First-year Experience with Ranibizumab in AMD

The anti-VEGF agent will present logistical and economic challenges for health care professionals and governments.

BY STAVROS A. DIMITRAKOS, MD; AND CHRYSANTHOS SYMEONIDIS, MD

Since the pathogenesis of age-related macular degeneration (AMD) was elucidated by Sarks in 1976, there has been a continual effort to develop an appropriate treatment for this potentially blinding condition. The only form of the disease that has proved treatable is neovascular AMD; no measurable benefits of treatment have been seen with age-related maculopathy and geographic atrophy.

Indications for treatment with thermal lasers, whether argon green, krypton red, or dye, were initially restricted to extrafoveal subretinal membranes. Recurrences occurred in up to 60% of cases, apparently because the occult component of the membrane was not included in the treatment.

Photodynamic therapy (PDT) expanded the indications for treatment to include subfoveal neovascular AMD membranes, although positive results were shown only in predominantly classic phenotypes.

Vascular endothelial growth factor (VEGF) inhibitors delivered by intravitreal injection further expanded therapeutic indications to include any type of subretinal neovascular AMD and these agents quickly displaced the use of PDT for treatment of predominantly classic neovascular membranes as well. Anti-VEGF agents currently approved for intraocular use include pegaptanib sodium (Macugen, OSI/Eyetech) and ranibizumab (Lucentis, Genentech). Both drugs prevent visual acuity loss compared with the natural history of the disease, and the latter has the potential to increase visual acuity in 33.3% of treated eyes.

When clinical trials of ranibizumab demonstrated maintenance and even improvement in visual acuity in patients with neovascular AMD, we began using this treatment in our patients in January 2008. We used the quarterly injection protocol described in the PIER (A Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration) study. Our experience was comparable with the results reported in the original studies, MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration); generally satisfying and in some cases astonishingly good.

It soon became apparent, however, that improvement in and maintenance of overall visual function introduced a cycle of drug dependence in our neovascular AMD patients that increased exponentially. These patients are in fact treatment-dependent in a manner comparable to patients suffering from malignancies, although with a much greater life expectancy.

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FIRST YEAR EXPERIENCE

In the first year of our use of ranibizumab, the treatment was administered to patients referred to our outpatient macula clinic (approximately 350 per year) with active subfoveal neovascularization of any type. In cases of occult CNV, treatment with intravitreal ranibizumab was considered if the patient was recently diagnosed with the disease or showed evidence of disease progression; new hemorrhage or subretinal fluid, as assessed by fluorescein angiography and optical coherence tomography (OCT); or recent decrease in visual acuity leading to a best corrected visual acuity of greater than 20/320 (0.0625 Snellen) or 24 ETDRS letters at 1 meter. No patients with permanent structural damage to the fovea or who had undergone previous laser, PDT or other anti-VEGF treatment were included.

Criteria to continue treatment after three loading doses of ranibizumab were further visual acuity decrease or vascular leakage at 8 weeks following the last injection. Treatment was discontinued when there was no disease activity as demonstrated by OCT or if the visual acuity remained stable at 8 and 12 weeks after the last injection. Visual acuity stability was defined as change of less than five ETDRS letters at 4 meters.

No adverse effects of treatment were observed. An additional screening visit was scheduled 2 months later, and, in the absence of further visual acuity deterioration, patients were discharged with the appropriate instructions.

During the first year of ranibizumab use for neovascular AMD treatment, 59 eyes of 47 patients (25% bilateral) were treated with 155 injections, an average of 2.6 injections per eye. In this 12-month period, 37% of patients were in the loading phase, 36% were under treatment, and 27% discontinued treatment for any reason.

Most patients under treatment received three injections (Figure 1). This could indicate either an acceptable visual acuity outcome or a follow-up that was too short or inefficient. During the early months of the year we performed approximately seven injections per month, and during the final months that number rose to 24 injections per month. This indicates a slope of 2 to 2.5, and projection suggests a rate of 50 to 60 injections per month by the end of the second year (Figure 2). This leads to the question of what will happen by the end of the third and fourth years, and so on.

PREVALENCE OF AMD IN GREECE

In Greece there are approximately 2,500 ophthalmologists, but only 10% of them specialize in fundus pathology and have the capability to perform diagnostics with fluorescein angiography and OCT. The Thessaloniki Eye Study suggests that these approximately 250 Greek ophthalmologists currently face 35,000 eyes with AMD to be treated, 17,500 undiagnosed patients with neovascular AMD to be identified, and 7,500 patients with bilateral neovascular AMD to be prevented from becoming legally blind.

If these ophthalmologists administer three injections...
per year to these 35,000 eyes, as we did during our first year’s experience, they will give 105,000 injections. If they administer 5.5 injections per year, as in the first year of the PrONTO Study of OCT-personalized treatment, they would give 192,500 injections per year.

Finally, these Greek ophthalmologists will have 35,000 AMD patients with a life expectancy of greater than 10 years to follow monthly with visual acuity assessment and OCT.

SOCIAL IMPACT

The social impact of AMD is considerable. Apart from consequences related to the reduced quality of life of the disabled patients, if the 7,500 people legally blind with AMD living in Greece should receive financial assistance from Social Security services of €500 per month, for an average life expectancy of 10 years, the annual government expenditure would be €6,000 per person, and the total amount would approach €0.5 billion for this group of patients alone.

In addition, following the PIER protocol, with an approximate charge of €1,000 per injection, the cost of intravitreal ranibizumab administration would total about €6,000 per patient per year in the first year of treatment, not including any other medical expenses.

The questions that arise from these estimates include when to start and how long to continue ranibizumab treatment in order to provide optimal care for our AMD patients while keeping the financial burden of this beneficial treatment under control.

The calculations presented in this article suggest that national health services must make projections about the potential costs of these treatments for small and large retina services and for subspecialized practitioners.

Future needs, in terms of human resources, technical assistance, and specialized care, as well as related medical expenses, should be considered on a national scale. In addition, physicians’ organizations must generate new guidelines regarding treatment indications and protocol limitations.

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