Thermal laser for myopic CNVM is of limited value, as treatment of subfoveal lesions induces severe immediate visual loss, and treatment of juxtafoveal and extrafoveal lesions is complicated by a high recurrence rate and long-term expansion of the laser scar.[13,75] Studies suggest that CNVM is most frequently subfoveal in myopia, and the rate of recurrence of CNVM is as high as 72% after laser photocoagulation. The scar expansion occurs most frequently at the foveal edge of the laser scar.[28,64,69] In fact, one study of 19 eyes with PM demonstrated progressive enlargement of the photocoagulation scar in 89%, with a resulting decrease in VA in 68%.[36]

2.2. *Photodynamic therapy*

Photodynamic therapy (PDT) was introduced as a novel treatment for choroidal neovascularization secondary to PM in the 1990s.[18] The main advantage of PDT over conventional laser treatment was selective thrombosis of new vessels while preserving adjacent neuroretinal structures. Cells with high expression of low-density lipoprotein receptors, such as neovascular endothelial cells and tumor cells, selectively uptake verteperforin. This allows for activation of the targeted dye using laser light to cause selective vascular occlusion by damaging the intralumal portion of the neovascular vessels, theoretically without harm to adjacent neuroretinal structures.[52,63] In fact, in most regions, PDT with verteporfin remains the only approved treatment for subfoveal CNVM related to PM.

The best evidence for PDT use in myopic CNVM is from the Verteporfin in Photodynamic Therapy study.[8] This multicenter, double-masked, placebo-controlled, randomized trial studied CNVM secondary to PM and occult CNVM secondary to AMD. In those with CNVM secondary to PM, the proportion of eyes with fewer than eight letters of VA loss at the 12-month follow-up was 72% in the treated arm versus 44% in the placebo arm ($P < 0.01$). This difference, however, was not statistically significant at 24 months when a loss of eight letters or more were found in 36% of the treatment group compared to 51% in the placebo group ($P = 0.11$). The change in VA between baseline and the 24-month examination was in favor of cases treated with PDT, with a median gain of 0.2 lines compared with a loss of 1.6 lines in placebo group ($P = 0.05$). This included an improvement by at least five letters in 40% of the PDT group versus 13% of the placebo-treated cases, and an improvement by at least 15 letters or three Snellen lines in 12% of the PDT group versus 0% of the placebo-treated cases.[8,44] The median final visual acuity distribution at 24 months was 20/64 + 1 for the PDT group, compared with 20/100 + 1 for the placebo group, with a trend towards a treatment benefit in the PDT group ($P = 0.07$). The authors state that the loss of statistical significance between the two groups may have been the result of the following factors: a true loss of efficacy in the verteporfin group, adverse effects on the retina with additional treatment during the second year, fluctuations of vision in the eyes in both groups, and/or the result of healing not seen in the PDT group between the 12 and 24 month examinations.

Overall, although better than observation, PDT has shown suboptimal results, with 13% having significant visual loss and 57% having persistent leakage at 1 year.[8,47,74] Furthermore, PDT can cause transient choroidal ischemia, which leads to a secondary up-regulation of vascular endothelial growth factor (VEGF), as well as choroidal vessel thrombosis, which is presumed to initiate later atrophic creep.[53,70]

2.3. *Anti-vascular endothelial growth factor*

Vascular endothelial growth factor-A has been implicated as the major angiogenic stimulus responsible for choroidal neovascularization secondary to AMD. Several major studies