Quadruple Therapy for AMD Significantly Reduced Retreatment Rates at 14 Months

Vitrectomy may help angiogenic factors diffuse from the retina.

BY FRANK H.J. KOCH, MD; AND ROBERT G. JOSEPHBERG, MD

A quadruple-therapy regimen for the treatment of choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) has shown promise in evaluation with 14-month follow-up. The quadruple regimen combines (1) core pars plana vitrectomy (PPV), (2) verteporfin photodynamic therapy (PDT) (Visudyne; Novartis, Basel, Switzerland), (3) intravitreal bevacizumab (Avastin; Genentech, South San Francisco, California), and (4) intravitreal dexamethasone.

In 2002, Albert J. Augustin, MD, and Frank H.J. Koch, MD, initiated a two-center protocol evaluating a combined treatment for CNV in AMD. The aim was to determine how much dexamethasone was needed to counteract the unwanted side effects of PDT and to what extent the simultaneous injection of bevacizumab would enhance the treatment outcome. In both centers, a core PPV of 0.35 to 0.5 cc was included in the protocol. Patients in the two centers were followed up independently.

Dr. Augustin published the results of his series last year, concluding that the combination therapy resulted in significant and sustained visual acuity improvement after one cycle of treatment, as well as a good safety profile and potentially lower cost compared with therapies that must be administered more frequently.
CNV IN AMD

This article reviews the results in 158 patients treated with the protocol at Dr. Koch's center and followed for 14 months. Patients with more than 50% classic CNV lesions (n=52) were assigned to quadruple therapy of core PPV, PDT, bevacizumab, and dexamethasone. Those with predominantly occult CNV (n=106) were assigned to triple therapy, the same as above but omitting the dexamethasone.

The core PPV was performed using a new instrument, the 23-gauge Intrector (Insight Instruments, Stuart, Florida). The visual acuity results with both triple and quadruple therapy were comparable to results of recent studies of monthly monotherapy with ranibizumab (Lucentis, Genentech), with significant improvement of visual acuity (Figures 1 and 2).

In addition, there was a significant reduction in retreatment rates in comparison with the ranibizumab studies, especially in the quadruple-therapy group, in which 75% of patients never needed a retreatment during the observation period of 14 months, and 25% needed only one additional treatment. No retreatment was needed before 9 months after the initial treatment. In the triple-therapy group, 12% needed retreatment after 3 months, 48% by 14 months, and 8.3% needed three interventions.

OTHER APPLICATIONS

With these encouraging results, combination therapy with core PPV and drug injection was performed in patients with diabetic retinopathy (DR) and branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Patients with DR (n=76) were divided into three groups: those with (1) DR and ischemic maculopathy (n=26); (2) nonproliferative DR without ischemic maculopathy (n=31); and (3) proliferative DR without ischemic maculopathy (n=19). Vitrectomy volume was 0.35 mL or as much as necessary. Follow-up, which was >6 months for all patients, included fluorescein angiography and optical coherence tomography (OCT).

Again, in these patients, significant increases in visual acuity and significant reductions in retreatment rates were seen.

In group 1 (DR with ischemic maculopathy), mean visual acuity was 20/180 at baseline, 20/150 at 3 months, and 20/140 at 6 months. In group 2 (nonproliferative DR without ischemic maculopathy), mean visual acuity was 20/50 at baseline, 20/40 at 3 months, and 20/35 at 6 months. In group 3 (proliferative DR without ischemic maculopathy, mean visual acuity was 20/70 at baseline, 20/63 at 3 months, and 20/50 at 6 months.

In group 2, nine of 31 patients required retreatment by 6 months, with core PPV repeated in only one patient. In group 3, four of 19 patients needed retreatment, with only two requiring repeat core PPV. Seven patients required scattered laser coagulation of ischemic retinal sectors.

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The combined regimen was also evaluated in 50 patients with retinal vein occlusions, including ischemic CRVO (n=13), nonischemic CRVO (n=8), and BRVO (n=29). All patients were followed for 6 months with examinations including fluorescein angiography and OCT.

In patients treated for CRVO with ischemic maculopathy, visual acuity improved from 20/800 at baseline to 20/400 at 3 months and 20/300 at 6 months. Retreatment was required in four of the 13 patients, and laser coagulation in six patients. In patients with nonischemic maculopathy, visual acuity improved from 20/100 at baseline to 20/70 at 3 months and 20/44 at 6 months. Retreatment was needed in two of the eight patients.

In patients with BRVO, visual acuity improved from 20/80 at baseline to 20/63 at 3 months and 20/48 at 6 months. Macular edema decreased from 300 nm at baseline to 280 nm at 3 months and to 215 nm at 6 months. Retreatment was needed in four of 29 patients and laser coagulation in two patients.

For patients with retinal vein occlusions, except for those with ischemic maculopathy, combined therapy including core PPV resulted in significant improvement.
in visual acuity at 6 months, and for all patients, a significant reduction in retreatment rates.

SUPPORTING EVIDENCE

What accounts for the improvement in efficacy seen with the use of core PPV?

Recently, Holekamp reported that a limited core PPV may induce complete vitreous liquefaction, resulting in up to 10 times greater retinal oxygenation. This may be supportive evidence for the role of core PPV in this combined treatment regimen. It has also been reported that the diffusion rate of all substances, including oxygen, drugs, vascular endothelial growth factor (VEGF), and others, increases from 200 to 3,000 times after core PPV. As a consequence, tissues containing fewer vascular components such as endothelial cells, and fewer extravascular components such as macrophages, may produce less VEGF.

PRACTICAL APPLICATION

The core PPV procedures in this study were performed using the Intrector, a 23-gauge device with a very sharp tip (Figure 3). It can be inserted easily and safely, as though the user were inserting a needle for injection. Pulling out the tip leaves a clean 23-gauge hole, which closes immediately.

The Intrector is a practical device, less expensive than a vitrectomy pack, and portable so that it can be used in the office, the ambulatory surgery center, or the operating room. It is quick to set up for immediate use, and it is inserted into the eye in a single step, with no cannula needed. The tip contains an injection/infusion channel and a separate cutting/aspiration channel.

Benz and colleagues reported the occurrence of reflux in more than 20% of patients after injection of 4 mg (0.1 mL) of triamcinolone with a 27-gauge needle. The controlled volume exchange with the Intrector eliminates these type of side effects, facilitating precise delivery of drugs (Figure 4).

In 1,000 patients in whom the device has been used, no complications to the core PPV performed with the Intrector at the time of surgery (including bleeding, hypotony, choroidal swelling, and vitreous traction or incarceration in the injection site) have been reported. Two retinal detachments after 2 months and another after 6 months occurred with the first design of the device. There was no evidence that the Intrector was the cause. No detachments have occurred at any time with the newer, final needle tip design. No patients have reported any side effects.

Because the device is designed for simultaneous aspiration/cutting and injection/infusion (of saline solution, drugs, air, gases, etc.), other indications are under investigation, including use in uveitis, endophthalmitis, tumor biopsy, enhanced pneumatic retinopexy, enzymatic vitrectomy, regenerative posterior capsular opacification after cataract surgery, floaters, hemorrhage, complicated cataract surgery, and malignant glaucoma.

Most important, the use of the Intrector should reduce the socioeconomic burden to patients by reducing the frequency and cost of treatments.

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