Lasers and Needles and Warm Woolen Mittens: an Approach to Treating DME

We are all apprentices in a craft where no one ever becomes a master. Ernest Hemingway

The approach to treating diabetic macular edema is evolving at a rapid pace. Coming up with a standardized protocol is almost impossible as new data keeps piling up--it is very much a moving target. Plus, the approach can differ from region to region, depending on local preferences and the resources available. Until we figure out a way to magically alter the words printed on this page, you really need to keep abreast of the field on your own. You also need to stay in touch with your neighborhood (or regional) retina specialists—they can not only give you lots of advice, but they can also keep you from doing things outside the local standard of care. In this chapter we are going to try to create a global

approach to DME for you to start with, and then you can adjust it depending on the latest data, your results, and regional preferences. But first a couple of things:

Thing 1

It is easy to get totally absorbed in the tools at your disposal, especially when you are trying to understand things like OCT's, lasers and injections. But never forget the fundamental importance of the patient's systemic control. Your new found abilities to treat the retina will be far less effective if you are not also actively encouraging the patient to take proper care of themselves. There will be much more of this in The Chapter Whose Subject Must Not Be Named—but it bears repeating because you can't give your patient the outcome you both want if you ignore this aspect of their retinopathy.

Thing 2

Any discussion of modern treatment techniques has to include a shout out to recent collaborative trials. Carefully constructed large-scale clinical trials have always been instrumental in defining how diabetics are treated, and one of the latest and greatest innovations for this has been the Diabetic Retinopathy Clinical Research Network (DRCR.net). The DRCR.net consists of around 200 academic and private retina practices in the United States, and it functions as a collaborative network designed to facilitate multi-center research on various aspects of diabetic retinopathy. It allows the rapid initiation of trials looking at the latest fads to see if they really work, and it is funded by the National Eye Institute rather than by private corporations, which raises the credibility level. If you want to dig deeper into why you do what you do, their website is a must read (drcrnet.jaeb.org). And the DRCR.net is not alone—investigators around the globe have organized similar collaborative efforts, such as the Pan American Collaborative Retina Study Group. A lot of the latest treatment techniques discussed in this book will draw heavily on the trials performed by all these groups.

One caveat, though. The investigators in the DRCR.net and the other groups are the cream of the crop—they are true Retina Playuhs. Do you remember how your first few cataract surgeries looked like someone set off a small bomb in your patient's anterior chamber, and now your surgery is so slick you can't find one cell on post-op day one? Some of that is from doing a lot of cases, but some of it is due to subconscious learning—you automatically sense what micromove is best for reasons that you may not be able to describe, and your outcomes are way better as a result. Well, the same thing applies after doing thousands and thousands of lasers and injections—subconscious perceptions develop that make everything just go a tad bit smoother for the Major Dudes than it does for the rest of us mortals. Plus, the patients in the DRCR.net studies tend to be highly motivated, and that makes a big difference. Finally, the patients in these studies are subjected to a 15-minute, high contrast refraction at every visit – which ekes out the best vision possible.

All this means is that you should not be disappointed if your results don't seem to match

the studies—and you should welcome the fact that the studies present a gold standard to strive for. Most importantly, you can't have your patients thinking that they will always do as well as the data suggests; Chapter 5 talks about this a lot. Also, remember that the results of any study apply primarily to patients with characteristics similar to those entered into the study in the first place. In other words, as you try to sort out how you will care for your personal patients, you will need to be flexible. Your patients may need a more custom approach that draws on the results of many studies.

But Back to the Subject of the Chapter

When trying to create a systematic approach to DME, the first concern is simply what tools are available to the treating ophthalmologist. If you are in a situation where you have diabetic patients but you do not have access to basic items such as laser and OCT, there is little that can be done. However, with motivation and persistence you can seek out organizations that can help you obtain equipment and training; check out Appendix 2 for suggestions. If you are one level up and have a laser but can't do intravitreal injections, you will find that each of the chapters on laser treatment includes advice about the approach to take when laser is your only option. The bulk of this chapter will assume that you have all the requisite toys and you can get your patients all the fancy drugs. Probably the one hang-up for most people around the world is that ranibizumab (Lucentis) and aflibercept (Eylea) are not options because of cost, and we'll cover that too. But on to the disease…

When treating macular edema, the first step is to be sure you are treating a diabetic problem. Chapter 27 is a whole discussion of the things that can look like DME but aren't—like vein occlusions or subtle intermediate uveitis. We will presume that you have ruled out all those other things.

The next step is to determine if you are dealing with an anatomic problem such as vitreomacular traction or macular pucker. Your clinical exam, and especially your OCT, will help with that. But it is not that simple. You also have to decide to what extent the anatomic problem is contributing to the leakage. If the edema is entirely due to the traction or pucker, then you can skip everything that follows and head straight to Chapter 19 on vitrectomy. On the other hand, if the patient has just a hint of surface wrinkling that doesn't seem to be contributing to the leakage, then you may be able to treat the retinopathy and ignore the surface wrinkling unless the edema proves refractory to your ministrations.

Unfortunately, nothing is simple, and many patients with a vitreoretinal interface abnormality and diabetic retinopathy end up with some degree of overlap, i.e., there is some leakage from microvascular damage within the retina from diabetes, and there is also some leakage caused directly by the traction or pucker. In fact, the two problems seem to synergize—a mild looking epiretinal membrane may accelerate the underlying retinovascular damage. It can be hard to know how much of the problem is due to trouble at the vitreoretinal interface versus pure diabetic retinopathy. Kind of like the distinction

between art and pornography, though, if traction from any cause is the main problem it is usually fairly obvious. If it is not obvious, or if the patient is uninterested in addressing the problem surgically, it makes sense to start treating the macular edema with laser and/or injections and then reassess the role of surgery depending on how successful your treatments are. There may even be times when the effects of traction are masked by the swollen retina, and as the retina thins out with treatment the superimposed traction becomes apparent (Figure 1).

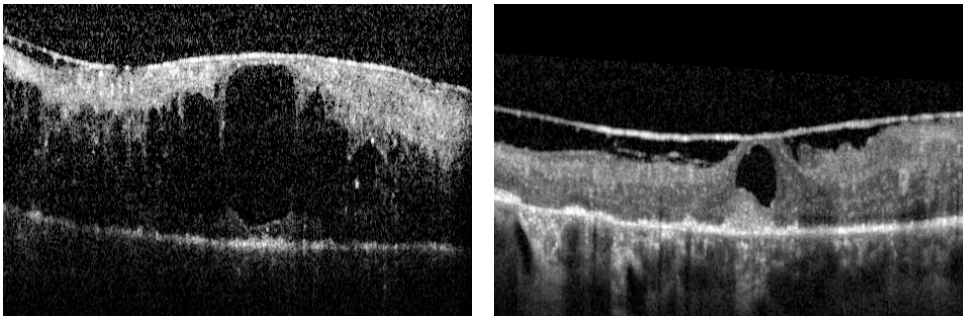


Figure 1: The OCT on the left shows a frighteningly swollen retina with an overlying epiretinal membrane (ERM). Successful treatment with laser and injections eliminated most of the edema, but on the right you can see a persistent cyst that is caused by traction from the ERM that became apparent as the retina deturgessed. By the way, you can also see that the ellipsoid zone (outer/inner segment line) is non-existent (as is most of the normal retinal anatomy). There is even some thickening of the subfoveal RPE, which suggests longstanding edema. When the retina is this slagged, it is unlikely that surgery to remove the traction would make any difference.

But wait. We need to discuss a side-topic that merits a change in font color.

There is one thing to think about in patients with edema from just about any cause, and it is something that you would automatically think of in one of your post-op cataract patients with CME.

It makes sense to consider the use of a topical nonsteroidal in patients with puffy diabetic retinas. This doesn't work for everyone—in fact, there was a DRCR.net study looking at this in patients with non-central DME who were largely phakic. There was a trend towards a response, but there was no statistically significant benefit.[1] There are other smaller studies that support the use of this medication, however.[2-5] The drops will not solve the problem in a poorly controlled patient with severe edema, and they don't work in everyone. And you should never postpone appropriate treatment in patients with progressive disease just to see if some topical ketorolac might solve the problem. However, it is an approach that can be very helpful for selected patients; it does seem to work better for pseudophakic rather than phakic patients.

For instance, in patients with a bit of swelling and a mild epiretinal membrane, the addition of a topical nonsteroidal drop may deturgess the retina enough that you may be able to avoid more aggressive treatment. Or in patients with diabetic macular edema alone--without any epiretinal membrane--the addition of a nonsteroidal can tip things in

the direction of stability so they need fewer lasers and injections. Plus, patients who get a good anatomic response will often also notice subjective improvement in their vision, and it is always nice if there is a little positive reinforcement to help with compliance.

It is not clear if one nonsteroidal is better than another (although patients are more likely to adhere to the regimen if you use a medication that requires fewer drops a day). One thing to be aware of if you are going to try this is that these drops can vary widely in their cost--you might want to have someone in your office call the surrounding pharmacies to get some pricing. It seems to take at least a month or two of treatment to see if there is an effect, and often patients need to be treated for several months to stabilize things before tapering them. If one or two different drugs don't have any effect, then it is not worth trying others. But it may be worth retrying them again after several months if you get better control of the patient's disease with other modalities. Again, this is not something that works for everyone—and it has yet to be fully proven in a large trial--but it really seems to help decrease the overall treatment burden in selected patients. It is interesting that the addition of an NSAID has been shown to possibly be helpful in other retinovascular diseases like vein occlusions and macular degeneration.[4,53]

Remember, though, that there may be a risk of corneal melting with chronic use of a topical nonsteroidal, especially in patients with compromised corneas (i.e., exposure, neurotrophic problems or dry eyes--all things that can be more common in diabetics). The concern of a melt was more of a problem with older generic preparations, but it is still a risk so warn patients about this and instruct them to discontinue the drop and get checked if they are having problems. And don't act like a retina specialist—when you see them in follow up make sure you actually look at their cornea.

But back to the issue of combined epiretinal membranes and macular edema. There are no firm rules here; in patients with combined disease you simply need to reassess both the retinovascular status and the effect of any traction at each visit. These patients often take a lot of time as you go over the ups and downs of surgery versus treatment with lasers and injections. They need to understand that although there may be risks to vitrectomy, there are usually risks to observation in the form of permanent structural damage from chronic traction. Of course, the situation is complicated by the fact that vitrectomy by no means guarantees a favorable visual outcome--even if there are no complications. There are some foveas that just conk out even with successful surgical correction, and these patients can end up worse after vitrectomy even if their OCT is improved. There will be much more on the specific role of vitrectomy in Chapter 19; the point here is to look for problems with traction before you start skewering eyes with photons and needles. And don't spend years trying to figure out if an epiretinal membrane or traction is the main problem. There is a feeling that waiting a long time and then referring the patient for surgery when all else has failed results in less successful surgery. If you aren't sure, just send the patient to a retina specialist.

Most of the time *mild epiretinal membranes associated with mild diabetic retinopathy are annoying but not dangerous—especially the ones that keep the vision in the 20/25 to 20/50 range. If you are not a retinal specialist, you may think that such patients will automagically benefit from a vitrectomy, but if you are a retinal specialist you will have realized that operating on such patients can help, but often in a very underwhelming way. As a result, unless patients are bitterly symptomatic it is often better to just treat any identifiable leakage caused by the diabetes, but recognize that you won't get rid of all the edema so don't beat the proverbial dead horse with excessive lasers and/or injections. Adding a topical non-steroidal may also help, and you do need to always keep in mind the option of doing a vitrectomy if anatomic and visual problems get worse (for instance if the ellipsoid zone (outer/inner segment line) starts to disappear). Unless the patient is really type-A, most of these people--particularly older patients--are content to be monitored.*

But there is one situation where you can really get burned: cataract surgery. There is something about adding cataract surgery to the presence of a little bit of retinopathy and a little bit of an epiretinal membrane—the combination can really go south unexpectedly. This doesn't mean surgery is wrong. It just means that both you and your patient need to understand the risk. And putting in a multifocal lens in such a patient is not a good idea – very simply, diabetic retinopathy causes a huge loss in functional photoreceptor cells, even in patients with 20/20 vision. The reduced contrast sensitivity due to the multifocal lens, combined with reduced contrast in the diabetic retina, can leave a patient frustrated (more on this in Chapter 25 on cataract surgery in diabetics).

Okay. Presumably you have ruled out other diseases that mimic diabetes, and you are fairly certain that you are not dealing with some sort of vitreous traction or epiretinal membrane that is the main problem. Now we can actually start talking about treating DME.

Talking About Treating DME

The main branching point is whether or not the patient needs treatment with laser alone or whether injections will be required. This usually comes down to understanding the definition of center-involving edema. To review, the DRCR.net defines this as having an ETDRS visual acuity score between 20/32 to 20/320 with definite retinal thickening in the center of the macula on clinical exam and central subfield thickness ≥250 microns (using a Zeiss Stratus, which means that you might need to add 50-ish microns depending on how your spectral domain machine measures retinal thickness – see the OCT section in Chapter 3 for details).

Now this is where it gets tricky. Patients don't tend to come in with a binary degree of central involvement; they tend to have variable amounts of peripheral leakage and variable amounts of center involvement. If the patient does not have any center-involving disease and has clinically significant macular edema based on the "disc within a disc"

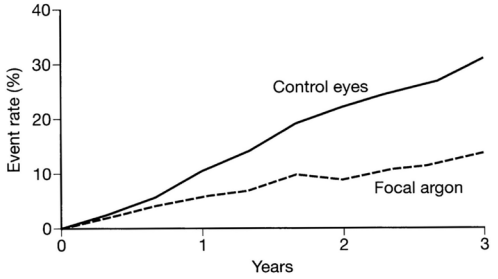
rule, then things are pretty straightforward. Usually a gentle laser combined with not-so-gentle encouragement to improve their systemic control is all you need. There are two full chapters on how to do this located elsewhere in this book, so you should be all set.

It gets trickier if there is some peripheral leakage but also some swelling at the center, as defined above. This is more "art of medicine" stuff, and there are widely different approaches. Some docs think that laser is a waste of time (and RPE) and go solely with injections—we will see that there is a lot of data to support this. But there is also a sense that laser treatment is a good adjuvant to the injections; injections provide short-term control, whereas laser is for long-term control. In other words, you get the injections in to stabilize and protect the fovea and use laser to treat any leaks that are away from the center. Eventually the overall leakage will decrease and the need for chronic injections will also decrease, along with all the attendant risks and costs. Now, is there any randomized, controlled trial data that supports this? Nope. Nada. Still, it is an approach that seems really right to many retina folks, and we will spend more time discussing the issue of lasers versus injections later in the chapter. But first a slight digression.

It is important to understand where retina people are coming from when it comes to lasers--it will help you decide your personal approach. But you need to somehow absorb decades of experience with lasers, and the easiest way is to hop on the Wayback Machine.

Back in the Eighties, the Early Treatment of Diabetic Retinopathy Study (ETDRS) generated the graph in Chapter 3 that shows the results of treating macular edema with laser. Figure 2 is a refresher.

Figure 2.



Those results were a breakthrough, but Figure 3 shows what it looks like if it is flipped around so you see it from the standpoint of a patient. Even with treatment, patients still deteriorated. It is just that their vision didn't suck as much as the controls.

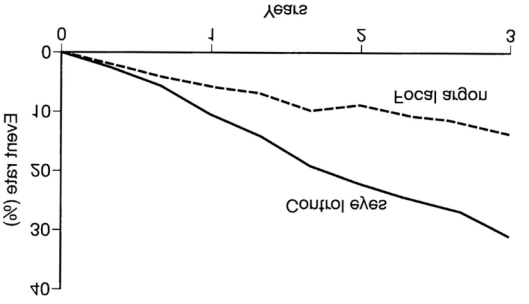


Figure 3: A patient's-eye view of the graph from Chapter 3 showing the ETDRS results for treating macular edema. This graph made doctors happy, but patients still worsened on average, even with perfect treatment. Note the elegant symbolism suggested by the flipped labels: The doctor has to totally wrap his or her head around the patient's point of view to really be able to relate. This was not done because it is easier to flip the original image without changing the labels—it was done on purpose for art's sake.

But ETDRS laser is old school, right? Absolutely. Over the years the original laser techniques were modified by making them gentler (upcoming chapters will review this at length). And although people were getting a sense that the newer techniques were working better, no one knew for sure. And then the DRCR.net published a study that dropped a real bass bomb on the house.[6] This study compared repeated use of laser versus repeated use of intravitreal steroids (albeit, short term off-label triamcinolone), and it was done before the big anti-VEGF studies (hence no anti-VEGF arm). Figure 4 shows the results—and this blew people away. Not only did laser smoke the steroids (and back then people thought for sure that steroids would be best), but look at that laser line—patients actually improved! So, for a brief time, laser was the gold standard, which made people feel really good about doing lasers.

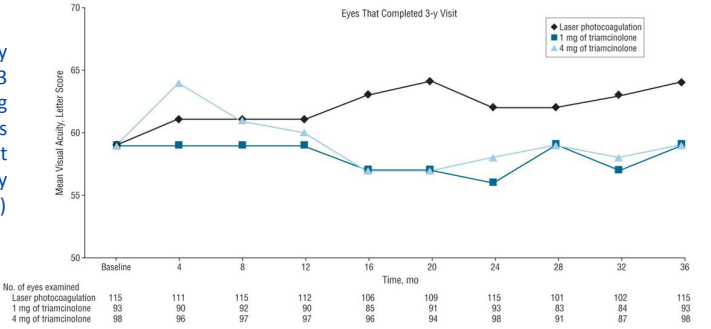


Figure 4: Mean visual acuity for the eyes that completed 3 years of follow-up comparing laser to two different doses of triamcinolone. Look at that laser line head north! (Courtesy of Archives of Ophthalmology.)

But remember, the DRCR.net results are from highly experienced doctors treating highly motivated patients—do not expect all your patients to do as well. For instance, Jyothi and Sivaprasad did an interesting study wherein they applied the DRCR.net laser protocol to a real world urban population—with poorer systemic control and more erratic follow up (Figure 5).[7] Suddenly the results of laser are not quite as stellar—in fact they start to look a lot like the boring old ETDRS results from 30 years ago. One can argue that maybe they just didn't have the same skill as the DRCR.net investigators, but it is far more likely that they were treating patients that couldn't or wouldn't take optimal care of themselves, and that makes a HUGE difference in terms of how well they respond to treatment.

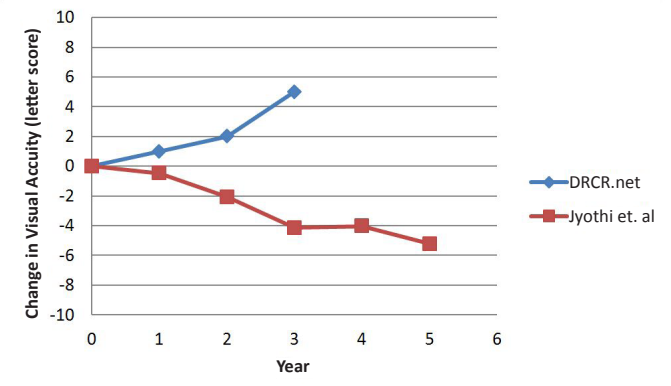


Figure 5: A graph of data from Jyothi and Sivaprasad.[7] The top line shows the 3-year results of the laser arm from the DRCR.net protocol that compared laser to triamcinolone. The lower line is what happened when the same laser protocol was used in a more diverse urban setting with patients with poorer systemic control and follow up. Do not let your laser patients think that the laser will automatically make them better.

What is the point of all this? It is that laser is a good thing—at the very least it will slow things down, and at best it can turn things around and actually get people better, albeit slowly. And all that explains why there is such a strong feeling that laser can help control macular edema and decrease the need for injections (assuming the laser is done parsimoniously and doesn't scar up the macula). It is just that no one knows for sure exactly how the laser fits in, especially in light of some of the anti-VEGF studies that suggest that laser may have little effect and in some cases may be deleterious. We will hit all this shortly; for now it is enough to understand that laser is a good adjuvant to include in your arsenal as long as you know how to use it wisely.

But speaking of quick fixes, now it is time to go from lasers to injections…

And when it comes to intravitreal treatments, the first thing to discuss is the use of triamcinolone acetonide (Chapter 11 talks about specific preparations). At first, people were shocked with the apparent efficacy of intravitreal triamcinolone for the treatment of diabetic macular edema. It was exciting to put a drug in the patient's eye and watch the edema completely disappear. It was also a lot of fun to have patients come back happy after a treatment for diabetic retinopathy—almost like a LASIK patient! All this created strong positive reinforcement to keep using steroids, but unfortunately, over time it became apparent that steroids didn't live up to their initial success. The efficacy seems to wear off with repeated injections, and of course there are always the potential side effects of cataract formation and glaucoma requiring surgical intervention. Perhaps the biggest indictment about the utility of steroids as a single treatment came from the DRCR.net study cited above where laser alone was more effective than triamcinolone.

As a comprehensive ophthalmologist, you may feel fairly comfortable with problems like cataracts and glaucoma. *But remember, cataract surgery in diabetics, and especially diabetics with macular edema, can make things worse. And as for glaucoma, yes, you can treat with simple things like drops and even laser trabeculoplasty,[8] but some patients get a whopping pressure spike that just won't go away. And those patients need surgery to lower the pressure. If you are at an academic center where you can walk your patient with steroid-induced glaucoma down the hall to a world expert on glaucoma, your risk-benefit ratio may be very different than if you are practicing in a smaller town where the same patient may be operated on by someone who does only 10 filters a year. On top of that, diabetics tend to be more likely to have filters that fail.[9] And then there is bleb-related endophthalmitis. Bleb endophthalmitis scares retina docs, and it should scare you too. It can show up years down the road and can put an eye in a jar really fast.*

Trading years of endophthalmitis risk for a few months of decreased macular edema is something that needs to be approached carefully as you decide how you want to treat these patients.

By the way, there is a suggestion in the literature that if the patients routinely have

pressures lower than 15 they are less likely to get a significant pressure elevation with steroids.[10] Some doctors will take the extra step of putting patients on topical steroids to try to suss out a potential steroid response. Other risk factors for elevated pressure include the presence of actual glaucoma, suspect glaucoma and a family history of glaucoma. Younger patients may also be at higher risk.[11] There is also growing data that patients with a narrower angle recess as determined by anterior segment OCT may be at increased risk.[12] And just because nothing is simple, once you have put steroids in an eye, you really need to keep monitoring the pressure for a while. The pressure can rise insidiously, and this may show up well after the drug should have worn off.[13,52]

One final note—if you do end up with elevated pressure after intravitreal steroids, one option to keep in mind is that performing a vitrectomy and removing the residual drug may lower the pressure without the need for glaucoma surgery.[14]

However, the data from the above DRCR.net study does not mean that there is no role for steroids. First of all, there are doctors that feel you can get some of the benefit of intravitreal steroids with less risk by using a periocular injection instead. A few studies suggest that there is an effect, but others suggest it is not dramatic, including a different pilot study by the DRCR.net.[15] Still, there may be some situations where this "kinder, gentler" approach to using steroids can nudge an eye in the right direction. We do not regularly use this intervention, but you are welcome to take a look at the literature and decide for yourself.[16,17]

As for intravitreal treatment, although the laser versus steroid study suggested that steroids alone were not particularly useful on average, there are certainly a host of other studies that suggest that some patients will respond nicely to steroids--they can be a useful adjuvant. For instance, as we will see in the next section, Protocol I from the DRCR.net did include a steroid treatment arm. Although the steroids were not very helpful in phakic patients, they could provide some long-term help in pseudophakic patients.

And this gets to another main point in this chapter. In many ways, the treatment of patients with diabetic macular edema involves a search for whatever approach provides the least amount of risk and fewest interventions. There are definitely some patients for whom steroids work great and they need far fewer shots than if anti-VEGF drugs were used—you just have to figure out who those patients are.

Also, there are some patients whose edema just does not seem to go away no matter what you do. Many times the addition of a steroid injection to the other interventions may help control things. For instance, many docs will start treatment with anti-VEGF agents, and if the edema persists after, say, 4 to 6 monthly injections they will add a steroid injection. You may even have rare patients that are simply refractory to everything, and who need frighteningly frequent steroid injections just to hold onto their vision. These patients don't come along very often, but if you automatically write off the use of steroids you will have a lot of trouble controlling vision loss in such patients.

Which brings us to the subject of longer acting steroid implants such as Ozurdex, Iluvien and Retisert. The use of these modalities may be limited by cost, as well as the almost inevitable development of cataracts and high risk of glaucoma. However, in patients that do well with steroids, these longer-acting treatments can be useful. In fact, there is a sense that the sustained low-dose delivery that these modalities provide may actually be more effective than the intermittent pulsed dosing that occurs with periodic steroid injections. As more studies are performed using these long-acting implants, we will get a better sense of how they fit into the armamentarium. They will probably be most useful in patients that respond to steroids with few side effects, or for those patients that only partially respond to anti-VEGF agents and are willing to accept the risk of glaucoma and cataract to preserve their central vision.[18-20]

Quick review of the implants: *Ozurdex has 0.7 mg of dexamethasone and is a small cylinder about .48 mm wide and 6 mm long. It is inserted via the pars plana using a special injector. It is biodegradable and lasts 3-4 months—patients may see a small telephone pole in their eye for a while and then it dissolves. One notable thing about Ozurdex is that there is a sense among clinicians that it is less likely to cause a big pressure spike compared to triamcinolone.[21] Iluvien is an even smaller cylinder and has .019 mg of fluocinolone acetonide. It is not biodegradable, but it lasts up to 3 years (**Figure 6**). Retisert has .59 mg of fluocinolone acetonide and is a small pellet that is inserted surgically via the pars plana and sewn in place. It lasts about 3 years also.*

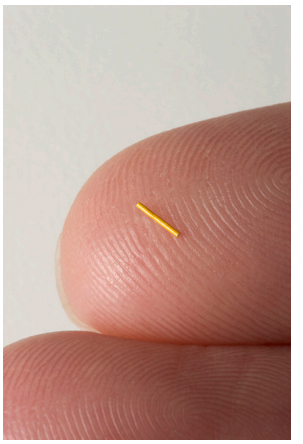


Figure 6:
Iluvien fluocinolone implant.
(Courtesy of Alimera Sciences)

Like triamcinolone, all these devices are effective for treating macular edema, but they all have the risks of glaucoma and cataract, plus they involve various degrees of leaving stuff inside the eye where it can cause trouble. For instance, Ozurdex and Iluvien can migrate into the anterior chamber in predisposed patients (such as those with a decentered IOL). Retisert requires surgery and a subconjunctival stitch that can erode; also, the medication pellet can become detached from the fixation plate and float around the eye. All of these devices are in various stages of being tested and approved (or turned down) around the world, so it is hard to say exactly how they will be used, but they will likely be a "last-resort" option for patients with refractory disease. One interesting fact that came out of the studies for the Iluvien implant is that it worked much better in patients that had had DME for over a year and a half—it didn't work as well for patients with fresh disease (although some question the statistics behind this conclusion).[22] This raises the possibility that different treatments may work better at different time points—something to keep in mind when you have a patient that doesn't seem to be responding—or stops responding—to any one therapy.

The next sentence is really important if you are just starting out using injections:

The key thing with intravitreal triamcinolone is to understand that it is not as good as you will think it is after the first time you put it in someone's eye.

Still, it does have a place, and for some doctors it is the go-to drug in patients that are pseudophakic with low pressures and no risk factors for glaucoma. It may also serve as an adjuvant to minimize the need for other injections, and for some patients it is the only thing that really works. We will get back to steroids in the end-of-chapter wrap up, so let's switch to the real stars of the show…

The Anti-VEGF Drugs: Bevacizumab and its expensive cousins

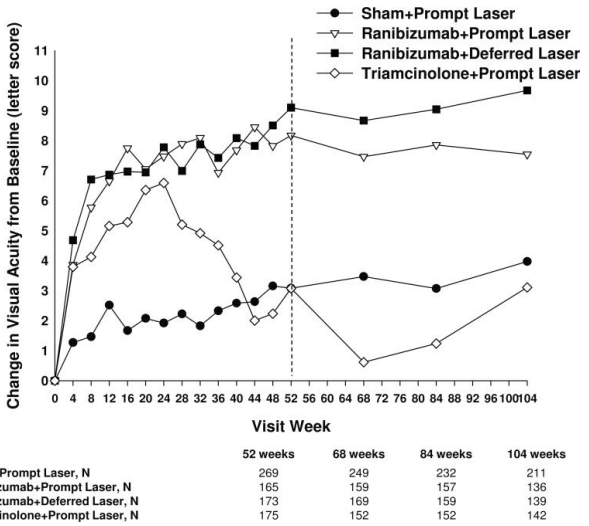
The anti-vascular endothelial growth factor (anti-VEGF) drugs have become the mainstay for treating center-involving diabetic macular edema. A real textbook could tell you why. Suffice it to say that blocking VEGF seems to seal leaky blood vessels. At first, everyone thought that they were just weak versions of triamcinolone, because it seemed that steroids gave a better immediate response. But as more studies have been done it is clear that regular anti-VEGF injections provide better control with fewer risks in general, and that explains why they are used so often.

You know this, but for completeness here is the gang: *Bevacizumab (Avastin) is a humanized monoclonal antibody against VEGF. It is not approved for use in the eye—it is an anti-cancer drug that eye doctors have co-opted because it has effects similar to the approved drugs, but is way cheaper. The usual dose is 1.25 mg (.05 ml). Ranibizumab (Lucentis) was the first drug approved specifically for use in the eye; first for macular degeneration and then vein occlusions and most recently for diabetic macular edema. It is a specially modified fragment of the bevacizumab antibody. Note that the dose of ranibizumab is different for different diseases; the dose for vein occlusions and macular degeneration is 0.5 mg, whereas the dose for DME is 0.3 mg (the studies suggested that there was no reason to expose patients to the higher dose when treating DME). As of this writing, the 0.5 mg dose is about $1950 a vial and the 0.3 mg dose is about $1400. So be very careful about which vial you grab, because if you use the higher dose on a diabetic, you will lose several hundred dollars when the insurance company refuses to pay.*

Aflibercept (Eylea) is a fusion protein that combines VEGF receptors with the Fc fragment of human IgG; it costs about $1850 a vial, it is the most recently approved drug for DME.[23] Finally, there is pegaptanib (Macugen), the first anti-VEGF drug, but it is weaker and not used very often so we won't be discussing it much. Macugen's big claim to fame is that because it does not block all isoforms of VEGF, it may not have any of the systemic thromboembolic concerns that the other drugs have (to be discussed). Some doctors will therefore use it in patients that they perceive to be at risk for thromboembolic problems.*

*****In the same way that bevacizumab is used in place of ranibizumab, the drug ziv-aflibercept (Zaltrap) is the chemotherapeutic version of aflibercept. There has been some work looking at whether ziv-aflibercept can be used in the eye as a cheaper substitute, but it is too early to make any recommendations.[57] If it works well, it will be a great money saver.

Perhaps the sine qua non of anti-VEGF trials for diabetic macular edema is the Protocol I study by the DRCR.net.[24] Figure 7 shows the rather striking results, and if you are going to treat diabetic patients with these agents, you really need to take some time to study this trial—it was brilliant and it can serve as a nice template as you try to develop your own approach to the problem. Here is an overview of the whole thing.



	52 weeks	68 weeks	84 weeks	104 weeks
Sham+Prompt Laser, N	269	249	232	211
Ranibizumab+Prompt Laser, N	165	159	157	136
Ranibizumab+Deferred Laser, N	173	169	159	139
Triamcinolone+Prompt Laser, N	175	152	152	142

Figure 7: The results of DRCR.net Protocol I comparing laser alone to ranibizumab with prompt and deferred laser and also to triamcinolone with prompt laser.

The protocol randomized patients into 4 groups. The first received standard laser (with sham injections). The second received laser along with intravitreal triamcinolone, and the triamcinolone could be repeated every 16 weeks. The final two groups were treated initially with monthly ranibizumab using the approach discussed below; of note, one of these groups received prompt laser at the start of treatment, whereas the other group received laser almost 6 months after starting ranibizumab if there was persistent edema. This last bit will become important as we try to figure out the role of laser in treating these patients. You can quickly see from Figure 7 that the ranibizumab groups did quite well, the laser alone and the laser and triamcinolone groups not so much.

It is important to understand the approach used for determining the need for a ranibizumab injection. The protocol required monthly visits through the first year and it used something called the "4-2-7" rule. Patients were given a monthly injection of ranibizumab for four consecutive months regardless of the functional or anatomic status of the retina at each visit. Once the patient received four monthly doses, therapy was based on how the retinal thickness and vision compared to the previous visit. If the central subfield thickness dropped to less than 250 microns or the vision improved to 20/20 then no injection was required—these were called the "success criteria". Otherwise, patients received two more monthly injections on the fifth and sixth visits. For months seven through twelve, if the treatment resulted in the success criteria, then treatment was deferred. However, if the success criteria were not met and patients were showing continued improvement then another injection was given at each visit. "Continued improvement" was defined

by a five-letter (one EDTRS line) increase in vision or a 10% decrease in CSF thickening relative to the previous visit. If the findings stabilized—i.e., there was no study-defined continued improvement—then treatment could be deferred for that visit and injections were resumed if the retinal thickening returned or the vision deteriorated on subsequent visits.

During the second year of Protocol I, re-treatment once again continued as long as successive improvement occurred over each visit. However, once the eye either stabilized or reached success criteria, then the frequency of the visits could fall to every two months and then to every four months if the eye continued to do well. But if the vision decreased or the edema increased then the patient was treated and monthly followup was resumed. On average, patients required eight to nine injections in the first year and this decreased to two to three in the second year. However, patients in the DRCR.net had good hemoglobin A1c numbers (7.3 in the group finishing 3 years).[25] Your mileage may vary if you are dealing with a patient population that is less motivated. One also has to wonder about how much of the improvement—and the lower number of injections during the second year—was due to seeing patients on a monthly basis and beating them over the head about systemic control. (And having them realize, like Pavlov's dogs, that if they don't do their very best to take care of their diabetes someone in a white coat will stick a needle in their eye.) You need to remember about the excellent control of the patients in this study as you try to bring this approach to your real world—you may not get anywhere near the same results, and you are more likely to need other modalities to optimize your outcomes.

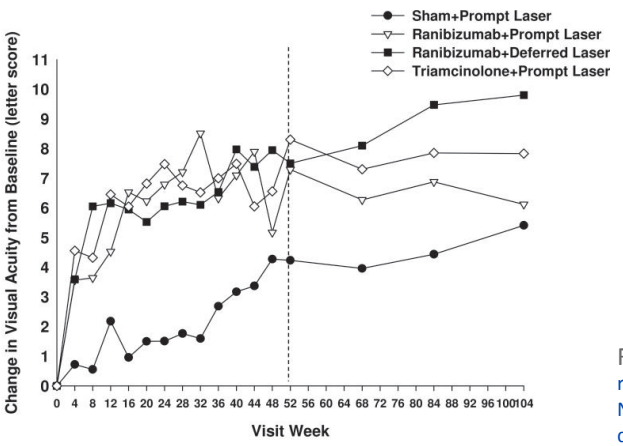
But getting back to the protocol, it is really important to get the concept of "continued improvement" down; it was very wise of the investigators to include this definition. In fact, in the DRCR studies, following the protocol injection frequency meant that after six injections monthly, you only treated edema if it was getting worse or getting much better with treatment – patients with edema and stable vision were just observed! It is easy to assume that when you are putting a $1400 medicine into an eye every month, the edema is going to go away. It often doesn't, and it is possible to beat a very expensive dead horse if you don't recognize this. In fact, if you look at the two-year data from this study, over 40% of the eyes in the ranibizumab groups still had a central subfield thickness of greater than 250 microns; they were still center-involved and still fairly boggy. And even at five years out, about one third of eyes still had edema.[26] You will find in some patients that no amount of continued intravitreal anti-VEGF drug will get rid of all of the edema. This is why the protocol included this out – you don't have to treat someone every month forever, you only have to treat them until you see things stabilize and then treat as needed if things worsen.

Now, this begs the question of whether you can get even better results if you add something else—and this is where the treatment of these patients turns into a mad scientist's laboratory with everyone having their favorite recipe (hence the serpentine nature of this chapter as it tries to cover all the different modalities). But understanding the DRCR.net Protocol I approach is a good platform upon which to build your particular anti-VEGF pyramid.

But yet another change in font color.

There are a couple of additional points to make based on the Protocol I results.

First, what about those steroids? The overall data shown in Figure 7 suggests that triamcinolone has an immediate effect similar to the anti-VEGF drugs, but that effect drops off and ultimately the drug doesn't work so well. But look at Figure 8—that shows the results with triamcinolone in patients that started out pseudophakic. That group did as well as the ranibizumab groups. This suggests that there is definitely a role for this drug, assuming that glaucoma is not a problem. It is also strange that this beneficial effect was not seen in phakic patients—and the lack of effect does not seem to be due to development of cataracts because patients were able to have visually significant cataracts removed (and many did—upwards of 70% by 2 years). It suggests that needing cataract surgery while treating DME may be more problematic in patients getting triamcinolone compared to using the drug in patients that have already had cataract surgery. This does not mean that triamcinolone should not be used in phakic patients—there may be patients who respond to nothing else. It simply means that, all things considered, triamcinolone may not be the best drug to start with in phakic patients. It is also a cautionary tale to remember when patients with diabetic retinopathy need cataract surgery; but we will save that for Chapter 25.



	52 weeks	68 weeks	84 weeks	104 weeks
Sham+Prompt Laser, N	78	75	73	78
Ranibizumab+Prompt Laser, N	41	41	41	41
Ranibizumab+Deferred Laser, N	40	40	40	40
Triamcinolone+Prompt Laser, N	46	43	42	47

Figure 8: DRCR.net Protocol I results in pseudophakic patients. Note how the triamcinolone group did much better—it is up there with the ranibizumab group. (Figures 7 and 8 used with permission, Archives of Ophthalmology)

The second, and really important, point is the difference between the group that had prompt laser when the anti-VEGF treatment was started and the group that had deferred laser (remember—"deferred" meant waiting almost 6 months after starting injections before doing laser for persistent edema). In this study it looks like patients with deferred laser did better, suggesting that laser should be postponed—or avoided—rather than jumping in and treating with laser immediately. It so happens that the deferred laser

group ended up needing a few more injections, and the investigators speculated that perhaps treating physicians were not as aggressive with the use of injections in patients that had received prompt laser (perhaps those investigators thought that the use of laser would decrease the need for injections, and with fewer injections patients did not do as well). Another explanation could be that doing prompt laser may have required more aggressive treatment that may have diminished vision over time—as we will see in Chapter 9, you need more power and can inadvertently create bigger burns when treating more swollen retina. Whatever the reason, it is important to understand that at least in this highly motivated group of patients there is good evidence to suggest that prompt laser is no better and possibly worse than waiting to do laser once the retina has been medically deturgessed.[25,26]

And Protocol I was not the only study that suggested that laser was either not useful or perhaps even deleterious. There are a host of company-sponsored studies--all beginning with the letter "R", strangely enough--that confirmed the DRCR.net results regarding the utility of ranibizumab for DME (READ, RISE, RIDE, RESOLVE, RESTORE). Each protocol was different, and none of them showed that laser alone or laser with ranibizumab provided better results than just injections alone, at least over the duration of the studies. There are also studies using bevacizumab showing the same thing, and all this raises questions about the utility of laser—so much so that at least one center has stopped using laser for DME.[27]

Wait. What?

Wasn't there a paragraph back there that said the opposite—that laser is really useful? Yep:

"There is also a sense that laser treatment is a good adjuvant to the injections; injections provide short-term control, whereas laser is for long-term control. In other words, you get the injections in to stabilize and protect the fovea and use laser to treat any leaks that are away from the center so that, over time, the overall leakage will decrease and the need for chronic injections will also decrease, along with all the attendant risks and costs."

How can that paragraph be reconciled with all the data from these trials suggesting laser is superfluous at best and maybe even deleterious?

To answer that, we have to take a brief trip to the Land of Abnormal Retinal Correspondence, where deeply held convictions are maintained in the face of, well, the data. There are several reasons why most retina specialists feel that laser has a definite role in spite of the results of these trials. A big reason gets back to the patient population—many patients simply don't have the inclination or wherewithal to take care of themselves like the patients in studies, and patients with poorer control seem to need more than just one type of treatment to treat their DME. You have to throw the book at them just to hold on to what they have.

A second reason comes from comparing the Protocol I results to the DRCR.net study that studied laser versus triamcinolone alone. Steroids alone did not do so well compared to laser, but steroids combined with prompt laser did much better in Protocol I, at least in pseudophakic patients (review Figures 4 and 8). Related to this is the consistent upward trend in vision for the groups in the other studies that had laser. Patients with laser tend to improve, but it takes a while (see Figure 4 again). The assumption is that over time the placement of careful laser will minimize the need for long-term injections, especially in patients with poor control. And as time goes by, it seems that more studies are suggesting this is actually the case.[28,29]

A third reason for embracing laser is based on the myriad ways that DME presents—there are some patients that have incredibly discrete leakage from microaneurysms that are away from the fovea, and treating those lesions will shut down the problem without the risk of injections. You just need to know when this approach is ideal, as well as to have skills to apply laser with minimal collateral damage. There are even newer laser techniques that use subthreshold treatments that don't seem to cause any damage, or that use highly accurate computer-guided treatment. These may be even safer and more effective than traditional laser, although definitive studies are pending (this will all be discussed in Chapter 6).

Finally, in many places around the world there are limited resources that make it impossible to follow the injection protocols perfectly—especially with the expensive drugs. In these situations, compromises have to be made and laser can be a low-budget vision saver. We will return to all this again at the end of the chapter.

Okay, okay. Full disclosure here. *There is another factor that has the potential to encourage the use of lasers: Depending on the nature of your healthcare system, doing lots of lasers can be very remunerative. As mentioned at other points in this book, it is hoped you are well above such concerns. Plus, it is likely that if laser allows one to spread out visits and injections, one might make less money in the long run with appropriate laser. Still, just like you would want to know about which company is paying for a given study, you should know that this particular gorilla lurks around discussions regarding the utility of laser for DME, and you should salt folks' opinions accordingly.*

Back to those anti-VEGF agents.

You can be aware of all the protocols for using ranibizumab and aflibercept, but the real question is whether or not your patient and/or your healthcare system can afford to use the drugs. If not, you will probably need to substitute bevacizumab. There are a host of studies suggesting that bevacizumab works rather well for DME, an example being the BOLT study, which compared bevacizumab alone to laser alone (the main injection interval in the BOLT study was 6 weeks compared to the 4 week interval used in ranibizumab studies). The bevacizumab group gained 9 letters at two years, which is similar to the ranibizumab results above (the laser group gained 2.5 letters).[30] So bevacizumab for DME is not exactly uncharted territory. And when it comes to treating age-related macular degeneration, the

Comparison of AMD Treatment Trials (CATT) demonstrated equivalence, at least between ranibizumab and bevacizumab. But that is a very different disease, and even in that study bevacizumab did not dry out the retina quite like ranibizumab, and no one has compared aflibercept to the other two in AMD.[31]

But the three drugs have been compared for treating DME—a study the DRCR.net just finished known as Protocol T.[32] The results of that study are summarized in Figure 9. Basically, aflibercept seems to be a bit stronger than the other two. But before you become the first on your block to destroy your healthcare system by using Eylea on every single diabetic, let's take a closer look.

The investigators looked at whether the initial visual acuity made a difference when choosing a drug, and it did. For patients whose vision was 20/40 or better, all three drugs worked about the same. But for patients with vision worse than 20/50, aflibercept was better on average. Plus, patients receiving aflibercept required fewer laser treatments.

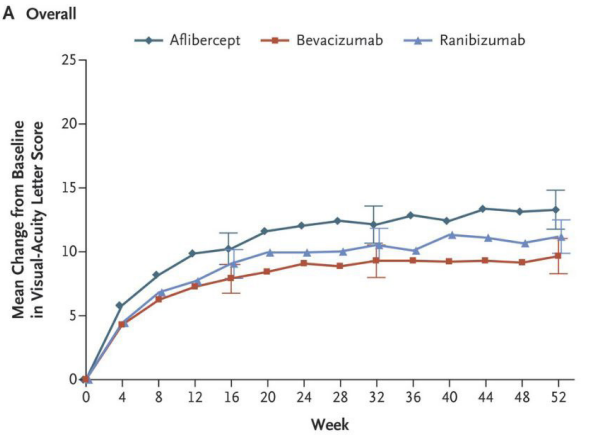


Figure 9a: The overall results for the Protocol T study showing that aflibercept is better, but not by a lot.

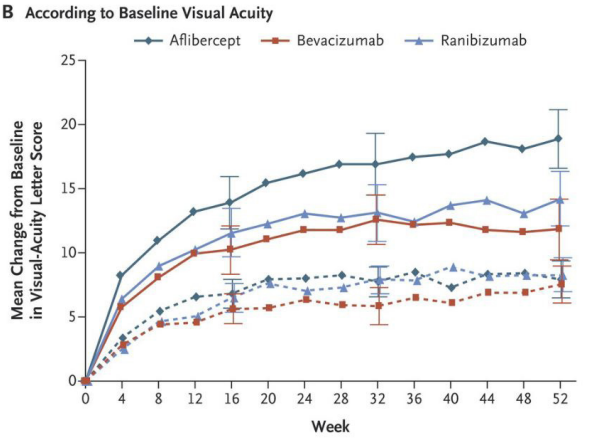


Figure 9b: When they looked at the results based on initial visual acuity, there was a bigger difference. The dashed lines show the results for patients with vision better or equal to 20/40. At that level of vision there was not any difference between the drugs. But the solid lines show the results for patients starting out with a vision of 20/50 or worse. For those patients, aflibercept is clearly better. (Both graphs used with permission from New England Journal of Medicine).

However, this does not mean that you are being a bad doctor if you don't start with aflibercept in every patient that is 20/50 or worse. First, remember that these are ETDRS visual acuities. There is no defined conversion factor between ETDRS visions and the acuities you get in your lane, but ETDRS visions tend to be at least a line or two better. So the efficacy of aflibercept may really kick in around 20/70-80 in the real world.

Also, in many places, those expensive drugs are simply not an option. And even if they are an option, patients may have huge copays with the pricier drugs. Most importantly, when you start treating patients you will learn that graphs can only show population averages; there are individual patients that do better with bevacizumab and there are also patients that just don't respond as well to aflibercept. Some patients actually need to use different drugs in rotation because of tachyphylaxis. And finally, the study didn't look at issues such as whether combination treatments including steroids and laser might change the results, or if patients with worse systemic control would respond differently (the average hemoglobin A1c in Protocol T was 7.7). As a result, it is not unreasonable to start with bevacizumab and see what happens. Of course, there are people that feel that it is profoundly wrong to do this, but until ranibizumab and aflibercept are available as a $25 generic injection, it is what it is.

In America, both Genentech and Regeneron (the manufacturers of ranibizumab and aflibercept, respectively) have patient access programs whereby they will provide the drug for patients who don't have the resources to pay for it. *They even have a copay assistance program so that patients making less than $100,000 a year may be able to get help covering the copay. (Basically, the companies make so much money off the drug that they developed a rather Byzantine set-up to help with the copay—they donate money to a separate charity that then sets aside money for the patient. This way the companies can still get most of the money from insurance when doctors give a dose.) All this can sometimes make ranibizumab and aflibercept even cheaper than bevacizumab, especially for indigent patients. It is a bit of a hassle for your staff, but it is well worth it to be able to have all options available for your patients. The policy in other countries varies on a geographic basis, and you may want to check with the regional representatives to see if any access programs are available.*

There are two big concerns, though. The first is that your bevacizumab will need to be compounded; and that adds some risk that patients need to know about (Chapter 11 talks about this more). The other problem is that doctors, governments and professional societies have wildly divergent views on the safety of bevacizumab. Unless you live in a cave, you know that the anti-VEGF drugs have potential systemic risks such as clots, strokes and heart attacks. Some people will be very dogmatic and insist that the only real data about how safe these drugs are comes from the controlled trials using the expensive anti-VEGF agents, and that it is wrong to use bevacizumab because the exact risk is not as well studied. Others don't think there is much difference, and don't distinguish between bevacizumab, ranibizumab or aflibercept as far as systemic risk.

Of course, the data about systemic safety is vague enough that you can find support for just about any opinion. For instance, one particular review suggests that bevacizumab has a greater systemic risk, but the company that makes ranibizumab paid for that paper.[33] Other population-based studies, and a Cochrane review, have not found a definite increased risk with either drug.[34-37] Yet another population study suggested that both bevacizumab and ranibizumab may slightly increase the risk of MI, but not stroke.[38] CATT suggested there was no big difference between the drugs, but the bevacizumab group did have more systemic problems that were not traditionally associated with bevacizumab—but the bevacizumab group was older and more likely to have problems anyway. Analyses of combined ranibizumab studies did suggest a possible association with strokes, which strongly suggests that there is at least a similar risk with bevacizumab.[39,40] And another study suggested that the risk might be greater with monthly ranibizumab compared to PRN dosing.[41] However, the Protocol T trial didn't find any definite safety concerns amongst the three.

Going deeper, bevacizumab does seem to affect plasma VEGF levels more than the other drugs, which is worrisome.[42] On the other hand, a recent editorial suggested that all the potential systemic issues—with all the drugs--may be spurious and are simply due to Type 1 statistical errors.[43] More recent studies concluded that there is probably some sort of small risk—especially in patients receiving monthly injections over a long period of time—and a large population study suggested the risk of a thrombotic event may be 1 in 127.[44,53,54] So there is likely a real risk, but you can almost pick your favorite results depending on your viewpoint.

However, the one thing everyone agrees on is that you can't ignore the issue.

Rather than becoming an epidemiologist, one thing to consider if you are going to give anti-VEGF drugs is to check with your regional experts regarding how they feel about these side effects. If they are really dogmatic about which drug to use, you might need to mirror their concerns because if your patients end up in their office for a second opinion you don't want your approach to be wildly different. They probably won't be so dogmatic, but their insights will still be valuable. And you for sure need to stay on top of the latest literature—if definitive studies ever do spell out the risk of one drug over another, you want to tell your patients before they read about it in the paper.

Then there is the question of whether you should use any of the meds in patients with known disease—for instance in patients with a history of stroke or cardiac disease (often an issue in diabetic patients). *Many of the studies using these meds in diabetes specifically excluded patients with a recent history of an MI or CVA, so it is hard to extrapolate the safety data to the kind of trainwreck patients you see in your clinic.[41] There is data from some of the anti-VEGF studies that suggests that such patients may be more at risk for problems with treatment. At this point, many texts will add something about how you should consult the patient's internist before administering anti-VEGF agents. This seems like a reasonable thing to do—until you realize that there is no internist in the world who can predict the real risk of intravitreal anti-VEGF agents for any patient. It would even be impressive if the average internist were really familiar with the use of anti-VEGF agents for retinopathy.*

This is one of those weenie things that we do as ophthalmologists in order to avoid any real responsibility. Basically, your level of "freaked-out-ness" over covering yourself will help you decide how far you want to pursue this—but you are ultimately the one doing the injection, and it is your job to stay on top of the data and the patient's systemic status in order to make the best decision you can. (Besides, getting some sort of vague clearance to do an injection is really only pretend protection. Plaintiff attorneys love it when doctors start blaming each other.)

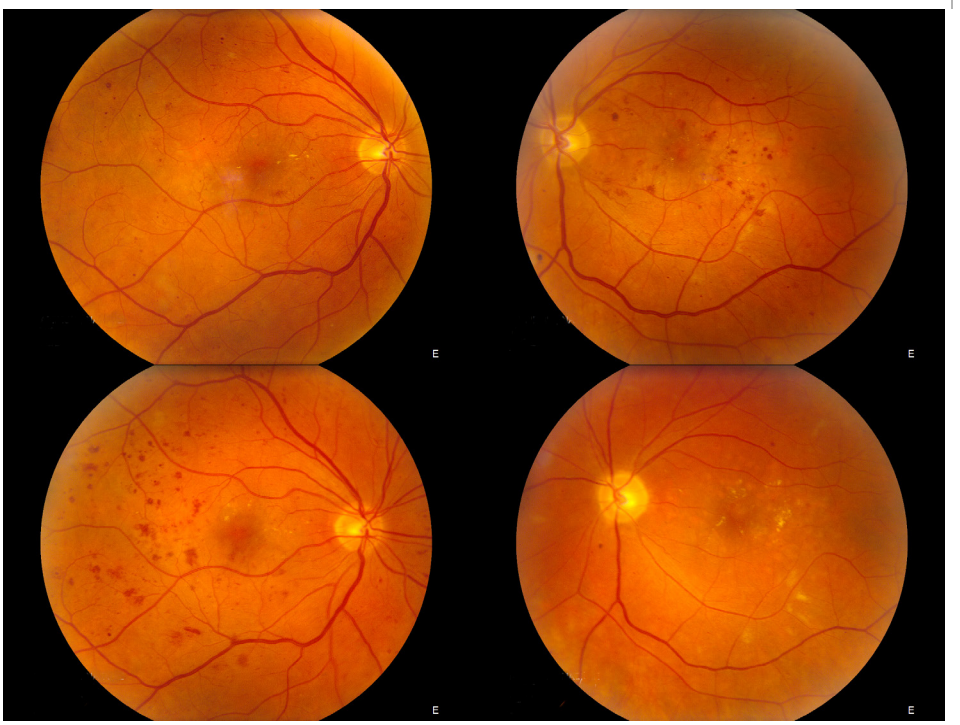
Sample the opinions of the experts in your area; you don't want to be an outlier. Most will acknowledge the risk, but will still treat. You do want to be sure you have gone over this clearly with the patient and their family members, and that the discussion is well documented and repeated. If the patient ever does have a stroke or heart attack (which is pretty much guaranteed in this patient population), you don't want anyone saying you didn't tell them. This is also a situation where occasional doctors will suggest using the older drug pegaptanib (Macugen), which is weaker than the other drugs but seems to be free of systemic risk issues. Or you may want to default to steroids like triamcinolone or Ozurdex, depending on the clinical situation.

It would be awesome if we could just tell you what to do in a few paragraphs—but no one really knows so you have to do your homework and come up with a plan on your own. Chapter 5 focuses on doing a consent in this situation and has additional suggestions.

While we are talking about the risk of systemic thrombotic events due to the anti-VEGF drugs, it is worth noting that there are cases of intraocular occlusive events occurring shortly after using these agents as well. Patients have developed artery and vein occlusions, capillary nonperfusion, anterior ischemic optic neuropathy and ocular ischemic syndrome. It is not clear if these problems are due to the drug itself (for instance, anti-VEGF agents are known to have a vasoconstrictive effect on the retinal vessels). Or it could be due to other problems such as the post-injection pressure rise, acute hypertension from patient stress, and/or underlying poor ocular perfusion that predisposes to vascular occlusion. These problems do seem to be more common in diabetics and patients with pre-existing vascular disease. Fortunately, events like this are rare, but be aware that this is yet one more thing that can go wrong.[57]

Having discussed some if the potential problems with the anti-VEGF drugs, it is good to know that most patients require far fewer treatments over the years. But the really amazing thing is that patients in the studies were less likely to progress to more advanced types of retinopathy such as severe nonproliferative disease or proliferative disease (this trend was also seen in studies using triamcinolone).[45] Anti-VEGF drugs are not just changing the ocular milieu on a temporary basis; instead they are having a more fundamental effect on the basic mechanisms of diabetic retinopathy—it reverses diabetic retinopathy with frequent use![46,47] The FDA recently approved both aflibercept and ranibizumab for reversing retinopathy in patients with diabetic macular edema. It is encouraging to think that the injections are actually helping to cure the disease. Figure 9 is an example.

Figure 10: (facing page) This patient needed fairly constant anti-VEGF injections in the left eye to control DME. The right eye needed far fewer injections. Note how over time the background retinopathy progressed in the bottom image of the untreated right eye—there is even subtle proliferative disease at the nerve. The eye requiring regular treatment looks much healthier over time.



By the way,* *Figure 10 *serves as a reminder for something else to keep in mind. If the DME goes away and the patient no longer needs anti-VEGF injections, you still need to watch them carefully. When the injections stop there may be a rebound-like effect and their background retinopathy may progress rapidly to proliferative disease, and the patient will have no symptoms until they start to hemorrhage. You want to catch that well before it starts—there will be more on this in Chapter 14.*

What if nothing is working?

You missed something. How is the patient's body—any blood pressure problems, renal failure, etc.? Are they on any drugs that can perpetuate edema (prostaglandin analogs, Actos—see Chapter 12)? Go back and look for other problems like uveitis, a vein occlusion or all the other stuff in Chapter 27. And double check for traction. But this is also where people start to try everything—add a topical non-steroidal, use laser, combine steroids and anti-VEGF drugs, see if any of the long-acting steroid devices are available and might help.

Also, don't give up quickly, especially with the anti-VEGF drugs. Some patients don't seem to respond to the first few injections, but if you are persistent they will slowly improve. And look at the graphs for both Protocols I and T (as well as any of the other anti-VEGF studies). Note that the vision improves a lot at first, but then continues to slowly improve over time. This is different from what happens in age-related macular degeneration (AMD), where the vision also improves at first, but tends to level off or even backslide over time. If you are used to treating AMD, you need to reset your expectations with DME and be willing to continue treating to push for the best possible vision. Depending on your healthcare system, you may be able to switch drugs—there are always patients that seem to do much better with a specific drug (remember the enhanced efficacy for aflibercept in patients with worse vision in Protocol T). And finally, have a low threshold for referral.

Retina folks actually like this stuff, and they might have something up their sleeve that you don't (like a vitrector).

And sometimes you just can't get rid of the edema—remember the Protocol I data that about a third of patients still had swelling even after 5 years of treatment.[26] There are patients where the edema is there forever, or where the damage is permanent and the vision doesn't get better even if you can eliminate all the swelling. Under those circumstances you may end up just treating the patient palliatively—simply giving them a shot of something whenever it looks like they are about get a lot worse. But a retinal specialist should really make this call—as mentioned above, patients who are stuck with chronic edema should be referred.

What about PRP for DME?

If you jump ahead to the proliferative disease chapters, it will become obvious that a lot of diabetics have very ischemic peripheral retinas due to capillary dropout. Because VEGF comes from the ischemic peripheral retina, and because VEGF causes vascular leakage, it is thought that by doing mild panretinal photocoagulation in peripheral ischemic retina, one can help control leakage in the macula. Some doctors will use wide-field fluorescein angiography to identify areas of peripheral non-perfusion and then treat those areas with laser.[48-50] In fact, such an approach is not new—it was suggested years ago.[51] As we shall see in subsequent chapters, one is always worried that panretinal treatment will exacerbate macular edema, so this thinking seems a bit counterintuitive. Plus, other experts feel that there is data from the ETDRS that suggests peripheral treatment is unlikely to be effective in this way. Keep an open mind about this, though. As more studies are done, it may be another technique that can be useful in patients with refractory disease--what we know "for sure" can change with time.

The End-of-Chapter Wrap-up.

If you are blowing off the rest of the chapter and just reading this section, you are really shortchanging yourself. We can't make you go back and read it all, but when you are visited by the Ghost of Christmas Future because you were a bad ophthalmologist, don't blame us.

So to review, first make sure you are actually treating diabetic edema and not one of the many things covered in Chapter 27. Second and third, beat on the patients to address their systemic control—that is the base of your therapeutic pyramid—and make sure that they don't have something else going on like renal failure, hypertension or pregnancy that is revving things up.

Then try to decide if there is any traction involved, and whether that traction is bad enough that a vitrectomy is warranted or if it is worth trying to treat the edema medically first. Then look at the areas of leakage. If it is peripheral to the fovea, and mild, you may not need to do anything—just watch it closely. If it is peripheral and worrisome (i.e., definite CSDME), your best bet is to do gentle laser and go back to the second and third steps above. If there is center-involving disease, you can still look at the areas of leakage. If you think that there are a few plump microaneurysms causing the trouble, and they are away from the fovea, you may still want to try laser. But if the leakage is more diffuse, or if there is a lot of central disease, you are going to need to go straight to injections (with or without laser depending on what the leakage looks like and where it is). If the patient is pseudophakic and does not have pressure problems, you may want to start with triamcinolone. If they are phakic, you will likely go with the anti-VEGF drugs, but your healthcare system and the patient's insurance company may be the ones that tell you which drug you will be using. Don't forget company sponsored access programs that may make it cheaper to use an expensive drug compared to having the patient pay for bevacizumab.

Also, if you are going in with anti-VEGF agents, remember the Protocol I results that suggested that it might be better to defer laser for a few months to see how things go—and then add laser if the disease is refractory. On the other hand, if there is a lot of disease and the patient has poor control, you may want to consider earlier laser because in these patients you may need to treat with everything you've got to stop their disease. As an aside, never forget about the potential utility of something simple like a topical nonsteroidal. They can be useful in some patients—and this can range from decreasing the number of injections to actually eliminating edema without the need for other treatments. Upcoming studies will better determine how these eye drops fit in.

One other thought on when to do the laser. *If you think laser is the right thing to add to a patient's treatment--but if the retina is really swollen--you might want to get rid of some of the swelling with injections first. It is a lot harder to laser through thick retina, and your spot is more likely to spread out, resulting in a larger scar. Chapter 9 will go into this in greater detail, but it is worth mentioning here.*

Mostly, remember to be flexible—you may need to combine treatments in difficult patients or switch back and forth between treatments depending on the disease or external issues such as insurance or problems with follow-up. For instance, some patients may need an occasional steroid shot to bolster the effect of chronic anti-VEGF therapy, or a little anti-VEGF can be added to extend the effectiveness of steroid shots. They may also need laser

touch-ups if new areas of eccentric leakage develop that don't merit the risk of intravitreal treatment.

Recognize that you are in uncharted territory as you do these things. So far there are no big studies that really define how to mix and match therapies, so keep up with the literature and check with your colleagues to make sure you are not missing anything.

And don't keep repeating ineffective treatments if you aren't making progress. Sometimes you can't get the swelling to go away no matter what you do. In that case, share the love and get a second opinion with a specialist—there may be something you missed or there may be a role for a vitrectomy (more on this in Chapter 19). But don't wait a long time to do that—if you are going nowhere, refer the patient somewhere before too much chronic damage occurs.

Finally, recognize that sometimes patients have refractory disease and that nothing is going to completely control the process. If neither you nor your local specialist can solve the problem, then consider backing off and simply using palliative treatment on a PRN basis to keep things from getting worse. Fortunately this doesn't happen too often, but it is good to know when to give up.

References

1. Friedman SM, Almukhtar TH, Baker CW, et al. Topical Nepafenec in Eyes with Noncentral Diabetic Macular Edema. *Retina*. Jan 19 2015.
2. Callanan D, Williams P. Topical nepafenac in the treatment of diabetic macular edema. *Clin Ophthalmol*. Dec 2008;2(4):689-692.
3. Hariprasad SM, Callanan D, Gainey S, He YG, Warren K. Cystoid and diabetic macular edema treated with nepafenac 0.1%. *J Ocul Pharmacol Ther.* Dec 2007;23(6):585-590.
4. Shimura M, Yasuda K. Topical bromfenac reduces the frequency of intravitreal bevacizumab in patients with branch retinal vein occlusion. *The British journal of ophthalmology.* Sep 2 2014.
5. Singh R, Alpern L, Jaffe GJ, et al. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy. *Clin Ophthalmol.* 2012;6:1259-1269.
6. Beck RW, Edwards AR, Aiello LP, et al. Three-year follow-up of a randomized trial comparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Archives of ophthalmology.* Mar 2009;127(3):245-251.
7. Jyothi S, Sivaprasad S. Five-year visual outcome following laser photocoagulation of diabetic macular oedema. *Eye (Lond).* Jul 2011;25(7):851-858; quiz 859.
8. Rubin B, Taglienti A, Rothman RF, Marcus CH, Serle JB. The effect of selective laser trabeculoplasty on intraocular pressure in patients with intravitreal steroid-induced elevated intraocular pressure. *Journal of glaucoma.* Jun-Jul 2008;17(4):287-292.
9. Law SK, Hosseini H, Saidi E, et al. Long-term outcomes of primary trabeculectomy in diabetic patients with primary open angle glaucoma. *The British journal of ophthalmology.* May 2013;97(5):561-566.
10. Smithen LM, Ober MD, Maranan L, Spaide RF. Intravitreal triamcinolone acetonide and intraocular pressure. *American journal of ophthalmology.* Nov 2004;138(5):740-743.
11. Jones R, 3rd, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. *Current opinion in ophthalmology.* Apr 2006;17(2):163-167.
12. Singer MA, Groth SL, Sponsel WE, et al. Association of OCT angle recess width with IOP response after intravitreal triamcinolone injection. *Retina.* Feb 2013;33(2):282-286.
13. Williams CP, Konstantopoulos A, Rowley SA, Luff AJ. Late intraocular pressure rise following intravitreal triamcinolone injection. *Clin Experiment Ophthalmol.* May-Jun 2007;35(4):385-386.

14. Agrawal S, Agrawal J, Agrawal TP. Vitrectomy as a treatment for elevated intraocular pressure following intravitreal injection of triamcinolone acetonide. *American journal of ophthalmology.* Oct 2004;138(4):679-680.
15. Chew E, Strauber S, Beck R, et al. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: a pilot study. *Ophthalmology.* Jun 2007;114(6):1190-1196.
16. Tunc M, Onder HI, Kaya M. Posterior sub-Tenon's capsule triamcinolone injection combined with focal laser photocoagulation for diabetic macular edema. *Ophthalmology.* Jun 2005;112(6):1086-1091.
17. Sato H, Naito T, Matsushita S, Takebayashi M, Shiota H. Efficacy of sub-Tenon's capsule injection of triamcinolone acetonide for refractory diabetic macular edema after vitrectomy. *The journal of medical investigation : JMI.* Aug 2008;55(3-4):279-282.
18. Lazic R, Lukic M, Boras I, et al. Treatment of anti-vascular endothelial growth factor-resistant diabetic macular edema with dexamethasone intravitreal implant. *Retina.* Apr 2014;34(4):719-724.
19. Comyn O, Lightman SL, Hykin PG. Corticosteroid intravitreal implants vs. ranibizumab for the treatment of vitreoretinal disease. *Current opinion in ophthalmology.* May 2013;24(3):248-254.
20. Cabrera M, Yeh S, Albini TA. Sustained-release corticosteroid options. *Journal of ophthalmology.* 2014;2014:164692.
21. Scaramuzzi M, Querques G, Spina C, Lattanzio R, Bandello F. Repeated Intravitreal Dexamethasone Implant (Ozurdex) for Diabetic Macular Edema. *Retina.* Jan 8 2015.
22. Cunha-Vaz J, Ashton P, Iezzi R, et al. Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. *Ophthalmology.* Oct 2014;121(10):1892-1903.
23. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal Aflibercept for Diabetic Macular Edema. *Ophthalmology.* Jul 8 2014.
24. Elman MJ, Bressler NM, Qin H, et al. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology.* Apr 2011;118(4):609-614.
25. Elman MJ, Qin H, Aiello LP, et al. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: three-year randomized trial results. *Ophthalmology.* Nov 2012;119(11):2312-2318.
26. Elman MJ, Ayala A, Bressler NM, et al. Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt versus Deferred Laser Treatment: 5-Year Randomized Trial Results. *Ophthalmology.* Oct 28 2014.
27. Jusufbegovic D, Mugavin MO, Schaal S. EVOLUTION OF CONTROLLING DIABETIC RETINOPATHY: Changing Trends in the Management of Diabetic Macular Edema at a Single Institution Over the Past Decade. *Retina.* Jan 14 2015.
28. Do DV, Nguyen QD, Khwaja AA, et al. Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment. *JAMA ophthalmology.* Feb 2013;131(2):139-145.
29. Solaiman KA, Diab MM, Dabour SA. Repeated intravitreal bevacizumab injection with and without macular grid photocoagulation for treatment of diffuse diabetic macular edema. *Retina.* Sep 2013;33(8):1623-1629.
30. Rajendram R, Fraser-Bell S, Kaines A, et al. A 2-year prospective randomized controlled trial of intravitreal bevacizumab or laser therapy (BOLT) in the management of diabetic macular edema: 24-month data: report 3. *Archives of ophthalmology.* Aug 2012;130(8):972-979.
31. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology.* Jul 2012;119(7):1388-1398.
32. The Diabetic Retinopathy Clinical Research N. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *The New England journal of medicine.* Feb 18 2015.
33. Kaiser PK, Cruess AF, Bogaert P, Khunti K, Kelly SP. Balancing risk in ophthalmic prescribing: assessing the safety of anti-VEGF therapies and the risks associated with unlicensed medicines. *Graefes Arch Clin Exp Ophthalmol.* Nov 2012;250(11):1563-1571.
34. Campbell RJ, Bell CM, Paterson JM, et al. Stroke rates after introduction of vascular endothelial growth factor inhibitors for macular degeneration: a time series analysis. *Ophthalmology.* Aug 2012;119(8):1604-1608.

35. Curtis LH, Hammill BG, Schulman KA, Cousins SW. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. *Archives of ophthalmology.* Oct 2010;128(10):1273-1279.
36. Moja L, Lucenteforte E, Kwag KH, et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. *The Cochrane database of systematic reviews.* Sep 15 2014;9:CD011230.
37. Ng WY, Tan GS, Ong PG, et al. Incidence of myocardial infarction, stroke and death in patients with age-related macular degeneration treated with intra-vitreal anti vascular endothelial growth factor therapy. *American journal of ophthalmology.* Dec 9 2014.
38. Kemp A, Preen DB, Morlet N, et al. Myocardial infarction after intravitreal vascular endothelial growth factor inhibitors: a whole population study. *Retina.* May 2013;33(5):920-927.
39. Bressler NM, Boyer DS, Williams DF, et al. Cerebrovascular accidents in patients treated for choroidal neovascularization with ranibizumab in randomized controlled trials. *Retina.* Oct 2012;32(9):1821-1828.
40. Ueta T, Noda Y, Toyama T, Yamaguchi T, Amano S. Systemic Vascular Safety of Ranibizumab for Age-related Macular Degeneration: Systematic Review and Meta-analysis of Randomized Trials. *Ophthalmology.* Jul 12 2014.
41. Yanagida Y, Ueta T. Systemic safety of ranibizumab for diabetic macular edema: meta-analysis of randomized trials. *Retina.* Apr 2014;34(4):629-635.
42. Zehetner C, Kirchmair R, Huber S, Kralinger MT, Kieselbach GF. Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab, ranibizumab and pegaptanib in patients with age-related macular degeneration, and in patients with diabetic macular oedema. *The British journal of ophthalmology.* Apr 2013;97(4):454-459.
43. Ahfat FG, Zaidi FH. Bevacizumab vs ranibizumab-an appraisal of the evidence from CATT and IVAN. *Eye (Lond).* Mar 2013;27(3):289-290.
44. Thulliez M, Angoulvant D, Le Lez ML, et al. Cardiovascular Events and Bleeding Risk Associated With Intravitreal Antivascular Endothelial Growth Factor Monoclonal Antibodies: Systematic Review and Meta-analysis. *JAMA ophthalmology.* Jul 24 2014.
45. Bressler SB, Qin H, Melia M, et al. Exploratory analysis of the effect of intravitreal ranibizumab or triamcinolone on worsening of diabetic retinopathy in a randomized clinical trial. *JAMA ophthalmology.* Aug 1 2013;131(8):1033-1040.
46. Campochiaro PA, Wykoff CC, Shapiro H, Rubio RG, Ehrlich JS. Neutralization of vascular endothelial growth factor slows progression of retinal nonperfusion in patients with diabetic macular edema. *Ophthalmology.* Sep 2014;121(9):1783-1789.
47. Ip MS, Domalpally A, Sun JK, Ehrlich JS. Long-term Effects of Therapy with Ranibizumab on Diabetic Retinopathy Severity and Baseline Risk Factors for Worsening Retinopathy. *Ophthalmology.* Feb 2015;122(2):367-374.
48. Takamura Y, Tomomatsu T, Matsumura T, et al. The effect of photocoagulation in ischemic areas to prevent recurrence of diabetic macular edema after intravitreal bevacizumab injection. *Investigative ophthalmology & visual science.* Aug 2014;55(8):4741-4746.
49. Patel RD, Messner LV, Teitelbaum B, Michel KA, Hariprasad SM. Characterization of ischemic index using ultra-widefield fluorescein angiography in patients with focal and diffuse recalcitrant diabetic macular edema. *American journal of ophthalmology.* Jun 2013;155(6):1038-1044 e1032.
50. Suner IJ, Peden MC, Hammer ME, Grizzard WS, Traynom J, Cousins SW. RaScaL: A Pilot Study to Assess the Efficacy, Durability, and Safety of a Single Intervention with Ranibizumab plus Peripheral Laser for Diabetic Macular Edema Associated with Peripheral Nonperfusion on Ultrawide-Field Fluorescein Angiography. *Ophthalmologica. Journal international d'ophtalmologie. International journal of ophthalmology. Zeitschrift fur Augenheilkunde.* Nov 26 2014.
51. Gardner TW, Eller AW, Friberg TR. Reduction of severe macular edema in eyes with poor vision after panretinal photocoagulation for proliferative diabetic retinopathy. *Graefes Arch Clin Exp Ophthalmol.* 1991;229(4):323-328
52. Aref AA, Scott IU, Oden NL, et al. Incidence, Risk Factors, and Timing of Elevated Intraocular Pressure After Intravitreal Triamcinolone Acetonide Injection for Macular Edema Secondary to Retinal Vein Occlusion: SCORE Study Report 15. JAMA ophthalmology. 2015;133(9):1022-1029.
53. Semeraro F, Russo A, Delcassi L, et al. Treatment of Exudative Age-Related Macular Degeneration with Ranibizumab Combined with Ketorolac Eyedrops or Photodynamic Therapy. Retina. 2015;35(8):1547-1554.
54. Avery RL, Gordon GM. Systemic Safety of Prolonged Monthly Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema: A Systematic Review and Meta-analysis. JAMA ophthalmology. 2015:1-9.

55. Schlenker MB, Thiruchelvam D, Redelmeier DA. Intravitreal Anti-Vascular Endothelial Growth Factor Treatment and the Risk of Thromboembolism. American journal of ophthalmology. 2015;160(3):569-580 e565.
56. Mansour AM, Al-Ghadban SI, Yunis MH, El-Sabban ME. Ziv-aflibercept in macular disease. The British journal of ophthalmology. 2015;99(8):1055-1059.
57. Mansour AM, Shahin M, Kofoed PK, et al. Insight into 144 patients with ocular vascular events during VEGF antagonist injections. Clin Ophthalmol. 2012;6:343-363.