Pharmacotherapy for Age-Related Macular Degeneration

Hamid Ahmadieh, MD

Ophthalmic Research Center, Labbafinejad Medical Center, Tehran, Iran

Recent developments in pharmacotherapy for retinal disorders may be considered as a turning point in ophthalmology. The introduction of new therapies for devastating conditions such as age-related macular degeneration (AMD), the main cause of irreversible blindness in the elderly, stemmed from the tremendous work by Folkman and colleagues who identified the pivotal role of the vascular endothelial grow factor (VEGF) in angiogenesis. Later it was revealed that among the different subtypes of vascular endothelial grow factor, VEGF-A plays a key role in inducing angiogenesis in neovascular AMD.

Before the era of pharmacotherapy for retinal disorders, no treatment modality for neovascular AMD could actually improve vision. Therapeutic options as thermal laser and photodynamic therapy (PDT) may halt disease progression in certain patients but as a rule, visual improvement cannot be expected. Even pegaptanib, an aptamer against the 165 isoform of VEGF-A which is FDA approved for intravitreal injection, yields comparable results to PDT. It was after the introduction of bevacizumab, the full length antibody against VEGF, and ranibizumab, its antibody fragment, that a "change" occurred. The results of MARINA, a randomized clinical trial comparing ranibizumab to placebo for occult and minimally classic CNV, showed not only preservation of vision but also improvement in visual acuity in about one third of treated cases.[1] A few months later, the beneficial short-term effects of intravitreal bevacizumab were reported by retina specialists at the Bascom Palmer Eye Institute.[2] Although various controlled clinical trials had been conducted as an obligatory process before FDA approval of ranibizumab, no clinical trial was ever performed on bevacizumab up to that time. Therefore, intravitreal injection of bevacizumab was considered to be off-label. With the widespread use of bevacizumab as a less expensive and more readily available agent for treatment of a variety of retinal disorders, particularly AMD, various questions have arisen. The first one is whether bevacizumab is really effective in AMD. Although multiple case reports and small case series have suggested encouraging outcomes, larger and well designed studies are necessary to confirm them. The possible additive effect of intravitreal triamcinolone is another issue worth investigating. The optimal therapeutic dose for bevacizumab also needs to be determined. Doses of up to 2.5 mg have been shown to be safe in experimental studies.[3] In clinical practice, the two commonly used doses are 1.25 mg/0.05 ml and 2.5 mg/ 0.1 ml.

The current issue of this journal contains two important studies dealing with pharmacotherapy in neovascular AMD. The first study by Riazi et al,[4] is a two-center randomized clinical trial with two study arms: the bevacizumab group which received 3 consecutive injections 6 weeks apart, and the combined therapy group which additionally received intravitreal triamcinolone as an adjunct to bevacizumab in the first injection followed by two injections of bevacizumab alone. The six-week results of this study revealed that IVB leads to significant visual improvement and central macular thickness reduction. However the investigators report that the addition of triamcinolone to beva-

cizumab does not seem to increase its efficacy in the short term. One interesting finding in the mentioned study is the possible utility of fundus autofluorescence for predicting therapeutic response to intravitreal bevacizumab. These observations need to be confirmed with further studies. Modarreszadeh and colleagues[5] provide us with the second investigation in the field of pharmacotherapy in AMD. The authors compared the efficacy and safety of the regular 1.25 mg dose of bevacizumab with that of the higher 2.5 mg dose. Their results indicate no greater effect by the higher dose, on the contrary, they suggest that the 2.5 mg dose may be associated with an increased risk of adverse events. Both mentioned studies, presented in previous meetings of the American Academy of Ophthalmology, may help us better understand different aspects of therapy with bevacizumab which has revolutionized the management of neovascular AMD and provide us with knowledge for safer and more effective treatment strategies in these patients.

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