**Dr Bressler**: The overview articles in this monograph summarize safety, efficacy, and other outcomes data from clinical trials of approved and investigational treatments for neovascular age-related macular degeneration (AMD).

The cases that follow are representative of what we see in clinical practice. With the approval of ranibizumab (Lucentis; Genentech, Inc.; South San Francisco, Calif) expected within the next year, it seems especially timely to discuss these cases in the context of current and future approaches to treatment. In other words, how would you treat each of these patients today, using only those treatments that are approved, and how would you treat them a year from now, on the assumption that ranibizumab will be available?

**CASE 1: Classic Neovascularization**

- 76-year-old patient with visual acuity of 20/40 in right eye; visual acuity had been 20/20 until 3 months ago
- Patient had laser photocoagulation through the center of the retina in the left eye (visual acuity of 20/400) 5 years earlier
- Fluorescein angiogram of right eye (Figure 1) shows juxtafoveal classic neovascularization

**CURRENT OPTIONS**

**Dr Bressler**: How would you treat this patient?

**Dr Mieler**: This appears to be juxtafoveal, a classic recurrence from a previous treatment scar. With the verteporfin (Visudyne; Novartis Pharma AG; Basel, Switzerland) data driven by the predominantly classic lesions, I would approach this, in most instances, with photodynamic therapy (PDT). If you want to go off-label, you could add corticosteroids, but my typical initial approach would be just PDT with verteporfin.

**Dr Bressler**: Now that you've treated the patient with PDT and gone through the risks and benefits, when do you schedule the next visit?

**Dr Olsen**: Typically, in 3 months, repeating the fluorescein angiogram at that time.

**Dr Bressler**: We saw the patient for a follow-up examination after 3 months, and the patient lost 2 lines, with visual acuity down to 20/64. We repeated the angiogram (Figure 2), and the lesion grew, and the foveal center is now under the area of neovascularization. There is additional fluorescence surrounding the classic neovascularization. How would you treat this lesion at this stage?

**Figure 1. Fluorescein Angiogram of Classic Neovascularization at Baseline**

Arrow on angiogram indicates the center of the macula. Courtesy of Neil M. Bressler, MD.
**Dr MacCumber.** This appears to be a relatively aggressive lesion. I would, again, consider PDT. However, I also would discuss the off-label use of intravitreal triamcinolone acetonide (Kenalog; Bristol-Myers Squibb; New York, NY) with the patient.

**Dr Bressler.** The patient says, “I can’t make that decision. I’ll do whatever you recommend.” What would you recommend?

**Dr MacCumber.** Because 1 PDT treatment wasn’t very successful, I would probably combine PDT with an intravitreal triamcinolone acetonide injection this time around. An alternative approach would be pegaptanib (Macugen; Eyetech Pharmaceuticals, Inc. and Pfizer Inc; New York, NY), but my first choice would be the former.

**Dr Klein.** I agree with that. I would probably use PDT with corticosteroids, but I think a large proportion of retinal specialists would opt for pegaptanib at this point.

**Dr Olsen.** I would retreat with PDT alone because one cannot determine the treatment effect after a single treatment and whether the lesion will ultimately respond. The vision is still fairly reasonable at 3 months after the initial treatment, and some decline in vision is expected. I would wait until after another session of PDT alone before considering the use—and the risks—of triamcinolone acetonide.

**Dr Mieler.** I agree that it’s not really fair to say that PDT didn’t work, as only 1 treatment has been employed. Yet, this is a monocular patient, as the other eye has a central ablated scar. I would tend to err on the side of being a bit more aggressive in getting this under control before this patient loses more vision, as in the fellow eye. I also would probably opt for PDT with verteporfin and corticosteroids.

**Dr Klein.** I agree for the very same reason. When I think about the natural history of neovascular AMD, a large proportion of vision is lost in the first 6 months. I get nervous about the prospect of doing the same thing again, especially with someone who is essentially relying on 1 eye only. I would want to go to a different treatment. In this case, I would opt for PDT with corticosteroids.

**Dr Bressler.** PDT with corticosteroids may be better, but it may not be, and it may be worse. I’m not heavily influenced by the fact that the fluid can go away with corticosteroids. I need to know that the vision will be better with PDT and corticosteroids than it would have been with PDT alone at 1 and 2 years. Most case series that have examined corticosteroid use have had a very short follow-up, in which we wouldn’t expect people to lose much vision and may even expect a slight improvement by temporarily getting rid of some fluid.

These retrospective case series of corticosteroids for neovascularization retrospectively showed that patients appeared to do better and led to a prospective trial of intraocular corticosteroids alone. That trial found that there was no benefit, although there was some argument that the corticosteroids should have been continued at follow-up.

Intravitreal corticosteroid use is associated with a small risk of endophthalmitis, and a larger risk of glaucoma and cataracts. This patient was pseudophakic, thus the cataract problem is not of concern. However, glaucoma is a concern if you have to continue using corticosteroids. For me, there is not enough evidence yet from case series that show beneficial short-term outcome, and the risk is still too great. I would continue with a second session of PDT alone in this case.

**Dr Olsen.** I agree with Dr Bressler’s comment about short-term follow-up. Also, this is a monocular patient, and PDT was tolerated very well the first time. Adding something with the potential for endophthalmitis in the only eye is adding risk when it may not be necessary and is not currently validated by existing data.

**Dr Bressler.** I wish we knew the outcome had we used corticosteroids or switched to pegaptanib. We treated the lesion with PDT again. It became more

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**Figure 2. Angiogram of Classic Neovascularization at 3 Months**

Angiogram reveals lesion growth and additional fluorescence 3 months after photodynamic therapy with verteporfin. Courtesy of Neil M. Bressler, MD.
fibrotic at this stage, but 3 months later the visual acuity remained at 20/64. At 6 months, there was some very slight growth (Figure 3). That’s the only change. Do you treat yet again at 6 months, or do you leave it be?

**Dr Mieler:** Although it certainly has not grown as aggressively as after the first treatment, there is still some growth, and there appears to be a small amount of subretinal fluid. I would retreat with PDT again. If you’ve made the decision to stay with PDT before, you should probably stay with it again.

**Dr Bressler:** We used PDT again, and it bled 3 months later. There was a very small amount of growth where the new lesion had been before, and we decided to treat it again at 9 months (Figure 4). At 12 months, there was no bleeding, although the lesion still had a light leak. We treated this a fifth time, and it remained stable from then on.

**FUTURE OPTIONS**

**Dr Bressler:** Let’s go ahead a year and assume that ranibizumab is available. How would you treat a patient who presented as this patient did a year from now?

**Dr MacCumber:** We have data from 2 studies: the Minimally Classic/Occult Trial of the Anti-Vascular Endothelial Growth Factor (VEGF) Antibody in the Treatment of Neovascular AMD (MARINA), which looked at minimally classic and occult with no classic lesions; and the phase II RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety (FOCUS) trial, which showed benefit for ranibizumab with PDT versus PDT alone for predominantly classic lesions. At this time, if the US Food and Drug Administration (FDA) approves on the basis of those data alone, I would treat with ranibizumab plus PDT.

**Dr Klein:** About a year from now, we will probably have the results of the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) study, which would cover lesions like this. If we assume that the results are going to be comparable to what we’ve seen so far in MARINA, and that the longer-term results of MARINA hold up, I would probably think about using ranibizumab alone. Unless I saw evidence that PDT would improve the outcome when used with ranibizumab, I would not want to chance the very small likelihood of vision loss with PDT.

**Dr Bressler:** But if the ANCHOR study shows that ranibizumab has the same sort of outcomes that we saw in MARINA compared to placebo, then we know that that would be an option. The FOCUS trial showed that PDT plus ranibizumab worked well. What we don’t have yet is a study comparing ranibizumab plus PDT with ranibizumab alone.
Dr Bressler: How would you manage this lesion today?

Dr MacCumber: Pegaptanib was approved by the FDA for choroidal neovascularization (CNV) regardless of its location, so it is not only a reasonable option for this lesion, but also an FDA-approved option. PDT also is certainly an option for that lesion.

Dr Bressler: Which of these 2 options would you choose first?

Dr MacCumber: With lesions like this, I usually discuss the options with the patient. I find that some patients are highly resistant to intravitreal injection.

Dr Olsen: I disagree with the angiographic classification of the lesion. All of the published studies on classifying lesion type indicate that agreement among lesion types is “good” but not “great.” A study by Friedman and Margo looked at agreement in fluorescein angiographic lesion types by retina specialists.4 They found that retina experts agree approximately 70% of the time and disagree approximately 30% of the time.

I would categorize this as a juxtafoveal classic choroidal neovascular membrane, and I believe that the penumbra of hyperfluorescence surrounding this lesion is caused by subretinal fluid staining of the soft drusen. There are several drusen that are greater than 125 µm in size, and I think they are staining from the subretinal fluid. If fixation were far enough away from the edge of that lesion, I would do standard thermal laser treatment. If it extended too close to fixation, I would then discuss whether to use PDT or pegaptanib with the patient.

Dr Bressler: PDT was done, but I think pegaptanib also is a good option for minimally classic lesions. Three months later, there is a little less early fluorescence in that lesion, but it’s still there. However, there also is a little more mid- and late-phase fluorescence around that area. There was no uniform interpretation, but it was still considered as CNV.

At follow-up, we often don’t differentiate when the lesion has been treated or whether it is classic or occult because scar tissue and pigment abnormalities begin to occur. Nevertheless, the lesion was treated again. At 6 months (Figure 6), the early and late phases looked very similar, although maybe slightly larger than at 3

CASE 2: Subfoveal Choroidal Neovascular Lesion

- 74-year-old patient with a choroidal neovascular lesion in the right eye; visual acuity is 20/50
- Relatively small, minimally classic lesion
- Lesion also has an area of fluorescence that has increased over time and was interpreted as occult neovascularization; late leakage from an undetermined source also is present in this area (Figure 5)
- Left eye has large drusen; visual acuity is 20/20

Figure 5. Angiogram of Subfoveal Choroidal Neovascularization at Baseline

Right side of angiogram at baseline shows classic neovascularization (brighter area of fluorescence, solid arrow) and a questionable area of occult choroidal neovascularization (ring of less fluorescent area surrounding brighter area, dotted arrows). Courtesy of Neil M. Bressler, MD.

Figure 6. Angiogram of Subfoveal Choroidal Neovascularization at 6 Months

Right side of angiogram at 6 months, after 2 sessions of photodynamic therapy (PDT), is similar to the findings seen 3 months after initial PDT, except for some very slight growth. Courtesy of Neil M. Bressler, MD.
months. PDT was done again, and the visual acuity dropped to approximately 20/100, a loss of 3 lines.

At 9 months (Figure 7), after 3 treatments with PDT, visual acuity dropped to 20/125, a loss of 4 lines. What would you do at this point?

**Dr Mieler:** All of these trials have looked at patients at 1-year and 2-year follow-up, without switching treatment modalities. Abandoning a therapy probably isn’t the right thing to do. However, I think we’re all looking for a quicker fix, and in this setting, I personally might become a bit disgruntled with just PDT alone. I probably would add intravitreal corticosteroids at this time or make the switch to pegaptanib. I’m not sure if that’s the right thing to do, but because definite progression has occurred over the course of 9 months, I would probably go with PDT and corticosteroids.

**FUTURE OPTIONS**

**Dr Bressler:** What if ranibizumab became available just as this patient was coming in for the 9-month visit? Would you consider switching or would you just do PDT with corticosteroids?

**Dr Mieler:** If the data remain as strong as initially reported, a switch would certainly be a consideration. However, this switch would still be based on no data per se because we’re talking about treatment options that are being switched in midstream. Those weren’t studied as part of any of the original trials.

**CASE 3: Recurrent Choroidal Neovascularization**

- 75-year-old patient with prior laser photocoagulation just outside the foveal center
- An area of recurrent CNV was treated once with PDT, but the lesion grew; visual acuity was 20/80 at initial treatment, but 3 months later it dropped to 20/125; change in fluorescence from PDT and some leakage of blood at the temporal border are present (Figure 8)
- Fellow eye has a fibrotic scar
- Patient is treated with pegaptanib; 6 weeks later, visual acuity drops to 20/160

**CURRENT OPTIONS**

**Dr Bressler:** Assuming that you all take a careful look 6 weeks after a pegaptanib injection, what would you do before the next injection? Would you take additional fundus photographs or do fluorescein angiography or optical coherence tomography (OCT)?

**Dr Mieler:** I would certainly obtain at least a fundus photograph and, in most situations, also obtain an OCT. In this particular case, I also would probably get a fluorescein angiogram because of the small area of new hemorrhage off the temporal border of the original lesion.

**Dr Bressler:** Is there anything you would see on the angiogram that would change your management?

**Dr Mieler:** Probably nothing. If you made the commitment to treat with pegaptanib, you are probably going to continue with it. The angiogram is not so much for decision making as it is to document the changes.

**Dr Bressler:** We took a picture with fluorescein (Figure 9), and found nothing too surprising. There was neovascularization in an area where it wasn’t seen before, and speckled fluorescence presumably from additional occult CNV that was not there previously. The lesion grew and another line of vision was lost. How would you treat it at this point? Would you give another pegaptanib injection or go back to PDT with corticosteroids?

**Dr Olsen:** I would stay with pegaptanib mainly because of the size and extent of the lesion. It’s a very large occult lesion that tends to do the worst with PDT.
**Dr Bressler:** We decided to use pegaptanib a second time and asked the patient to come back in 6 weeks. By then, there were no signs of bleeding. Would you image at this time?

**Dr MacCumber:** Yes. I would probably get an OCT. I would want to know the extent of macular edema and subretinal fluid as a guide for future pegaptanib injections.

**Dr Bressler:** Would you withhold a pegaptanib treatment if you saw no fluid?

**Dr MacCumber:** I would not at this point because I think 2 injections is too soon to consider that option. However, OCT can help when you see a patient in the following 6 weeks and 12 weeks; it gives you an idea of a baseline.

**Dr Bressler:** I agree with this. Whenever we have a new treatment and we don’t completely understand it, we like to look at the eye and get as much information as we think may help us in our treatment decision process. OCT shows whether fluid is present, and fluorescein angiography shows the extent of the lesion. Imaging information helps us decide whether to stop injections or continue them. It’s an important decision because each injection carries a risk—albeit a very small one—of infection or retinal detachment.

We decided to get yet another fluorescein angiogram because the lesion grew a little bit further after the second injection (Figure 10).

**Dr Klein:** This is an example of where OCT can help in the decision-making process. I agree that you don’t want to stop pegaptanib after a few injections unless the situation was deteriorating. If you start to see growth on the angiogram and loss of vision, a series of OCTs showing no reduction in thickness would help you decide against continuing the injections and possibly steer you toward trying something else. Because the overall effectiveness of pegaptanib is comparable to that of PDT, treatment results may be similar for many lesions. At that point, you may want to consider adding corticosteroids to PDT.

**Future Options**

**Dr Bressler:** Because 95% of patients treated with ranibizumab avoided loss of 3 or more lines, do you think you’ll be getting more OCTs, or the same, or less when ranibizumab becomes available? Will OCT help you find the 5% of patients you shouldn’t be treating, or will it suggest that you should withhold treatment in some patients?
Dr Klein: It’s hard to say right now. I do think OCT will become more useful relative to fluorescein angiography in eyes treated with intraocular injections of antiangiogenic agents. Knowing the size, borders, and type of neovascular lesion is not as important with injections as it is when treating and following eyes with laser-based therapies, such as PDT.

Dr Bressler: Trials evaluating pegaptanib and ranibizumab in neovascular AMD specifically excluded patients with pathologic myopia. However, there is a small trial evaluating PDT in pathologic myopia, and it is worth discussing the management of these lesions in comparison with the management of CNV in AMD.\(^5\)\(^6\)

How would you treat this lesion today, and how would you treat it once ranibizumab becomes available?

Dr Olsen: This is a tough lesion type to treat. Today, I would recommend PDT for this lesion based on the data that we have.\(^7\) Recent longer-term studies suggest that fewer than 10% of patients with neovascularization in pathologic myopia improve long term with PDT.\(^7\) In my experience, I’ve been very disappointed in the outcome. If there were data on pegaptanib or ranibizumab, I would lean toward whichever agent had the best data at the time. Because these individuals are typically in the Medicare age range, insurance coverage for each of these treatment options also would be an important issue. Pharmacotherapies would definitely spark my interest simply because of the mechanism of action and the limited potential gain I’ve seen with PDT.

Dr Bressler: Let’s say ranibizumab is available, but we only have studies on AMD. We are all in agreement that we would probably switch to ranibizumab when it becomes available for many AMD lesions because the outcomes were strikingly better than those seen with verteporfin or pegaptanib for CNV in AMD. That is, 95% of patients avoided loss of 3 or more lines and 25% to 33% gained 3 or more lines. What does that mean when we don’t have a trial for pathologic myopia? Would you inject patients with longer eyes and abnormal vitreoretinal interface abnormalities?

Dr Mieler: Extrapolating results into different settings certainly carries some risk. If you compare the PDT trials, you’ll see that patients with pathologic myopia fared better and required fewer treatments (than patients with CNV secondary to AMD) to achieve stabilization and had better visual outcomes. Can we extrapolate that same information from pegaptanib and/or ranibizumab? I don’t know, but I think most of us would be willing to do that.

I agree with Dr Olsen about treating this with PDT initially. Will I treat it with pegaptanib or ranibizumab at some point in the future? I don’t have the answer, but I would certainly be willing to explore that.

Dr Bressler: I usually like to extrapolate to other conditions unless there’s a good reason not to. The only thing that concerns me about injections in pathologic myopia is not the effect on neovascularization, but the theoretical difference in risk. I don’t know

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**CASE 4: Pathologic Myopia**

- 74-year-old patient with pathologic myopia and a recurrent neovascular lesion
- Patient had prior laser photocoagulation near the center of the fovea
- Neovascular lesion recurred, extending up to the center of the fovea (Figure 11)

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**Figure 11. Pathologic Myopia**

Fundus photograph taken at the initial examination of a patient with pathologic myopia reveals recurrence of a neovascular lesion extending up to the center of the fovea. Courtesy of Neil M. Bressler, MD.
what it’s like to inject a pathologic myopic eye 12 times or maybe even 24 times, but I suspect that the rate of retinal tear or detachment may be higher compared to the rate seen in the AMD population.

**Dr MacCumber.** I agree. Although many of these eyes would already have a posterior vitreous detachment (PVD), I think that any inflammation associated with ranibizumab would act to promote a PVD, and thus, also potentially contribute to retinal tear formation.

**Dr Bressler.** Most of that inflammation was seen in the FOCUS trial, which used lyophilized ranibizumab. A different formulation was used in MARINA, and it was associated with very little inflammation.

**Dr Olsen.** The basic neovascular process in high myopia and the reaction of the pigment epithelium makes this the type of lesion that really needs to be studied with pharmacotherapy. The reason I say that is because standard laser photocoagulation, submacular surgery, and PDT produce a very reactive, hyperplastic pigment reaction or progressive atrophy around the lesion. An antiangiogenic agent may be the gentlest way we know of to treat neovascularization in pathologic myopia. I suspect that in the long run, you are going to get a similarly poor response no matter what you treat with.

**Dr Klein.** If ranibizumab continues to do well in clinical trials for AMD, there will be a very strong impetus to use it for neovascular lesions in other settings without worrying too much about what’s going on with randomized trials. I agree that there is a problem in this case with myopia. Hopefully, within a year or so, we’ll find that we can inject less frequently, which may be particularly helpful in cases of high myopia.

**REFERENCES**


