Dr D’Amico: The overview articles in this monograph highlight findings from clinical trials for proven and investigational therapies for neovascular age-related macular degeneration (AMD). Treatments with proven effectiveness include laser photocoagulation, photodynamic therapy (PDT) with verteporfin, and intravitreal pegaptanib. In this discussion of therapeutic options, it seems appropriate to also include PDT in combination with intravitreal triamcinolone because its use appears to be very widespread in the medical community. Another area for discussion is PDT plus intravitreal pegaptanib, which has not yet been assessed in a controlled trial setting. We begin by discussing therapies that have not yet proven to be effective or ineffective but are currently being studied.

Transpupillary Thermotherapy

Dr D’Amico: Does anyone on the panel feel that transpupillary thermotherapy has any role in the modern treatment of neovascular AMD?

Dr Rosenfeld: Based on the intent-to-treat analysis we heard earlier today, I don’t think transpupillary thermotherapy has any role in the treatment of “wet” macular degeneration.

Dr Schachat: 1 would agree, and it is important that we keep in mind the level of evidence for our stated views. A prospective, blinded, controlled trial comparing treatment to sham injection showed that transpupillary thermotherapy didn’t work.

Feeder Vessel Treatment

Dr D’Amico: Let us continue with another candidate therapy, feeder vessel treatment, perhaps most advanced in the hands of Dr Giovanni Staurenghi (Figure 1).2 Is this a therapy that one would consider at present?

Dr Schachat: The evidence supporting this treatment is a prospective case series as opposed to a placebo-controlled randomized trial, which represents a suboptimal level of evidence. Although some positive results are reported, a healthy fraction of patients experience recurrence. I would not consider using it in my medical practice in the absence of a controlled study.

Dr Rosenfeld: One of the limitations of feeder vessel treatment is that there doesn’t seem to be any uniformity or consistency in how it’s applied.

Dr Ho: Also, many clinical settings do not allow for the near simultaneous diagnosis, imaging, and treatment that are required.

Dr Regillo: Even if physicians were interested in exploring this treatment, the diagnostic equipment is not...
widely available. Although it may eventually be shown to be of clinical value, at this point it is not yet proven.

**Radiation Therapy**

**Dr D’Amico:** There have been several trials and anecdotal accounts of radiation treatment of AMD lesions. What is the current role of radiation in AMD therapy?

**Dr Gragoudas:** Our data indicate that radiation is a modality that can provide a benefit in patients with AMD. Unfortunately, our studies did not have a control group, thus the level of evidence is not high. Two randomized, controlled trials conducted in Europe did not demonstrate an effect, possibly because the dosing was insufficient. Two other smaller randomized trials showed some benefit. Now that other treatments are proven and available, it will be very difficult to conduct a trial with irradiation. Radiation is a one-time treatment and may be considered in some patients who cannot tolerate other treatments.

**Dr Ho:** The problem with the trials to date is that they used varied dosing, ranging from 16 to 28 Gy, and reported conflicting results. Although the radiation does render some biological activity, in this day and age, the evidence is not compelling.

**Dr D’Amico:** We’ll categorize radiation as potentially with merit, but certainly not ready for clinical prime time.

**Surgical Therapy**

**Dr D’Amico:** Surgical approaches include the removal of the subretinal neovascular membrane and macular translocation by 360° or limited retinotomy (Figures 2 and 3). I have previously presented a meta-analysis of reports on this procedure published before 2002, which concluded that limited retinal translocation does not result in substantial visual benefit in very many patients. Subretinal surgery for AMD is similarly disappointing. Although quality of life improves in select patients, on the whole, the subretinal surgery trials in adults have not shown efficacy for visual restoration. How does the panel feel about applying translocation or subretinal choroidal neovascularization (CNV) excision in clinical practice?

**Dr Rosenfeld:** Before the availability of pegaptanib, in our practice, most patients did not qualify for any approved therapy. Therefore, 360° retinotomy was an option for patients whose second eyes were affected and were deteriorating rapidly. Now that pegaptanib is available, I find it difficult to recommend translocation with 360° retinotomy because of the likelihood of vision loss and the surgical risks.

**Dr Ho:** In a limited number of centers worldwide, physicians have developed surgical expertise and experience and have reported that they are able to minimize the severe side effects of surgery, such as proliferative vitreoretinopathy and retinal detachment. However, I would agree that in light of current pharmacologic therapies, translocation surgery and submacular CNV excision do not play a major role as treatment options. In my practice, we don’t remove membranes, but we do consider surgery to displace large submacular hemorrhages.
**Dr. D’Amico:** Based on our observations and the articles in this monograph, we would mostly agree that treatment options for neovascular AMD include:

- Observation
- Thermal laser photocoagulation
- PDT with verteporfin
- PDT plus intravitreal triamcinolone
- Pegaptanib intravitreal injection

**Investigational:**
- Pegaptanib plus PDT with verteporfin
- Pegaptanib plus intravitreal triamcinolone

Given the treatment options, we should consider how we may apply them to individual patients using the following case examples:

### CASE 1

**79-year-old patient with 20/60 vision for 3 days**

Fluorescein reveals CNV with 90% classic neovascularization

**Treatment strategy?**

**Dr. Regillo:** I will not use photocoagulation for subfoveal CNV at this time now that we have better options. I think the best options today are pegaptanib as monotherapy, pegaptanib plus PDT with verteporfin, or triamcinolone plus PDT with verteporfin. Although pegaptanib plus PDT with verteporfin has not been studied extensively, a very small phase II clinical study has suggested that a combination of these 2 therapies may yield better results than the use of either drug alone.11 Acknowledging the limited available data, I would consider treating with this combination or the combination of triamcinolone plus PDT with verteporfin. However, as a monotherapy, pegaptanib would be my choice.

**Dr. Schachat:** In fact, there are data on the efficacy of pegaptanib plus PDT with verteporfin. In the phase III trial of pegaptanib, the treating physicians were given the option to use this combination (in addition to the trial treatment) in 161 patients with predominantly classic lesions.12 Therefore, I think attempting this combination would be a very reasonable option. I would explain to the patient that there are some proven, safe, and effective options that would likely yield similar results, then I would ask whether the patient prefers a laser treatment every 3 months or an injection treatment every 6 weeks.

**Dr. Rosenfeld:** My biggest concern with PDT is the small but real risk of severe vision decrease immediately after treatment. In the predominantly classic subtype, the risk is approximately 0.7%, but the risk is 4% in minimally classic and occult subtypes for a 20-letter or more vision decrease.13 I’m not going to take that risk when, in my experience, an intravitreal injection is a safer procedure. In the absence of a head-to-head controlled study of the efficacy of PDT with verteporfin versus pegaptanib, I would choose the safer procedure, which is pegaptanib injection.

**Dr. Gragoudas:** I don’t see any advantage to using PDT in such a case based on the current evidence, thus I would treat with pegaptanib.

### CASE 2

**71-year-old patient with 20/50 vision and a 3 week history of vision loss**

Fluorescein reveals juxtafoveal CNV with classic neovascularization

**Treatment strategy?**

**Dr. Ho:** I would tell this patient that there are 2 potentially effective treatments, pegaptanib or PDT plus intravitreal triamcinolone, acknowledging that the level of evidence for safety and efficacy of PDT plus intravitreal triamcinolone is incomplete at this time. I would review the efficacy data with the patient, explaining that the 2 treatments have not been directly compared. I would then discuss safety issues, including acute severe vision loss in predominantly classic...
patients treated with PDT. However, the reality for many patients is that other issues also come into play. For example, the patient may not want to trouble her daughter with driving her to the doctor’s office for an injection every 6 weeks, and thus would then opt for less frequent laser treatments.

**Dr Gragoudas:** In my opinion, if you are going to use combination therapy it would be preferable to treat with pegaptanib plus PDT. I don’t see any reason to treat with intravitreal triamcinolone plus PDT, given the well-known complications of steroids (increased intraocular pressure and cataract formation). In addition, before initiating discussions of the potential treatment options and combinations with the patient, the retinal specialist should have a good idea of what treatment he prefers. Weighing the options can be complicated and, in the end, the patient will likely ask what you would do.

**Dr Rosenfeld:** It’s important to state that when I pick a treatment strategy, it doesn’t mean I will necessarily stick with that strategy. I would recommend pegaptanib to this patient, but tell him that he is going to experience continued vision loss—that we are just going to slow the progression of the disease. However, in the back of my mind, I am thinking that I want to hit a homerun with this patient. I want to see vision and anatomic improvement. Therefore, I will be following my patient closely and will not hesitate to switch to another treatment if at 12 weeks the lesion is larger with more leakage.

**Dr D’Amico:** I think we are all saying that counseling and pretreatment discussions are tremendously important now that we actually have a choice of treatment options. Dr Regillo, how does this juxtafoveal patient get treated in your office?

**Dr Regillo:** Ideally, I would consider PDT and, with very close follow-up, add in triamcinolone or pegaptanib for any significant growth of the CNV complex into the foveal center. However, I would do something slightly different with PDT, although there is no evidence to support it. To avoid the possibility of acute vision loss, when I treat a juxtafoveal lesion with PDT, I avoid the 500-µ border on the foveal side, thus the foveal center is not exposed to the direct effects of PDT.

**Dr D’Amico:** Let us assume you have a fluorescein showing a juxtafoveal lesion. The patient wants you to make the decision. Do you use PDT and instruct the patient to return in 1 week for a pegaptanib injection? What is combination therapy? How do we use it?

**Dr Regillo:** I’d be more inclined, whether I’m using PDT with pegaptanib or with triamcinolone, to give the pharmacologic agent 1 or 2 weeks before PDT.

**Dr Schachat:** I’m assuming this is a “close” juxtafoveal lesion because if it is somewhat distant, I would use thermal laser. If so, this is a case that raises some concerns about treating the center of the fovea with thermal laser. We did a retrospective analysis of our juxtafoveal PDT cases to see how many progressed during the PDT treatment because we know that 90% are still leaking at 3 months and 80% at 6 months, and so on.14 Approximately 50% progressed into the center of the fovea while we were using PDT.15 PDT has the real risk of not achieving as good an outcome as thermal laser.

Pegaptanib may well be our first treatment choice because it appears to have an early effect at 6 weeks.12 There is even some evidence that earlier treatment may lead to a better result. Therefore, if you are going for a homerun, I would consider pegaptanib. If you are looking for an average result, I personally view PDT as less risky. There is the risk of severe vision decrease with PDT, but the treatment does not involve injections into the eye.

**Dr Rosenfeld:** In regards to PDT plus triamcinolone, we’ve seen a great deal of success in our own clinical practice that supports the findings by Spaide et al of improved visual outcomes and a decreased need for retreatment.16 However, PDT plus intravitreal triamcinolone combination therapy may not be equivalent to PDT plus intravitreal pegaptanib, and it may even be worse. Triamcinolone may be better at treating the inflammatory sequelae of PDT. Therefore, we cannot assume that combination therapy using PDT plus pegaptanib will be the same as PDT plus triamcinolone. What we can be sure of is that combining PDT plus pegaptanib will be far more expensive.

**Dr Gragoudas:** Your point about the anti-inflammatory benefits of triamcinolone is arguable. Typically, we do not see severe inflammation associated with AMD after PDT treatment. Furthermore, I don’t think the antipermeability effect of triamcinolone is comparable to that of pegaptanib.

**Dr Regillo:** Another viewpoint is that pegaptanib does have anti-inflammatory effects based on its anti-vascular endothelial growth factor properties.

**Dr Rosenfeld:** In my opinion, rather than go to 2 expensive therapies and frequent follow-up visits for the patient, the next step would be to use PDT plus triamcinolone, as we have more clinical experience with this regimen at this point in time.
**Consensus response (one exception):** Treat with thermal laser.

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**CASE 3**

67-year-old patient with a blur at, and just to the side of, fixation

Fluorescein reveals completely extrafoveal CNV with serous fluid extending into the macula

Treatment strategy?

**Dr Ho:** I would treat this patient with pegaptanib.

**Dr Rosenfeld:** I would get an optical coherence tomography (OCT) to see the extent of cystic maculopathy and subretinal fluid. If OCT findings support leakage and the fluorescein is equivocal, I would recommend pegaptanib. However, if the OCT findings are also equivocal, I would likely observe the patient. Although lipids are present and are strongly suggestive of occult neovascularization, occult lesions have periods of activity and inactivity. The lesion may have leaked slightly and this could be a resolution phase. However, if the OCT shows fluid and there is a chance to improve vision if the fluid resorbs, I would treat this patient.

**Dr Regillo:** My inclination would be to treat this patient with pegaptanib, although Dr Rosenfeld does raise a very good point. If some of this vision loss appears to be related to retinal pigment epithelium mottling as opposed to true exudation, the clinical course is somewhat questionable. OCT testing would be useful and, if there is subretinal or intraretinal fluid, I would treat with pegaptanib.

**Dr Gragoudas:** If it is confirmed as an occult neovascularization with 20/100 vision and lipid, I would administer pegaptanib.

**Dr Schachat:** In the absence of evidence of disease progression, I would observe it. Some lesions do remain stable. With disease progression, I would favor pegaptanib for a large occult lesion and I would consider PDT for small occult lesions with disease progression.

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**Unanimous response:** All advised treatment with pegaptanib, unless the lesions were small, in which case 1 consultant (Andrew P. Schachat, MD) recommended PDT.

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**CASE 4**

75-year-old patient with 20/80 vision for several months

Fluorescein reveals mottled retinal pigment epithelium with leakage and some subretinal hemorrhage, with minimally classic CNV

Treatment strategy?

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**CASE 5**

82-year-old patient with 20/100 vision of unknown duration

Fluorescein reveals mottled hyperfluorescence and a trace of lipid strongly suggestive of occult neovascularization

Treatment strategy?
CASE 6

82-year-old patient (identical twin of previous patient) with 20/50 vision of unknown duration

Fluorescein reveals mottled hyperfluorescence with diffuse late leakage suggestive of occult neovascularization, but there are no signs of recent disease progression (eg, subretinal hemorrhage and change in vision)

Treatment strategy?

Drs Rosenfeld, Schachat, Gragoudas, and Regillo: Observe the patient with close follow-up.

Dr D’Amico: Would you fault somebody who said this patient should be treated with pegaptanib?

Dr Gragoudas: No, I think that after a period of observation we will treat this patient with pegaptanib at any rate.

Dr Ho: We’ve all seen patients with 20/50 vision with borderline angiograms who do not have CNV. This may not be an exudative eye. I would observe closely, use Amsler grid monitoring, and recheck in 6 to 8 weeks.

REFERENCES
