Implications of Extended-Release Devices

BY CARL REGILLO, MD

In January, the Centers for Medicare and Medicaid Services implemented reimbursement changes for an important vitreoretinal code: 67028, intravitreal injection of a pharmacologic agent. Payment for this code was reduced from approximately $200 to $125. As George Williams, MD, reported in these pages in January,[1] this change came as the result of ongoing review by the Medicare Payment Advisory Commission (MedPAC) of potentially misvalued codes. One of the criteria by which MedPAC selects codes for review is increases in utilization; not surprisingly, as Dr. Williams noted, 67028 was at the top of the list in this category. Utilization of this code increased from approximately 4000 instances in the year 2000 to a projected 1,000,000 in 2010—a 25,000% increase.

Vitreoretinal specialists know why utilization of intravitreal injection has increased so dramatically in the past 10 years. During that time there have been tremendous advances in pharmacologic therapy for retinal disorders. This is particularly true for exudative age-related macular degeneration (AMD), a disease for which there was no pharmacologic therapy 10 years ago. The visual acuity of patients with exudative AMD can now routinely be maintained or improved with injections of vascular endothelial growth factor (VEGF) inhibitors. In addition, we have found that intravitreal injection of anti-VEGF agents and/or steroids can be effective in reducing edema and improving vision in a number of other conditions, including diabetic macular edema (DME) and retinal vein occlusions. However, in all of these cases, repeated injections are needed to maintain the effects of these drugs.

With every passing year we see expanding indications for anti-VEGF agents. Both the approved ophthalmic formulation ranibizumab (Lucentis, Genentech) and the off-label oncology drug bevacizumab (Avastin, Genentech) work well for treatment of AMD, DME and edema due to vein occlusion. However, for all these conditions, the effects are short-lived—6 to 8 weeks at the most—and multiple injections are often required to control edema. Not only might treatment for all these conditions be needed indefinitely, but many patients who initially benefit from anti-VEGF or steroid injections experience a diminished effect with long-term treatment.

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Intravitreal injection of triamcinolone acetonide has also demonstrated efficacy in decreasing the edema associated with diabetic eye disease and with retinal vein occlusions. But again, the duration of efficacy is limited, lasting no longer than 6 months.

With these frequent injections comes increased risk of side effects and complications, including potentially sight-threatening intraocular infections and, with steroid injection, the development of cataract or glaucoma.

SUSTAINED DELIVERY

In this setting—with increasing utilization of intravitreal injections that offer only limited duration of efficacy and pose some potential risk—the value of an effective

method of sustained drug delivery to the posterior segment is clear. A number of sustained-release devices have been investigated, including a dexamethasone intravitreal implant (Ozurdex, Allergan, Inc.) that received US regulatory approval in 2009, and a fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences) that is currently undergoing US Food and Drug Administration (FDA) review.

Thirty-six-month results of two clinical studies of the Iluvien implant were recently announced.[2] Collectively called the FAME study, these two phase 3 pivotal clinical trials (trial A and trial B) were designed to assess the safety and efficacy of the fluocinolone acetonide intravitreal implant in the treatment of DME. Patients in each trial were randomly assigned to one of two doses of the implant, dispensing either approximately 0.2 µg or approximately 0.5 µg of drug per day. The primary efficacy endpoint was the difference between treatment and control groups in percentage of patients whose best-corrected visual acuity (BCVA) improved by three or more lines (15 or more letters) from baseline on the ETDRS eye chart at 2 years.

The 24-month results of the FAME study were presented last year,[3] and based on those data Alimera submitted a new drug application to the FDA in June for approval of the lower dose of Iluvien. The implant was granted priority review, but in December the FDA asked the company for more data. The 36-month data will be part of the information the company provides to the FDA early this year.

In trial A through month 36, for the primary endpoint of three-line gain in BCVA, the treatment group showed statistically significantly greater therapeutic effect compared with the control group. At month 30, 28.9% of patients (P=.011), and at month 33, 28.4% of patients (P=.042) in the treatment group gained three lines, compared with fewer than 17% of patients in the control group. The therapeutic effect was maintained at month 36. Results were similar in trial B.

With data from the two trials combined, a statistically significant effect of treatment was seen at week 3, and this effect was maintained through 36 months, with a three-line gain in 28.7% of the treatment group vs 16.2% in the control group at month 24 (P=.002), and 28.7% vs 18.9% at month 36 (P=.018).

Regarding safety, intraocular pressure (IOP) increases to 30 mm Hg or greater at any time point were seen in 18.4% of patients by month 36, and 4.8% of patients had undergone a surgical procedure to reduce IOP. Incidence of cataract in patients who were phakic at baseline was 81.7% by month 36, and 80% underwent cataract surgery.

The side effects with the implant are comparable to what we have come to expect with intravitreal administration of steroids over the past decade. The safety profile is better with the lower dose implant than the higher dose, and the lower dose is the one that has been submitted for approval by the FDA.

PRACTICE EFFICIENCY

The Iluvien is a small implant that is inserted into the vitreous with a 25-gauge needle. This procedure can be done in the office. The availability of an office-based procedure with an effect that lasts up to 3 years could have a significant impact on retina practices that are currently stretched to the limits by the volume of regular repeat injections. If an implant such as the Iluvien is approved for use, it would be likely to provide tremendous added convenience for our patients.

In addition, it is logical to suppose that a continuous steady state of drug delivery over an extended time frame will provide an added visual benefit over monthly or less frequent injections. With gaps between treatments, recurrences of edema can compromise vision over time, and patients may not be able to recover their vision as well if there are large or frequent recurrences. Theoretically, then, sustained delivery could yield better long-term results than intermittent therapy. This potential has not yet been evaluated in a head-to-head comparison between Iluvien and intravitreal injection.

We must continue to follow these patients carefully, so the availability of a sustained-release implant will not eliminate visits for patients with CNV in AMD, vein occlusions, or DME. Certainly we will continue to see diabetic patients with retinal complications every 3 or 4 months. Additionally, if steroid use causes IOP elevation, we may have to see patients more frequently. Still, it is to be hoped that the ability to deliver a low dose of drug steadily for an extended period of time will yield better results, and more convenience and options for our patients. ■

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