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PIER data suggest a need for tailored injection schedule

Patients could receive injections as needed rather than every quarter, according to one investigator.

The schedule for injections of ranibizumab should be tailored to each patient based on clinical evaluation, according to an investigator involved in clinical trials of the drug for treatment of age-related macular degeneration.

At the Retinal Physician Symposium in the Bahamas, David M. Brown, MD, FACS, presented year 1 results from the 2-year PIER (Phase 3b, Multi-Center, 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 AMD) trial. That study included 184 patients with predominantly classic, minimally classic or occult with no classic wet AMD.

The PIER trial used a less frequent schedule of injections than two other phase 3 trials of Lucentis (ranibizumab, Genentech), the ANCHOR and MARINA trials, Dr. Brown said. In those two 2-year trials, subjects were randomly assigned to receive injections of Lucentis in 0.3 mg or 0.5 mg doses or control (sham injection in MARINA, photodynamic therapy in ANCHOR) once a month.

"In MARINA and ANCHOR, the subjects received injections every month for 24 months," Dr. Brown explained. "In the PIER study, they got three monthly shots and then mandatory quarterly injections, not based on whether they needed it or not."

Tailored treatment

Investigators in the PIER trial used the reduced schedule of injections in hopes of getting the same results as the MARINA and ANCHOR studies, Dr. Brown said. Initially, results were similar to the other studies, but after the first 3 monthly treatments the mean visual acuity in the ranibizumab-treated eyes returned to baseline, rather than improving further as it had in the other studies.

"For the first 3 months, it was just like MARINA," Dr. Brown said. "We saw a nice visual acuity improvement. But then when we went to mandatory quarterly dosing, the average patient's vision dropped back down to baseline. This shows that we cannot just mandatorily treat on a quarterly basis and maintain the visual gains seen with the first three monthly injections."

Physicians' options, Dr. Brown said, include following the MARINA and ANCHOR protocols and continuing to give monthly injections or "trying to come up with a rational treatment approach with decreased injections."

"What makes sense to me and many others," he said, "is to treat with ranibizumab until we eliminate all signs of choroidal neovascular membrane leakage on optical coherence tomography and then re-treat as frequently as needed to maintain this 'anatomic' success. By tailoring our treatment to the retina's anatomic response, I am hopeful that we can maintain the visual acuity gains that we get with the initial Lucentis dosing."

Trial outcomes

According to Genentech officials, after the three monthly injections, the group receiving 0.3 mg of ranibizumab demonstrated a mean increase of 2.9 letters on a visual acuity chart, and the group receiving 0.5 mg showed an increase of 4.3 letters. The control group lost a mean of 8.7 letters at 3 months.

After the 5-, 8- and 11-month injections, the treated patients returned on average to baseline visual acuity, while subjects in the control group continued to experience visual loss, according to Genentech.

These results have led investigators to think that automatic quarterly treatments may be less effective than more frequent dosing or tailored dosing, Dr. Brown said.

"The only trial data available other than PIER (ie, ANCHOR and MARINA) had phenomenal results with monthly mandatory injections," he said. "The expense and incremental risks of 12 intraocular injections per year could be diminished if any of these monthly injections could be eliminated without affecting visual gains. I am hopeful that a tailored approach can be done by following patients closely and monitoring them with OCT and other clinical tests."

An effective tool

Dr. Brown said it was "a shock to a lot of people" that patients in the PIER study did not maintain the improvements that were seen in the MARINA and ANCHOR trials.

"You can't just do mandatory quarterly injections. We are going to have to follow the patients, I think, every 4 to 6 weeks by OCT [optical coherence tomography] and if there is evidence of fluid then reinject," he said.

The best tool to help tailor treatment is OCT, Dr. Brown said.

"Some people are still using fluorescein angiography, but the majority of our response to treatment will be guided by OCT," he said. "OCT shows you the anatomic response to the treatment."

The device acts as a high-resolution optical biopsy that can demonstrate the presence of subretinal fluid, intraretinal fluid or sub-RPE [retinal pigment epithelium] fluid indicating active CNV leakage, Dr. Brown said.

"I use the macular thickness map protocol on the Stratus OCT [Carl Zeiss Meditec], which has six high-resolution cross-sectional views of the macula spaced 30º apart," he said. "I look at every scan, just like a radiologist looks at every image on an MRI. The automated foveal thickness measurement is almost always inaccurate in wet AMD. Just as a cardiologist doesn't rely on the EKG automated diagnosis, I rely more on my interpretation of the individual images than the retinal thickness measurements generated by the machine."

Patient response

Dr. Brown said that in practice, outside the clinical trial setting, patients with AMD who are candidates for Lucentis will likely be given three monthly injections and then will be monitored regularly with OCT after the 3-month treatment.

"We're going to have to get the retina flat and then see how well people will respond visually," he said. "OCT at least gives us an anatomic response to treatment. For the first time, we finally have an anti-VEGF agent that effectively anatomically corrects the retina in most patients. If I can keep that retina anatomically correct, I am hopeful that the patient can maintain those visual acuity gains."

He continued, "If they don't have any recurrent fluid on OCT, then we won't inject, but if they do, we will reinject. The question is, how many patients are going to need how much treatment, and will we be able to maintain visual acuity gains more analogous to ANCHOR and MARINA with this approach?"

Dr. Brown estimated that the average patient might need six or seven treatments in the first year and hopefully fewer treatments in subsequent years.

"We don't know that, though, until we get further out in following patients who are in these trials," he said.

"But to be honest, this is better for physicians because it makes you a doctor again," he continued. "You have to see if your patient is responding or not, and you have to tailor treatment to the way the patient is responding."

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