

The following are highlights of a panel discussion after Dr Pieramici's presentation, which addressed questions from the audience. Dr Bressler served as moderator of the discussion.

FLUORESCEIN ANGIOGRAPHY

Dr Bressler: Should patients who are referred by comprehensive ophthalmologists to a retina specialist for suspected choroidal neovascularization (CNV) expect to get a fluorescein angiogram? Do you always need angiography? The MARINA (Minimally Classic/Occlud Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Age-Related Macular Degeneration) trial showed that ranibizumab worked in a series of minimally classic lesion compositions on fluorescein angiography and in occult with no classic lesions with recent disease progression,¹ whereas the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration) trial showed that it worked in predominantly classic compositions regardless of whether recent disease progression had occurred.² Because these 2 studies seem to cover essentially all lesion types, is a fluorescein angiogram still necessary?

Dr Pieramici: Patients should probably expect an angiogram for 2 important reasons. First, we need to establish the diagnosis of CNV. Just because we see some fluid or even a small hemorrhage in or under the retina doesn't necessarily mean that there's neovascularization. Other ocular disorders (eg, pseudophakic cystoid macular edema) may produce these findings. We need to determine whether CNV is actually present.

Second, you don't necessarily treat every choroidal vascular lesion; at least, I don't. For example, if a patient has an angiographic occult choroidal neovascular membrane, but there's no hemorrhage and the patient is not experiencing vision loss, I may monitor him or her for a period of time and initiate treatment only if there is disease progression. One of the aspects of monitoring to determine if the disease is getting worse is to look for signs of progression on angiography. Most patients with significant age-related macu-

lar degeneration (AMD) who are referred to me by a comprehensive ophthalmologist are going to have a fluorescein angiogram.

TRIAMCINOLONE AND PEGAPTANIB

Question from the audience: I've had patients with CNV who were treated with intravitreal triamcinolone acetate. What role, if any, does that play with regard to bevacizumab and ranibizumab?

Dr Pieramici: There was a time when photodynamic therapy (PDT) was the treatment of choice and we were trying to maximize its effect. Before bevacizumab was used off label for CNV, we didn't have much else, so we tried triamcinolone off label in combination with PDT. Some anecdotal evidence and case series suggested that this combination is better than monotherapy PDT, but there hasn't been a good randomized phase III clinical trial comparing combination therapy with triamcinolone to PDT alone or to anything else. Therefore, if we're viewing phase III clinical data as the gold standard, we haven't reached that yet. There are some trials that are under way, but we don't have that sort of evidence yet.

Question from the audience: Are you using pegaptanib, and if so, when are you using it in your patients?

Dr Lim: I don't use pegaptanib very much at this point in time, simply because its efficacy is not as great as that seen with ranibizumab or even (from the anecdotal evidence) with bevacizumab. Except for some patients with diabetes, a population in which pegaptanib has been tried as an adjunct for macular edema and is also used preoperatively, I do not use it at this time in my patients with AMD.

Dr Bressler: Same answer. Although we have no head-to-head trial between pegaptanib and ranibizumab, which would provide the strongest evidence, it doesn't mean that we don't have any evidence. If we look at similarly designed pegaptanib and ranibizu-

mab trials, we do have evidence that 5% of patients given pegaptanib improve at 1 year compared to 30% to 40% in the ranibizumab trials. That makes a very strong case that you don't need a head-to-head trial to figure out that the drugs differ in efficacy for neovascular AMD.

WHO SHOULD TREAT NEOVASCULAR AMD?

Dr Bressler: We now have much better treatments for CNV than we had in the past, and they apply to many cases. Granted, some cases of occult neovascularization with no classic CNV on angiography might not need immediate treatment, especially such lesions in patients who are asymptomatic and these patients can be followed. However, when treatment is required, as it is in many cases, who should initiate it? Should the comprehensive ophthalmologist treat CNV? Should it be a retina specialist? Or should both be treating it?

Dr Tornambe: Treating macular degeneration is a matter of keeping up with the literature and the current treatments. When pegaptanib first came out, the thought was that it would be given every 6 weeks, without paying attention to what was actually happening to the neovascular lesion in the patient's eye. It was assumed that ophthalmologists would follow the protocol strictly, giving an injection every 6 weeks for the next 2 years, no matter what! That never sat well with retina specialists because we don't like to treat patients with cookbook treatment approaches. We like to have some feedback and some evidence that the treatment is effective.

Having said that, we now treat neovascular membranes with drugs that inhibit neovascularization (ie, bevacizumab, which is approved for the treatment of colorectal cancer, and ranibizumab), but we approach these lesions quite differently than the way oncologists treat cancer neovascularization. When oncologists use bevacizumab, they continue to use it until the tumor enlarges; then they stop, having decided that the drug is not effective. Retina specialists, on the other hand, tend to reason, "Let's give one dose and then watch it. If it looks like there is growth or leakage, we'll give another dose."

We have a different way of thinking about treating neovascularization than our colleagues in oncology. They may be right, but most retina specialists have observed an occasional lesion that completely regresses with a single intravitreal injection and are therefore

reluctant to inject a drug monthly into the vitreous cavity unless there is evidence that it is necessary. Recent clinical trials, such as the Safety Assessment of Intravitreal Lucentis for AMD (SAILOR), are looking at this issue, and data from those studies may help us in deciding when to treat and, more importantly, when not to treat.

If we ever find the magic bullet and know exactly what the treatment sequence is, the government will probably allow physician assistants to give these intravitreal injections. However, until we've been able to standardize the treatment on a standard protocol, I think that comprehensive ophthalmologists can handle it if they keep up with current thinking about what the best treatment is, which probably changes every 3 or 4 months. There's no reason why comprehensive ophthalmologists can't treat AMD, but they need to be available to obtain and interpret the angiograms and OCTs (optical coherence tomography). They also need to be available in those very few cases of endophthalmitis, inflammation, retinal detachment, or other problems.

Dr Lim: Comprehensive ophthalmologists need to be comfortable with the diagnosis of endophthalmitis and have somebody readily available who can treat it so that patients are not referred in an emergent situation after an intravitreal injection.

Dr Bressler: I think this approach to treatment is very difficult for us. The evidence suggests that if you give an injection every month for 2 years, you will definitely help the patient compared to not giving injections at all. What we don't know is whether we will get the same result if we give the injections less often. It's an easy decision when you have a patient who is 20/80 before an injection and 20/50 a few weeks later, and when the retina has gone from very thick to not quite as thick. It's easy to give that injection again because you know the patient has improved. However, when that patient gets to 20/25, and the retina is flat, and the angiogram just stains with fluorescein for 8 months in a row, you have to ask yourself if you should inject again. The answer is that we don't know, so maybe we shouldn't inject and just watch to see if the retina stays flat and vision remains at 20/25 forever.

The problem with neovascular AMD is its biology, which suggests that many lesions leak, grow, and swell again after anti-VEGF (vascular endothelial growth factor) therapy has done its job "mopping up"

the VEGF that caused the vascular leakage and growth in the first place. Saying, "No big deal; I'll just start treating it again," is not the answer. We don't know if treating new vessel growth after the discontinuation of initial anti-VEGF therapy will produce the same outcome as treating new vessel growth monthly without waiting for some deterioration or swelling of the retina or leakage on fluorescein angiography to develop.

This is a very difficult issue. At present, many of us tell our patients that they are going to need a treatment every month for at least 2 years, and that we'll look very carefully and see if we're comfortable withholding treatment at some point. However, this approach may change 3 or 6 months from now as investigators are studying the issue, or 12 months from now as we get more data. Until then, it is very important for all of us to stay on top of this issue.

Dr Lim: I would like to add that it is always an analysis of the risk/benefit ratio for your patient. In some scenarios, when the vision has been stable—say, 20/25 or 20/20—we're very tempted to inject less frequently or even not give an injection because of the risk of endophthalmitis.

One other flip side of anti-VEGF therapy that we have to remember is that we don't know all of the long-term side effects of nonselective VEGF inhibitors beyond 2 years. There are some potential side effects. You may lose the neuroprotection of VEGF and you lose fenestration effects of VEGF. Those are other things that I think we're going to be able to elucidate in the future.

ROLE OF PDT

Question from the audience: Is PDT becoming obsolete?

Dr Pieramici: It is almost obsolete as a primary monotherapy, particularly when you have another monotherapy that's much better. However, PDT is being investigated as part of a combined therapy approach, and there is some preliminary evidence suggesting that there may be a benefit to combining PDT with anti-VEGF therapy as a way of reducing the number of injections.³ Time and careful studies will determine if this is possible.

I don't think PDT is completely dead in the water yet, but its use as monotherapy will be very, very infrequent. There are only a few scenarios where I would use PDT as monotherapy. I might use it again in a

patient who has been previously treated and responded very well, perhaps one of the 4% or 5% who improve after PDT. I would recommend it in a patient who has significant subretinal fibrosis and limited visual potential for recovery, or in an elderly patient who can't make trips back and forth to the office but needs some form of treatment to keep the lesion from continuing to grow.

RANIBIZUMAB VERSUS BEVACIZUMAB

Question from the audience: When you look at ranibizumab versus bevacizumab, does the difference in cost between the two influence your treatment choice?

Dr Bressler: The cost of ranibizumab is approximately \$2000 to the doctor and there might be some additional percentage increase cost to the patient. By comparison, a compounding pharmacy might charge, let's say, \$50 for a dose of bevacizumab. If the cost difference influences your treatment decision, we should also ask how it figures into your decision when treating a new patient with neovascular AMD.

Dr Tornambe: That's the \$64 000 question. I start all my patients on bevacizumab, and if it doesn't work, which is not common, I use ranibizumab. I've been involved in the SAILOR trial and I've run a concurrent bevacizumab trial prospectively, which was not randomized. After 9 months of doing both, I don't notice a really big difference between the 2 drugs, and I'm not convinced that they are that different in short-term efficacy, action, or reinjection rate.

I tell patients that I've been doing a bevacizumab study and looking at the results, and that I feel the results are comparable to those seen with ranibizumab. If patients want ranibizumab, I'll give them ranibizumab, even though, at this moment, I don't believe it's any better than bevacizumab. I want to emphasize that this is my clinical impression and I certainly would not criticize anyone who advises ranibizumab in all cases. Ranibizumab has been proven very effective in extensive, well-performed clinical trials.^{1,2}

Although ranibizumab is much more expensive than bevacizumab, Genentech has done a marvelous job in making ranibizumab available to patients who can't afford it. If a patient earns less than \$75 000 a year, the company will either pick up the 20% that Medicare doesn't pay, or pick up the entire cost through a foundation. I think it's a very compassionate policy.

At this time, I use a pneumonia treatment analogy to explain why I use bevacizumab first. I tell patients that we have many drugs that can treat pneumonia. One costs 50 cents a dose and another costs \$20 a dose. Because both will effectively treat pneumonia, why not try the 50-cent drug first?

Dr Bressler: Dr Lim, how do you approach this?

Dr Lim: I have a slightly different approach. I have not been doing a prospective trial similar to Dr Tornambe. However, knowing that we have excellent phase III multicenter clinical trial data and excellent safety data on ranibizumab, I start my patients on ranibizumab as a first-line treatment. I am perhaps not brave enough to use a drug off label as first-line therapy when there is an approved drug that is reimbursable. Because ranibizumab is also available to patients who cannot afford it, I would still use it as first-line treatment, even in my less affluent patients.

Dr Bressler: We have 2 opposing opinions. Dr Pieramici, what do you do?

Dr Pieramici: I'm probably somewhere in the middle. I've been investigating bevacizumab for the past 2 years, and we've published a retrospective review of patients treated with bevacizumab for neovascular AMD.⁴ In my mind, there's an obvious biologic and visual effect with this agent. I know that bevacizumab is working in patients, but I question whether there may be perhaps a small difference in efficacy (compared to ranibizumab) that one cannot determine from clinical experience alone. Maybe, if we did a careful prospective clinical study, we'd find only 25% or 30% instead of 40% of patients gaining 3 or more lines of visual acuity with bevacizumab. We really cannot be certain that the safety or efficacy is similar between the drugs because in the retrospective reviews that have been reported, patients were lost to follow-up. In a prospective clinical trial, we're apt to have more complete follow-up.

If a controlled clinical trial is completed, and both bevacizumab and ranibizumab turn out to work just the same at the end of the trial, I won't be surprised. I also won't be surprised if it turns out that bevacizumab is a little bit less effective than ranibizumab. Would I be surprised if bevacizumab worked out a little bit better? Perhaps, perhaps not.

Dr Bressler: There is no right answer here, but we should also look at the question separately for the patient and for society. For the patient, I think there's enough evidence from case series that bevacizumab

clearly works better than letting AMD run its natural course. You only have to do 10 cases to have a few that improve with bevacizumab to recognize that, so we don't need a large, randomized clinical trial to say that bevacizumab is better than doing nothing when that anecdotal experience is combined with the clinical trial data on ranibizumab.

However, does that tell us that bevacizumab is almost as good as ranibizumab? Does it have 30% of patients improving by 3 or more lines, or is it only 20%? I don't think we can tell that from anecdotal reports and our own experience. To pick up those differences we'd need maybe 500 subjects, 250 in each arm, to know with confidence that it really is 20% versus 30% with one or the other, or 30% versus 40%. Because I don't know that, I tell the patient that I don't know if bevacizumab would be almost as good as ranibizumab or even better. I tell the patient for whom cost is not an issue that I am relying on the best evidence I have, and that's with something in which I know the exact numbers, not whether it's a little worse or a little better. It's also in which I know exactly what the safety is among several hundred people, not the safety among tens of thousands of people because there may be a slightly increased risk for some problem we don't know about yet. However, at least I know there isn't a big or moderately increased risk for several thousand people. I don't know that for bevacizumab yet, and I hope that there will be no increased risk.

However, for society, it's a different question. For society, it costs perhaps \$500 million a year, perhaps \$1 billion a year, added to our Medicare budget, which is only \$550 billion. If you add \$1 billion to that, you're adding a significant percentage of cost. Fortunately, we have the government to encourage a trial that will compare the 2 drugs in the hope that it would save money in the long run. If another drug or a more cost-effective treatment doesn't come along, then at least we've run that trial and we'll have an answer.

RISK OF ENDOPHTHALMITIS

Question from the audience: We know that the risk of endophthalmitis in cataract surgery is now approximately 1 or 2 per 1000 cases. How does that compare to the risk of endophthalmitis with intravitreal injections for AMD? Is it comparable, or is it higher or lower?

Dr Pieramici: Endophthalmitis is very infrequent,

at least if you review the clinical trial data for pegaptanib, in which patients received an injection every 6 weeks and the risk was less than 1% per injection.⁵ Carefully preparing the eye with povidone iodine and using a lid speculum before injection reduces the risk. I usually tell patients in our clinical practice that the risk is less than 0.1% per injection with either ranibizumab or bevacizumab.

Dr Bressler: I tell patients that endophthalmitis is rare, but not zero. I also tell them that when it happens, they'll recognize it, and that it's treatable most of the time. In most cases, it is not a fulminant endophthalmitis, and it can be managed with intravitreal antibiotics, particularly if the causative organisms have been identified and they are not very virulent bacteria.

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