Anti-VEGF Therapy and PDT: How, When and Why

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During the 2009 Retina Congress in New York City, a group of experts was brought together to discuss current therapies in use in the treatment of age-related macular degeneration. Anti-VEGF therapies have revolutionized our retinal practices and significantly improved our patient outcomes. This discussion recognizes some of the challenges that remain and focuses on alternative therapies and incorporating modalities that may complement our current standard of care.

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GS: It’s been 3 or 4 years since we started using anti-VEGF therapy. Kevin, what’s been the general experience regarding therapy and outcomes? Has it mirrored what you’ve seen in MARINA and ANCHOR, in clinical practice?

KB: Overall I’ve had a positive experience. It’s given us a more optimistic outlook of diagnosis and treatment of wet AMD. After the Avastin craze initially we realized that Avastin wasn’t the definitive answer to treatment of choroidal neovascularization. Once Lucentis was approved all that changed. I think for those patients with very similar clinical results. The retina community presently is divided in terms of which product they use while awaiting the results of the CATT trial. I think the MARINA and ANCHOR studies are two well-organized trials that demonstrated some of the most impressive outcomes to date that we’ve seen in treating choroidal neovascular secondary to AMD. The two-year results show what can be accomplished when treating patients on a monthly regimen, with 90 percent stabilization of vision, and with 30 to 40 percent of patients experiencing some visual improvement. In the real world everyday practice, I think it’s been very difficult to duplicate the MARINA and ANCHOR trial results.

MN: The reality is, if we look at the exclusion criteria which were used, (exclusion of subretinal fibrosis, RPE atrophy, etc.), they don’t reflect the real world patients that we see. Results with pan-VEGF blockade are impressive and certainly better than the days of monotherapy with Maugans or PDT. Obviously the patients that we treat, because of differences from ANCHOR and MARINA patients, don’t mirror the study results and so I think that I feel somewhat disappointed some three years after the introduction of Lucentis.

GS: Why have we not seen some of the results of MARINA and ANCHOR in clinical practice?

SR: The drugs themselves are fantastic, and I think there are many reasons why the real world experiences don’t mirror what the study results show, and part of that is because we don’t treat in a manner similar to the study protocol. Most of the patients I’ve maintained on extended monthly treatment resemble the published results, so in general I don’t think we can fault the studies or the drug. When Lucentis just came out we were already evaluating less arduous treatment schedules such as PRN and PPD and other regimens. This was all before we incorporated the actual protocol regimen into our practices; if we were three years out now and all the doctors had been using it strictly in a monthly fashion, we may be commenting on the great visual outcomes. But due to many reasons, that is not the case. Part of it is because the patient population is different, but part of it is also because we use to check patients on the treatment regimen, and a lot of it is because we see no end in sight.

ER: I would agree with that and I think that there are two big issues that change real practice from what was done in the studies. The first is patient travel difficulties; these people are 80 years old and they need some help to get them into the office, and they are constantly being treated for something other than monthly treatment. And the second thing, as I think Kevin pointed out, the population of patients we deal with, maybe 60 percent fit into patients that would qualify for one of the trials.

MN: The biggest problem I have with ANCHOR and MARINA is the fact that there’s only one variable (number of injections over time) that is measured and therefore it is a suboptimal predictor of vision.

GS: For the next question, we can have three categories. The first is the patients who respond, the patients who respond but then need to be injected, and the patients who respond with no leakage. (three responses). That’s success according to old criteria, but I think we’re going to have to change. Improvements in diagnostic imaging such as SD-OCT and high speed ICG angiography will improve our ability to treat and monitor the AMD patient. It is dry and there’s no leakage, that’s success.

GS: I think that leads to our next question, which is what sort of lesions, in our clinical practice, seem to do the best with anti-VEGF therapy?

SR: It’s pretty clear that whichever AMD treatment one chooses, that’s the one that will work. So that’s why it’s important to have an understanding of the different types of lesions, in our clinical practice, seem to do the best with anti-VEGF therapy?

ER: It’s been 3 or 4 years since we started using anti-VEGF therapy. What is going on.

AA: I think the first thing we have to come up with is how we can define failure, because success is different for different patients. Albert, how do you define failure?

GS: Resolution of subretinal fluid is the optimum response. I have taken to getting FA twice a year just to see if there’s growth at the membrane, which can happen without fluid, and I also count as responders those who have chronic subretinal fluid that you can’t get rid of, yet they still have very good vision.

ER: If even they have persistent subretinal fluid, but the vision is good, you consider them responders?

GS: It’s successful according to old criteria, but I think we’re going to have to change. Improvements in diagnostic imaging such as SD-OCT and high speed ICG angiography will improve our ability to treat and monitor the AMD patient. It is dry and there’s no leakage, that’s success.
GS: What is the objective definition of failure and what’s the subjective definition of failure?
SR: The drug isn’t designated, pharmacologically, to save vision; the drug is designed to treat a certain biological target, and that is all. Any of the treatments that we discuss today are going to reduce your chances that you will lose vision and some of these treatments have a 30 to 40 percent chance of improving your vision. I do tell them that there is probably a 95 percent chance or more that I’ll get anatomical success, by those objective criteria of fluid and hemorrhage improvement. Since we know so little about this disease I use my criteria for success or responding if there is measurable anatomical improvement in fluid and hemorrhage. So, with no change in subretinal fluid, or retinal edema, that’s a failure. If there is a decreased amount of subretinal fluid or collapse of the CRE spaces, resolution of subretinal hemorrhage, then I would say that drug has achieved what it was intended to do. The pathobiology of the disease system has not necessarily responded to the single drug regimen, but that is not the drug’s failure. It’s analogous to macular hole surgery when you’ve properly passed the ILM, gassed the eye, and the macular hole is completely closed, but the vision stays 20/200. Have you surgically failed? I wouldn’t say you’ve surgically failed; you’ve achieved your goal of your intended treatment, to close the macular hole. The patient is not seeing improvement because of the biology of the retinal system and factors beyond your control. I try to tell my patients that we can achieve some level of anatomical and therapeutic success.

KB: If I do three consecutive injections and they have increasing subretinal fluid on OCT, increasing blood, decreasing vision, or if you do fluorescein angiography (which I usually don’t after just three injec-
tions) and you see an increase in the lesion size, I think that’s definite failure. You have to correlate it also to the frequency and the number of injections.

GS: The objective measurement of increasing fluid, persistent fluid, leakage, and/or growth of leakage on the angiogram, and the subjective would be, basically, continued loss of vision?
ER: I think that the primary thing is what Albert said, which is loss of vision. I don’t know if I’d define failing to gain vision as a failure, but I would define losing vision as a failure.

MH: I think the fact continued therapy is required, doesn’t mean it’s a failure. The patient is a success as far as I’m concerned, but the fact that there’s still activity on says to me, obviously we need more than anti-VEGF therapy.

MN: I’d like to make another definition: primary and secondary failure. Primary failure indicates incomplete or no response to anti-VEGF therapy, and secondary failure indicates the initial resolution of leakage, however recurrent exudation ensues.

SR: Secondary failure, in the way you’re describing, is infrequent in my practice. With monthly treatment, once we’ve achieved primary success, and we’ve maintained them on monthly treatment, there have been very few patients who show decreased vision secondary. Now, they may lose vision due to ongoing RPE atrophy which continues after the first year or year-and-a-half of therapy. Secondary failures may also be considered as patients who present with recurrent fluid on their extended seven week visits. Again, this may be a more failure of my treatment protocol. It may also reflect inadequate diagnostic tools to know whether and when a lesion has completely responded. If we could accurately determine even low-grade lesion activity, we could better define re-treatment criteria.

MN: That may be true, however, there are some patients who have new neovascular processes that are in different locations from the original vessels.
SR: But they were getting monthly treatments initially and were doing well. When they were extended, they fail to respond, but do only when the drug is given in a way that it’s not necessarily intended. That’s precisely what I’m trying to say. I agree that there are secondary failures but I’m trying to put more of the onus on us as physicians and on our diagnostic tools and treatment criteria, rather than the drug.

GS: It’s a failure of the way we’re treating the disease.

MN: There is no question that many of these cases represent anti-VEGF dependent processes and extending the therapy past a critical point creates recurrent leakage. However, there are patients who have new areas of neovascularization that were not present before. Therefore, I perform a fluorescein and ICG on every patient, initially to sub-classify exudative ARMD, and then every three months after therapy is initiated.
SR: That’s going to be critical, what criteria we will use to determine when we start changing our treatment program, whether it is extending treatment or moving to a PRN treatment protocol.

GS: Are there some clues that help us recognize these failing lesions?
SR: There is a pattern of punctuate RPE activity, even when the OCT is completely dry, that likely represents ongoing lesion activity. When you monitor these hot spots over months, they evolve, with some disappear-
ing and new ones appearing.

MN: Some of those patients have polypoidal vasculopathy.
SR: That very well could be, they either evolved into or revealed an underlying polypoidal pattern.

GS: Let’s say you already had given your patients monthly injec-
tions. If you’re going to stop, at that time do you get an angiogram to make sure, that if you see this that you tell them they can’t stop?
SR: I’ll do OCTs, if they’re getting monthly treatments, and if they’re not responding to being on 2 or 6 months, I’ll do an angiogram. I’ve had some patients, where the OCT is clear, but where the angiogram shows these RPE hot spots. I will usually treat these patients until those spots clear or stabilize. I would stress here that in my opinion, angiography should play an important role in determining retreatment and may be currently underutilized.

GS: I think we do an angiogram when we’re either going to stop therapy, change therapy, or when the therapy’s not doing well. I think that’s a take home message from the group, that you still need an angiogram since it’s a choroidal disease.

MN: Every new exudative ARMD patient gets an IFA/IgG to determine whether they are likely to be an anti-VEGF responder or non-responder. Polypoidal vasculopathy is quite common. It might be present in some form in up to 25 percent of my exudative ARMD patients and it is quite common in Caucasians. The other common ICG-diagnosed lesion is arteriovascularized or mature vasculature.
KB: But that’s initially. I think a lot of people, including myself, do it initially, but the question is how often do we do it on follow up.

GS: So Mark, let’s say you took a hundred patients who had failures, in whom you do an angiogram, do 90 percent or more of these patients do something on the ICG.
MN: I would say that the ICG diagnoses the cause of failure in the majority of the patients.

MN: In Kevin’s and my experience I think it’s 80 percent, and maybe the other 20 percent we don’t see anything special on ICG or don’t know how to read them.
MN: The Heidelberg machine allows for dual visualization. There are times ICG does not reveal new vessels, however, I can look for breaks in Bruch’s membrane or RPE on the corresponding OCT.
KB: It’s also good to just mention for ICG imaging these days we’re using high speed ICG with the Heidelberg. I think it’s made an unbeliev-
able difference compared to the old ICG technology, when you really had to have quite a remarkable imagination to see anything going on. The new high speed ICG technology has really made great strides and improved our ability to visualize both the choroidal and retinal vasculature. Utilizing the old technology, if you can make a diagnosis 30 percent of the time you really feel like you’re an expert.

MN: The difference is the transit phase. The video function of the ICG camera gives the information that is needed.
GS: I think that’s a critical point.
AA: I never left ICG, so we do this more or less on a routine basis in our wet AMD patients. We do at least one ICG in the very beginning when the lesion is not 100% classic. Thereafter ICG is performed as needed. We get a lot of information from it, I never calculated it, I wouldn’t say 100 percent, but up to 90 percent, additional information in identifying the cause for a failure.

GS: I think as high speed ICG evolves and as we obtain it during differ-
ent stages of the disease, our use and interpretation will change. Some of these patients with chronic membranes may do better with alternative therapies than the ICG.

MN: I would have to agree. As I look back and say, when does ICG make a difference, does it do it for only some cases, and point me in the right direction, or is it something that helps me 15 to 20 percent of the time? Now as we tailor therapies for the future, this may be more relevant. With multiple offices it’s a huge investment, and that’s why ICG is not necessarily available in every office. We have it in two offices.
SR: I think all the imaging modalities we’re discussing, basically are all telling us that the more imaging we do, we find a greater percentage of the lesions that are still active. It suggests that we may be under-treating this patient population.
MH: Or it means that AMD is not simply a disease of VEGF overexpression.
SR: That’s definitely another part of it.

GS: So going back to the ICG issue, I think another critical issue to potentially use ICG is, we know that we use it for failures, 70 percent that we say we are VEGF dependent. Can you use ICG to identify the patients who are doing well? On ICG, do you find treatable lesions for those patients?
MN: Patients who are anti-VEGF sensitive usually do not have ICG findings. They typically have early classic subretinal neovascularization. Patients who have persistent or recurrent leakage typically will have lesions on ICG, either polypoidal vasculopathy or arteriovascularized neovascularization.
GS: So as we go all forward with this imaging modality that may become more important and critical.
AA: Since a patient fails extension or other discontinue of treatment, it is unlikely that patient will ever be able to be completely off future therapy. So the biggest sign of future failure is their first failure to respond.

GS: OK so in those patients, they have six injections, you stop the seventh, and fluid recur. What do you do?
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SR: That’s when the psychological support comes into play. I say to the patient, “We tried to go out to seven weeks and it didn’t work, we’re going to bring you back to four weeks for a little while longer, and then next time we’ll extend it a little slower, maybe week by week.” Perhaps these patients are also “failures” to some extent.

GS: Those are responders that need persistent therapy.

SR: But what does ICG show in those patients? That’s what I want to hear.

GS: Whatever you call those patients, I think that’s a critical group to examine with ICG.

MN: These are the anti-VEGF dependent patients. Interestingly, these patients have variable response to anti-VEGF therapy. If you look at patients with persistent leakage one week after a Lucentis injection, the leakage will be gone. The problem is not that the treatment doesn’t work – it’s effect is not sustainable. However, the failure to respond in a predictable and sustainable manner makes an endpoint to therapy uncertain.

KB: At the same time, on those patients I do like to get an ICG because if we use a polyfosphenylen laser I may consider doing selective PDT on this patient, with combination anti-VEGF therapy.

GS: Albert, what do you do?

AA: Unfortunately we have accepted monthly treatment, or 6-weekly treatment or whatever, and nobody is asking any more what we are doing to the retina. This treatment – when applied frequently – may lead to retinal atrophy and may do harm to the RPE. We really need to go back to basic research, and we really need to understand the pathophysiology of the disease much better.

SR: We do know there is a certain percentage of patients who will need ongoing therapy, but we don’t know individually who they will be at the start of treatment. There have been some groups of doctors who basically reserved combo therapy for failed patients, and the results weren’t great. All the virgin eyes studies that used dexamethasone and low fluence PDT and an anti-VEGF, actually had good results compared to standard of care therapies such as Lucentis or Avastin. I think that the studies employing Kalexog, full fluence PDT, or enrolling non-virgin eyes really put a lot of confusing and confounding factors into the analysis of combo therapy. I should state that there are a lot of combo therapies protocols and publications out there, and they are not all the same. We should discuss therapies with virgin eyes, using low fluence, dexamethasone and an anti-VEGF, which seems to be the combo protocol with the best visual and retinal treatment results. So let’s say that some of these prospective trials do show favorable results, why would physicians not use this as a primary therapy?

MN: At this meeting (Retina Congress) I presented 20 patients who had primary combination therapy, based on the first ICG. The results mirrored ANCHOR and MARINA and did so with a markedly reduced treatment burden.

SR: Right, so my question is why is that not reflected in clinical practices?

MN: Because you have to have the ICG.

AA: We have an approved treatment, which is monthly plus PRN ranibizumab. After several injections everybody’s injecting when he thinks that it’s the right time. On the other hand, combination therapy works nicely. And we are already in a phase of identifying subgroups who will respond even better.

MH: I think there are two reasons, ANCHOR and MARINA, two excellent trials. I have no multicenter prospective, large number patient studies, which is level I evidence – that is the best advertising and it certainly has been as Albert pointed out.

GS: That’s right and it gives you reason to do it.

MH: With tremendous clout and influence from a well-funded company, anti-VEGF monotherapy has become the de facto standard. For another therapy to be successful, you would need an equivalent study. There is no large, multicenter prospective trial. RADICAL, which is wonderful in concept, has 160 patients (40 in each arm) so is not of the same power, in terms of hundreds of patients. It’s combinations of therapies, that’s being discussed here, and so I think if you look prospectively at PDT, plus steroid, plus anti-VEGF, – is there value? Well show me where that is. We don’t have large clinical trials. The second part frankly is what’s happened over the past ten years. People bought their PDT lasers back in 2000, 2001, and 2002, they believed in 2005 and 2006 that they “did not need them”, and people got rid of their lasers. And for those with multiple offices, who don’t have a laser in each location, it’s logistically difficult to do PDT. We’ve had discussions with fellows, and when you ask them how many PDTs they’ve done, the answer was five. A second year retina fellow from an incredible retina fellowship, five PDTs and what disease? Central serous! So we have basically trained in the last five years a cadre of retina specialists, who may not have access to a laser, and they don’t have experience with the PDT laser. I think these are the two forces driving behavior.

ER: In a busy private practice, many of which have sold their PDT lasers, those who haven’t sold them often don’t use them enough to have a staff that knows how to actually set it up in an efficient manner. You need to have more than non-inferiority certainly to convince them to buy one and even dust it off. They’ve got the clinic set up, so that they’re injection machines, and a PDT in the middle of the day throws everything off. If you try to persuade them that some combination therapy may work, they’ll quote the MARINA and ANCHOR trials, but none of them treat according to those trials. They all treat and extend.

GS: And their results may not mirror the trials.

ER: They don’t.

GS: Since we are talking about PDT, Mitu, can you describe your PDEX trial?

SR: The PDEX study was a prospective, randomized, masked trial looking at group I patients receiving reduced fluence PDT, dexamethasone, and Lucentis, compared to group II patients receiving the gold standard monthly Lucentis injections for 12 months. We wanted to ask two basic questions. First, were there more cases of vision loss; and that was no. The second question was whether the vision results were the same between the two groups, and the answer appears to be yes, with a treatment burden of 25 percent compared to group II. So the big fear of vision loss with combination therapy was not noted in this or any other trial using this protocol.

GS: So now we’re using reduced energy, ICG-guided or ICG-directed PDT, for specific type of lesions, either as primary, or in the secondary group, and I think it may be important for people to think in terms of making PDT safer than before.

SR: And I think we should stress that every combo therapy isn’t the specific combo therapy protocol we are discussing here. We must critically look at the actual protocols.

AA: This makes the major difference between MONT BLANC and many other studies, that MONT BLANC is not a low fluence trial – it is a full fluence trial.

GS: Yes, and very few people use full fluence.

SR: The RADICAL does appear to reveal what Henry Hudson refers to as a “dex effect”. I have thought about using Triesence or even doing studies with the Ozurdex in combo regimens. You know that my whole goal is to slow the disease process and extend.

MH: That’s a good question and I’ll tell you we have several rationales, one is taking Albert’s model of doing PDT followed by steroid injection 16 hours later.

GS: So PDT, steroids, then anti-VEGF.

MH: Another option is reduced duration PDT, and then within one to two hours, intravitreal dexamethasone (800 micrograms). As you know the closure of the vessels plus PDT happens in minutes, you start to get that VEGF upregulation pretty quickly. It doesn’t quite mirror the 16 hours that Albert described – the steroid is weakly anti-VEGF, a pretty potent anti-inflammatory, and out of the eye within 24 hours. The ranibizumab was injected 3–7 days after. A third protocol, presented by Dr. Delia Sang at ARVO, is basically same day triple therapy. Reduced duration PDT, 500 micrograms of intravitreal dexamethasone, and then intravitreal Avastin same day.

GS: Ed, I know you have a different approach, what do you do?

ER: Mine is driven by the travel distances for people. So we do reduced fluence PDT and Avastin, same day.

SR: We try to make it fast and efficient for our patients too. I tell my patients that they are getting the PDT infusions, that way when you come in to flush the remaining PDT, I give them their intravitreal injections in that 4 minute window. This is followed immediately by instilling and then the PDT treatment. I give the dex with the PDT, not necessarily just to suppress inflammation, but to suppress inflammation-induced fibrosis associated with CNVM, but also to suppress inflammation induced by PDT which may exacerbate the lesion.

GS: All three the same day.

Top: 89-year-old woman with pre-treatment vision of 20/400; color and OCT show subretinal fluid. Bottom: Early and late FA frames show leakage from CNVM.

Top: 12-month post-treatment color and OCT show resolution of subretinal fluid. Bottom: Early and late FA show relative blocked fluorescence without leakage after 1 cycle of triple plus therapy.
GS: I think we can conclude from that that most people in this group are not doing PDT before three months, repeating it. Now what about patients who have some fibrosis to begin with?
SR: If somebody comes in with fibrosis and 20/200 vision and they have fluid and have hemorrhage, I offer them a prolonged course of monotherapy, with stable vision and little chance for improvement, vs. limited combination therapy, which will likely achieve the same results with much fewer treatments. Some of these patients, who are 85 years old or older, often choose a protocol that will limit the number of visits.
ER: I agree with that 100 percent.
MN: If a patient has fibrosis and has lost their macular vision, and they are on a blood thinner, such as Plavix or Coumadin, I'll do PDT alone. I do this for three reasons. First, if there is any activity on NFA or ICG, these patients are at high risk for further bleeding despite the early fibrovascular changes. Second, by the time the vision has deteriorated to 20/200, I don't feel that the risk/benefit ratio is optimal for intravitreal injections. Third, the chance of having decreased vision from PDT monotherapy is negligible.
ER: I would agree with you, the rationale being, you have somebody where you could be committing them to endless therapy, at great expense, possibly to them but certainly to the taxpayers, and here you have a treatment that may take care of the process, right away.
GS: So how do people in this room manage bilateral disease besides bilateral injections with anti-VEGF? Does combination therapy have a role in those patients from the very beginning? How do you do it in these patients, sequence and timing and so forth?
MN: I do PDT the same day. And I will do dexamethasone in one eye the same day as the PDT day, and I have them come back the next day and do the second eye dexamethasone injection. This is what I've done most of the time. I have done some same day anti-VEGF injections in both eyes. That's an absolute minority.
GS: Anybody else do it differently for bilateral disease?
MN: I do a randomized clinical trial. I do monotherapy in one eye, and a combination in the other.

AA: We do PDT, both eyes, same day, then the next day we do the better eye with dex and anti-VEGF, and then we wait another day and do the other eye.

GS: Another day… so no bilateral injections.

ER: We do bilateral injections all the time. I've done six in a day. So we are quite comfortable in Minnesota doing that, part of it is travel distance. But we do separate lid speculum, separate prep, it's like a separate encounter, just the same day.

GS: For people who want to use bilateral combination therapy, the consensus is you do PDT the same day, then you do the injections whichever way you're comfortable, either bilateral or unilateral next day or so.

GS: So what's somebody's threshold here, in this room, is it a stroke at four weeks, is it a stroke at 8 weeks or is it a stroke at 12 weeks, post, where you will differentiate what anti-VEGF you're going to use?
ER: I have waited six weeks.

MH: For a heart attack, MI, I wait two months and obtain the blessing of the cardiologist. As far as a recent stroke, I'm very uncomfortable with that scenario, because we don't know the safety zone, and it's up to a year later for neuronal rescue. In fact we presented, several years ago, a case with recent MI treated with PDT, steroid, and Macugen, with beautiful resolution, the vision improved from 20/400 to 20/50, and I would do that combination for patients who have stroke. I checked with neurology, the neurologist said...
he’s comfortable with a year out. It’s remote, but I’ve had a level of discomfort even at one year.

KB: I agree, but I usually use six months as a cutoff for a cataract or TIA.

AA: Six weeks or so, it’s two half-lives.

GS: In terms of special situations, what about PEDs? Those are probably some of the most difficult patients that we treat. And I think we, in the past, were actually afraid to do PDT on these patients but now with high speed ICG, its smaller spot size and more direct PDT, what is the group’s thought on this?

ER: They do really well, depending on where the lesion is. Without ICG it’s the world I live in. I base my thinking on several things, one is the bad old days 20 years ago, where a PED with a notch was basically unreatractable except you could laser the notch, assuming there was a choroidal neovascular membrane there and 20 percent of the time get some success. That’s one consideration for my thinking. The second is Scott Cousins’ teaching on ICG-guided PDT. Depending on where the lesion appeared to be on FA, if extraretinal I’ve been treating with laser and Avastin, if subfoveal it’s PDT and Avastin, very targeted, tiny spots, and it’s worked phenomenally well. And I’m sure that’s what you’re getting with ICG-guided.

MN: The retinoschialional anastomosis of RAP can be anywhere in the RPED. With all other RPEDs, the source is either occult membrane formation with mature arteriolar neovascularization or sub-RPE in the form of polypoidal vasculopathy. These lesions are usually in the RPED notch. The beauty of ICG is the precise localization of the neovascular target. AA: You only treat the lesion identified by ICG, or you treat the whole thing?

ER: Oh treating the whole PED is a disaster.

AA: I think that’s the key, just treating the vessels and not the whole PED. I think many rips come from the fact that we made big mistakes in the very early PDT era, we just treated the whole PED.

GS: So another take home message from the group is that besides monotherapy for PEDs, focused PDT therapy, either with or without ICG may be beneficial. Choice would be dependent on the individual patient and physician but rips of the RPE can still occur with either therapy. SR: There seems to be a tremendous amount of polarization that goes within the retinal community when discussing combo therapy vs. monotherapy. Each of these treatments may be useful in particular settings and we should all keep an open mind when discussing their relative merits.

GS: I think that’s right. You want to have a custom designed, custom tailored therapy for whatever you’re facing.

SR: And there’s room for it, there’s room for every type of treatment in this very diverse patient population.

AA: This custom therapy only can come from better understanding of the disease.

ER: This is analogous to the stenectomy vs. scleral buckling discussion.

GS: I talked about this the other day. We’re taking procedures that worked in the past, we tried new procedures, but you now know that old procedures still have room with the new procedures.

MH: I recently gave a talk on “What’s New in Diabetic Retinopathy.” After an update on pharmacotherapy and surgery, I referenced the original DRS and ETDRS studies, and I said, what’s new is old. Laser works. What’s new is that “old” treatments may still work!

GH: I think you bring up a very good point. Let’s not forget about an old treatment, and let’s not base the old treatment on ways of doing things. I think a point is to evolve in those therapies.

SR: So you’re talking about PEDs. We have recently started the Lucentex trial; it is a comparison of combo therapy using Lucentis plus dexamethasone vs. Lucentis alone. It is similar to the PDEX trial in format, but without the PDT. The very early analysis may suggest that the combo therapy group works slightly better in the PEDs. The data is very preliminary. In the combo therapy group, every time the patient gets ranibizumab it is in combination with dexamethasone. They get four straight injections of ranibizumab plus dexamethasone in group I, versus ranibizumab alone in group II. The patients then go to PRN treatment based on any evidence of lesion activity.

SR: Right. It seems that others have also tried this combo regimen with chronic PEDs with some similar levels of success. A more rigorous analysis and study is obviously required.

GS: I think, of some of those things where they even showed 10 or 12, what ever injection they gave, the PED goes up and down but there’s not much of a difference between where you started, and where you ended up.

MH: Right.

GS: Mark and Ed, what has been your experience by having PDT in the mix of all these other therapies, from a financial standpoint?

ER: Well it is tiny in comparison to the anti-VEGF drug volume and dollars but we get paid from Medicare, and from, I believe all the local carriers, for PDT, and half for the injection, and we get paid for the drug, same day.

MS: We get paid for it.

GS: So we’re beyond the point where it’s a problem.

ER: Right.

GS: When people schedule these PDTs during the day, do you have a different day that you do them, do you have an injection day, etc. For people who want to try this, logistically or efficiency-wise, what’s the approach that’s worked best for you?

KB: In the old days we had a scheduled treatment day, and we found that was one of the most inefficient ways we could spend our time. It was a poor use of our time, and inconvenient to our patients to force them to come back for just the treatment. I just add them on. Again, I think the key is to have trained personnel that are very comfortable with the procedure. For physicians that still do their own dosing and injections for PDT, this will undoubtedly complicate their day. I recommend they spend the time and money to train the appropriate personnel to maximize their efficiency. The more personnel you have that are comfortable with PDT, the easier the flow.

GH: Same thing for me, anywhere in the day, though a critical part there is obviously watch when you’re booking. You’ve got X number of hours per day, if you’re going to do four PDTs in a day, don’t book four PDTs in an hour. Scheduling is critical, that’s it’s no more than one per hour. I have a separate injection clinic which is purely for injections and I’ll rip some pretty thermal lasers or a rare PDT in the schedule.

ER: We just integrate them throughout the day, we definitely try to have them not too close together at all. We like to leave it so that, if you see somebody you can add them.

AA: Our department just does it on demand. There is no need to organize it, we are doing surgical and medical ophthalmology all the time.

SR: No special day.

GS: I kind of do the same thing. The only thing I do differently is I try to do PDTs starting in the afternoon rather than the morning, because the mornings are much busier, and it sets up the day.

GS: Mark maybe you can comment a little bit on RADICAL. What is your take home message from the RADICAL that people should know?

MH: That I think there’s a role for combination therapy in your practice, and RADICAL appears to be demonstrating the benefit of combination therapy, in terms of improved visual acuity and reduced need for repeat injections.

GS: Mtsu, you talked earlier about the PDEX trial, what are the results so far?

SR: The PDEX trial compared triple therapy with reduced fluence PDT, dexamethasone and ranibizumab (group I) to patients receiving 12 monthly ranibizumab injections (group II). I had one initial treatment on Day 0, followed by PRN treatments thereafter. I cannot fully reveal the results here while we await publication, but in general there appeared to be no inferiority in terms of visual outcomes, but with reduced treatment frequency. We are in the process of analyzing additional interesting features such as angiographic differences, OCT differences, RPE atrophy and other variables.

MH: My study of 20 primary combination therapies in patients with arteriochoroidal neovascularization and polypoidal averaged 37 weeks between combination treatments. Interestingly, there was a very strong negative correlation with duration of effect with polypoidal vasculopathy, with the average time of duration in this subgroup being 25 weeks or so. The antiangiogenic effect and leakage resolution does not last.

GH: How does the PDEX trial, your own trial, changed what you do in practice?

SR: Most of our treatment naive patients are now enrolling into the Lucentex trial and we are still analyzing the results before making any internal or external recommendations.

GS: I think that point really needs to be made, that the trials we’re talking about are reduced energy. Whether you do reduced time, or reduced duration, or reduced intensity is an open question, but the bottom line is we were using less energy.

SR: The only combo studies so far that have shown equal outcome in terms of vision used dexamethasone, reduced fluence, and an anti-VEGF. I’ll make one other critical point as to not to overstate the vision results of the PDEX trial. I believe the reason we had outstanding vision even in the triple therapy group was that they still maintained monthly follow-ups. That is an important point. No study has shown that a PRN follow-up schedule is comparable to a monthly follow-up schedule, aside from any treatment modalities, we can’t do it.

GS: That’s an important point. You still need to see them, but the patient might not get treated. Now you may be able to push that further, as you can figure out which ones had the recurrence, in the PDEX trial.

SR: We need to look at 3-5 year data to see which patients in each group required ongoing therapy after completion of the trial.

GS: The extension trials are showing that these people are still needing injections.

ER: And that’s a little bit what I was talking about earlier, now with all this anti-VEGF treatment we’ve altered the natural history of the disease, which used to run its course and end.

GS: I think the last question is that, if anybody has a crystal ball in this room, in two years, how do you expect these therapies to evolve?

MH: Therapy evolution is one thing, harsh reality of Medicare reimbursement and regulations is the second. So the crystal ball says to me that within two years, will my practice change in terms of doing...
more triple therapy? No, I’m probably doing what I’m going to do but I’m a real believer in options so I will continue to do triple therapy, and still use a lot of monotherapy, I don’t see a new agent coming out in the next two years, so therefore there will be no change on that basis. I think quite frankly what I’m going to wait for are the results of randomized things like the PDEX and RADICAL trials, and to see the results of CATT. Also we will see if Medicare is going to regulate our use of bevacizumab versus ranibizumab, or institute a limit to injections.

GS: Albert what do you see in Europe, if you had a crystal ball, in terms of AMD therapy in two years?

AA: I think what we are going to be learning is that we need to eradicate the CNV. I don’t know what we will use in the future to eradicate the CNV. I don’t see a radiation device being implemented on a routine basis. I think to eradicate the CNV plus drugs, that’s the future. So I really believe in combination therapy, not because I did some pioneer work. It’s the only way to antagonize this disease entity effectively.

ER: Well I think the biggest impact will be the, now I’m looking into the crystal ball so I have excellent vision into the future, and the CATT trial will come to show that Avastin is minimally, not significantly, if at all, inferior to ranibizumab. That will set forth some interesting things but more interesting for Genentech than for the rest of us. And I think I’ll continue to do combination therapy as I do and I’ll have months where I do more and months where I do less depending on how the last three months went, and that’s probably the only change.

GS: Do you think that ICG will play more of a role?

ER: ICG will play more of a role I’m sure.

AA: The ICG story nicely shows us that more and more people are looking inside the disease, which is very interesting.

GS: Yes because we’re trying to image things that we never really did and I think we should know the results of EVEREST.

SR: There’s no doubt in my mind, first of all, that monthly monotherapy is a great therapy. And if you do monthly monotherapy for 24 straight months in patients they will end up with very good vision. Now will it mirror exactly what we saw in the clinical trials? Perhaps not, but it may not be too far off. So if your practice can schedule monthly injection for 24 straight months, I think that’s great. I think if you or the patient cannot, we have to determine what other options are available to these patients. Some form of combination therapy, using current and future VEGF or PDGF therapies may be options. Whatever happens, I believe that, based on the inherent biology, some form of combination treatment will be the future of wet ARMD treatment.

GS: But the problem is we don’t have those compounds for the next two years.

ER: Can I just say one thing, since that crystal ball is still working? We may be looking at biomarkers.

MN: My prediction is that polypoidal vasculopathy is going to turn out to be a major player in the pathophysiology of exudative ARMD. The old paradigm that polypoidal is only found in Asian populations is not true.

AA: I fully agree.

GS: We’re going to see a much bigger role for ICG.

MN: As more ICG studies are performed, polypoidal changes and other intrachoroidal pathology will be visualized, especially as the resolution increases. In addition, I believe that systemic treatment will become a part of the combination therapy as it will be needed to address the intrachoroidal disease.

KB: I think we’re becoming more and more like our colleagues the oncologists with combination chemotherapy regimens, not just one agent, that’s going to really be the answer for success. As for me I’m a recent convert to triple therapy, I’ll be doing more triple therapy in my own practice and as already said I think ICG is really going to play a key role in diagnosing lesions that aren’t responding.

GS: This has truly been a real world discussion in terms of management of ARMD. We all agree that anti-VEGF therapy has made a tremendous impact in the lives of our patients but sometimes other therapies may be necessary in the treatment algorithm. It will be important for us to realize that a subset of wet ARMD patients may respond better with a multi-modal treatment approach. The timing of using these therapies may be individualized in accordance with the disease. ICG imaging will evolve allowing us greater detection and a targeted approach. Failures will continue to be present and management will continue to be a challenge. Once again I would like to thank each and every one of you for taking the time to talk about real world issues that affect our patients’ lives and our choice of therapies.

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Dr. Shah is on the speaker’s bureau for Alcon, and on advisory boards for DORC, Neovista, Heidelberg, Novartis, and QLT.

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