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Online this Month

The Ophthalmologist @OphthoMag
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3:30 PM – 25 Aug 2015

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6:09 PM – 21 Aug 2015

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http://ow.ly/QZdYt
12:02 AM – 25 Aug 2015

The Ophthalmologist @OphthoMag
Did you know? The average age of contact lens wearers worldwide is 31 years old #factoftheday
12:45 PM – 29 Jul 2015

D’Amore Lab – Can Treat This!

Check out the award-winning music video by the D’Amore lab at Schepens Eye Research Institute, USA, on YouTube, which provides information on AMD set to song. We also interview Patricia D’Amore on page 50.
http://bit.ly/1NHQVoV

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8:36 PM – 24 Aug 2015
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50 Patricia D’Amore, Director, Howe Laboratory, Director of Research, Schepens Eye Research Institute.
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A recent study on the impact that the introduction of clinicaltrials.gov has made on the reporting of clinical trial results got me thinking (1). Clinicaltrials.gov was created thanks to a US law passed in 1997 that required all researchers (from the year 2000 onwards) to pre-specify the methods they were going to employ in the trial – and the outcomes they were going to measure.

Why did the US government mandate this? At the time, some companies were being accused of commissioning many small trials, but only reporting the ones with positive results – or cherry-picking data by switching out a trial’s primary endpoint evaluation post hoc to a secondary one that gave better results. But how much of this was hyperbole by the pharma industry’s critics?

It’s reasonable to assume that the impact of clinicaltrials.gov on the number of trials displaying positive results is a good marker of how fairly the pharmaceutical industry had been treated. According to the aforementioned study, the launch of clinicaltrials.gov fifteen years ago did have had a striking impact on the proportion of favorable trial results reported – but not in the way you might think. The study authors examined 55 large clinical trials of cardiovascular disease interventions published between 1970 and 2012. An impressive 57 percent of those studies performed before the year 2000 reported positive effects; after 2000, it dropped to just 8 percent. Pretty damning, until you realize that a US government body (the National Heart Lung, and Blood Institute) funded all 55 trials.

I suppose that raises two questions. First, has mandatory and open registration of clinical trials (and its associated scrutiny) halted a massive phenomenon of cherry-picking? Perhaps. Or second, has it stopped sloppy scientific methods that previously led to immense false positive bias? Possibly. But I believe it’s mostly down to the disappearance of low-hanging fruit as we neared the turn of the millennium. This was certainly the case for cardiovascular disease where, by 1970, the first β-blocker had only recently been discovered, and commercially available statins and angiotensin inhibitors were still over a decade away. The big wins were won well before 2000, and patients entering clinical trials by that date were better treated, making it harder for a new drug to beat standard of care.

However, I don’t think that the low-picking fruit argument applies to ophthalmology. We’re still in the new blockbuster phase for many drugs, and of course devices (like MIGS stents) are always going to be disruptive to pharmacotherapies. I therefore wonder if a similar analysis in ophthalmology might tell a different story?

Mark Hillen
Editor
Upfront

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We welcome suggestions on anything that’s impactful on ophthalmology; please email mark.hillen@texerepublishing.com

New Kid on the Block

Can amniotic stem cells suppress pathologic retinal neovascularization?

Stem cells are always a hot topic – they hold huge potential to treat many diseases of the eye, and famously, Holoclar (a stem cell-based treatment for moderate to severe limbal stem cell deficiency caused by burns) was the first therapy of this class to be approved in Europe. When it comes to the research and development of stem cell-based therapies, there are essentially four main stem cell types being used: embryonic, adult, induced pluripotent and human parthenogenetic. But now a fifth, amniotic mesenchymal stromal cells (AMSCs), is under investigation. AMSCs are derived from the amniotic membranes of the human placenta and, thanks to their unique immunological properties, may be particularly suited for treating retinal disease.

Researchers from CHA University in Seoul, Korea, have successfully evaluated the role of AMSCs in treating diseases like diabetic retinopathy, age-related macular degeneration, and retinopathy of prematurity (1). In vitro examination of AMSCs revealed that they express higher levels of the growth factor TGF-β1 than other mesenchymal stem cells. This factor is the key to the AMSCs’ ability to suppress endothelial cell proliferation, thus inhibiting neovascularization of the retina. It may seem counterintuitive that an inducer of angiogenic factors would inhibit neovascularization, but previous studies have revealed that, although TGF-β1 promotes endothelial cell proliferation at low concentrations, it has the opposite effect – inhibiting proliferation – at high concentrations.

After establishing their function in vitro, the next step was to test the behavior of AMSCs in vivo. The cells were injected intraperitoneally into mice with oxygen-induced retinopathy – and were not only able to migrate successfully to the injured tissue in the retina, but, once there, were able to suppress the pathological neovascularization that was present, and it appears that the TGF-β1 secreted by AMSCs was responsible for this antineovascular effect. Of course, this research is at an early, preclinical stage, but if AMSCs can replicate in humans their behavior in mice, this would appear to be a significant breakthrough that might help deliver on the huge potential of stem cells. MS

Reference

From Intestine to Eye

Gut microbes may be responsible for activating the T-cells that cause autoimmune uveitis

The link between intestinal microbial flora and autoimmune disease is well known, with multiple animal studies showing links between gut bacteria and arthritis (1), colitis (2) and nerve sheath demyelination (3). Now it turns out that uveitis can probably be added to that list (4).

R161H transgenic mice are a particularly good animal model for studying the disease processes that underpin uveitis; their possession of T-cells specifically engineered to react to the conserved retinal protein, interphotoreceptor retinoid-binding protein (IRBP), allow them to spontaneously develop autoimmune uveitis. Researchers at the National Eye Institute used the R161H mice to try to address a particularly puzzling question: if the proteins targeted by these modified T-cells in R161H mice exist only in the immune-privileged space of the eye, then how do the attacking T-cells become activated and cross the blood-retinal barrier?

The researchers examined the mice before they showed any signs of uveitic disease, and noted a greatly elevated expression of autoreactive T-cells in their intestines – and it turns out that those T-cells were capable of producing IL-17A, a well known pathogenic cytokine in autoimmune uveitis. Hypothesizing that bacteria in the gut might be involved in T-cell activation, they tried raising mice in a germ-free environment where they were unable to acquire normal intestinal microbiota. What they found was that although some signs of uveitis were present in those mice under these conditions, it was very mild in comparison to mice raised in a normal environment. When the mice were moved from a germ-free to a regular environment, they fulfilled their destiny to develop full-blown uveitis.

It’s not yet certain exactly how intestinal microbes prime T-cells to attack the eye, but the researchers suggest that the microbes may produce a molecule similar to IRBP. When the T-cells are exposed to this molecule, they begin seeking out and attacking it in other places – including in the retina (Figure 1). That theory was reinforced by another experiment the scientists conducted, exposing T-cells to a mixture of proteins extracted from gut bacteria. After intraperitoneally injecting those activated T-cells into normal mice not predisposed to uveitis, they developed a uveitic phenotype.

If this research can identify the bacterium, molecule or process that prompts T-cells to target the tissues of the eye, then perhaps one day we might have an effective and targeted therapy for ocular inflammation that could replace corticosteroids – and the collection of adverse events associated with chronic usage. MS

References
The Poor Man’s Aflibercept?

Like bevacizumab before it, ophthalmologists are trying off-label ziv-aflibercept (formulated for systemic use) in the eye. Masterstroke or madness?

Have you ever wondered why there are two international nonproprietary names (INNs) for one very well-known VEGF inhibitor? Regeneron designed and produced the recombinant fusion protein, aflibercept; they (with Bayer) went on to develop it for ophthalmic use (INN: aflibercept [Eylea]); and partnered with sanofi-aventis to develop it for use (in combination with other chemotherapeutic agents) in treating metastatic colorectal cancer. In this latter context, its INN is ziv-aflibercept (Zaltrap). The FDA’s reasoning was that INNs should vary if they have: “different marketing applications held by different manufacturers, different formulations [particularly osmolality, at ~250 mOsm vs. ~ 820 mOsm], different routes of administration [intravitreal vs. intravenous]; and are [each] manufactured at different sites” (1). Despite these differences, thrifty ophthalmologists have identified a potential way of saving money: use ziv-aflibercept in the eye.

The osmolarity differences could be a dealbreaker – hyperosmolar solutions injected intravitreally can result in retinal toxicity and even retinal detachment (2), but a study of ziv-aflibercept in rabbit eyes and human retinal cultured cells (ARPE-19) found no evidence of any toxic effect (3). The next (and very brave) step would be to test ziv-aflibercept in human eyes. One research team based at the American University of Beirut in Lebanon did exactly that (4): six consecutive patients (four with AMD, two with DME) received intravitreal injections of 0.05 mL ziv-aflibercept – meaning that they received just a 1.25 mg dose – if the patients had received regular, ophthalmic aflibercept the dose administered would have been 2 mg – but 1.25 mg is still within the concentration range where aflibercept has shown therapeutic efficacy in patients with AMD (5).

Despite the lower dose, all six patients experienced an increase in visual acuity after one week. Patients’ mean logMAR visual acuity improved from 1.40 at baseline to 0.86 at one week post-injection; mean central macular thickness had decreased from 482 μm at baseline to 345 μm after seven days. But ultimately this exercise was about the cost-savings associated with Zaltrap instead of Eylea – which the study authors estimated to be about 20 times lower – potentially making ziv-aflibercept cheaper than bevacizumab for ophthalmic use.

But back to reality – this was six patients, receiving one injection, with a one-week follow-up period. Administering intravitreal injections of ziv-aflibercept will continue to rest in the realms of the brave until considerably more data is available on its use. The study authors concluded: “It could also provide a second line of therapy in eyes with wet AMD or DME resistant to bevacizumab therapy in underprivileged countries”. MH/MS

References
First, Do No Harm

A new study concludes that most surgical procedures used to treat optic disc pits are of no benefit – and may even be harmful

Optic disc pits, rare congenital depressions or excavations of the optic nerve, are typically treated by surgery. The pits provide a passageway for vitreous humor to enter the subretinal space, causing retinal detachment and impacting patients’ vision. Because no medical therapies for optic disc pits exist, most surgeons perform a pars plana vitrectomy to allow the pits to close over, often combining the treatment with other procedures such as peeling of the inner limiting membrane (ILM). But is all this surgery really necessary? Researchers from the University of Alberta, Edmonton, Canada, say no.

“We went back and looked at the different surgeries that we can do to help solve this problem and what worked and what didn’t,” Jaspreet Rayat, an ophthalmology resident at Edmonton’s Royal Alexandra Hospital (1). “What we found is that a lot of surgical techniques that are commonly used are unnecessary and over the top. It’s like taking a baseball bat to a nail when a little hammer would do.” Rayat is lead author on the study which involved examining the surgical outcomes of 32 eyes of 32 patients with optic disc pits and serous macular detachments (2). The authors concluded that, while early intervention with vitrectomy and posterior vitreal detachment maximizes surgical success (with a foveal reattachment rate of 81.3 percent and visual acuity improvements of approximately five lines), additional procedures such as gas tamponade, ILM peeling or temporal endolaser showed no benefit.

Not only do the additional procedures offer no added value, but they may in fact be harmful to patients’ vision. Rayat said, “Some of those procedures, such as doing laser surgery, can actually cause damage to the vision that will never be recovered. In the case of injecting gas in the eye, it can create bubbles that can remain in your eye for weeks, decreasing your vision and preventing you from enjoying your life. So using a cautious approach in these cases is prudent.” He and his colleagues suggest that, when addressing optic disc pits, it’s best to start in as conservative a manner as possible and only implement additional procedures if they are necessary. As Rayat says, “You don’t have to throw the entire kitchen sink at the problem.”

References
Interleukin Forward to a Promising Future in AMD

A novel signaling pathway that leads to choroidal neovascularization has been identified – with obvious therapeutic potential

Macrophages are involved in many of the pathological processes that occur as people age. In diseases that involve angiogenesis (like wet AMD), it’s the M2 macrophage type (which is usually characterized as a tissue-repairing cell) that’s associated with this process, as it has the ability to promote angiogenesis (1). Previous studies have noted that both M2 macrophages and the level of a specific cytokine, interleukin-10 (IL-10), are elevated in aging eyes before macular degeneration leads to detectable vision loss – but until now, researchers haven’t known why.

Researchers at the laboratory of Rajendra Apte at the Washington University School of Medicine, St. Louis, USA may have the answer to that question (2). Their study reveals a particular pathway in senescent eyes, wherein IL-10 activates a signaling molecule known as STAT3 (Figure 1). The signal from STAT3 induces the alternative (macrophage) activation pathway, generating a particular M2 macrophage subtype that leads to pathological choroidal neovascularization. But the researchers didn’t stop there – after establishing IL-10 and STAT3 as key regulators of M2 macrophage presence in the eye, they investigated the possibility of targeting those molecules to reduce macrophage presence and neovascularization.

Mice treated with an antibody designed to block the IL-10 receptor showed a fivefold reduction in vascular proliferation compared with control mice, a finding echoed when the researchers examined mice with a genetic knockout of the receptor. Furthermore, macrophages from the transgenic mice showed nearly double the ability of those in normal mice to inhibit endothelial cell proliferation in cell culture, and also had a higher proportion of M1 macrophage markers, indicating that the macrophages in those mice were less M2-like – possibly due to the absence of IL-10/STAT3 signaling. To test the function of the STAT3 molecule, the researchers created a new “floxed” transgenic mouse whose myeloid cells (including macrophages) lack functional STAT3. That deficiency, like the IL-10 receptor knockout, inhibited the induction of M2 macrophage markers – so the researchers tried injecting the STAT3-deficient macrophages directly into the eye. Mice receiving those intravitreal injections displayed significantly less choroidal neovascularization than those receiving control macrophages.

Apte’s team went on to investigate the role of STAT3 in the pathogenesis of wet AMD in humans. Western blot analyses of human peripheral blood mononuclear cells (PBMCs) isolated from patients with AMD (and compared with PBMCs from non-AMD age-matched controls) revealed STAT3 expression was significantly greater in patients with AMD than those without, and immunohistochemistry showed that the molecule was associated with M2 macrophages in the choroidal neovascular membranes of patients with AMD. This research raises the hope that compounds that successfully target STAT3 in mice may one day yield a therapeutic option for humans with AMD.

References
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Imaging modalities like OCT, and AO-SLO have transformed our ability to stage and diagnose retinal disease. But in many respects it’s only showing you the pathologic structural changes that occur after the damage has been done. Take the example of diabetic retinopathy. By the time a patient begins to notice problems with their vision, they’ve lost a significant portion of it – and a hefty number of cells in the retina too. Much like age-related macular degeneration (AMD) and glaucoma, interventions at this point are almost palliative: current therapies try to slow the diseases progression, but they can’t replace what’s lost.

But what if you could detect disease processes before permanent damage has happened? At a point where early, disease-altering interventions – some as simple as lifestyle changes – could be made? Sound unrealistic? Apparently not. It seems there is a way - by using mitochondrial function as a marker of retinal health. As you’ll no doubt remember from high school, mitochondria are the organelles found in all eukaryotic cells that perform aerobic respiration to produce chemical energy in the form of adenosine triphosphate (ATP). They’re also involved in cell signaling, differentiation and apoptosis. And there’s a growing body of evidence that mitochondrial dysfunction can have big implications for retinal disease (1). In the axons and somata of retinal ganglion cells, the oxidative phosphorylation machinery within the mitochondria are impaired by reactive oxygen species (ROS), but the organelles themselves are suspected to be a major ROS source within the eye. This can result in a vicious cycle of oxidative stress accumulating over time, eventually leading to retinal ganglion cell (RGC) death, which is likely to be important in glaucoma and optic neuropathies. Oxidative stress is also a major factor affecting other retinal cells depending on the disease – for example, photoreceptors and retinal pigment epithelium in AMD. This metabolic deterioration is thought to play a part in diabetic retinopathy, glaucoma, AMD, and other retinal diseases (2), and mutations in mitochondrial DNA - both inherited and acquired - are implicated in a range of conditions, including Leber hereditary optic neuropathy (LHON) (3) and chronic progressive external ophthalmoplegia (4).
Now, a device has been developed that provides noninvasive mitochondrial imaging, giving insight into the metabolic function of retinal cells and flagging problems at a point before cell damage occurs. When the mitochondria malfunction, flavoproteins, which act as electron acceptors in the electron transport chain, are left in an electron-poor (oxidized) state (see Figure 1). By exposing the retina to blue light, the OcuMet Beacon can detect the green fluorescence they emit, which can then be quantified as an FPF (flavoprotein fluorescence) score (see “How Retinal Metabolic Analysis Works”).

The technique is still being validated, but initial studies have shown potential. For example, in diabetic patients versus age-matched controls, FPF levels were found to be significantly higher in patients with diabetes, including those with no visible retinopathy, implying that retinal metabolic stress is apparent before anatomical changes occur (see Figure 2) (5). In a small study of primary open angle glaucoma, again, FPF levels were found to be higher in glaucoma patients compared with controls, with greater variability between fellow eyes (6).

For glaucoma, the technique could offer a promising additional method for staging the disease, as IOP and optic nerve imaging can be fairly crude assessments – IOP doesn’t always correlate well with the extent of vision loss and once the optic nerve has become damaged, the disease has already progressed quite a bit. But the compelling uses are clearly screening – catch a disease and effect a sight-saving intervention before cellular damage occurs – and endpoint assessment in clinical and preclinical trials of therapeutic intervention.

What’s holding the Beacon back today is data. The correlation between FPF and subsequent damage to the retina or the optic nerve needs to be more completely characterized – and that’s something that’s only built over time. But normative databases exist already, and are continually being expanded, with every new datapoint contributing to a better understanding of the relationship between FPF, oxidative stress, normal aging, and disease status. However, it doesn’t take precognitive abilities to see that in a decade’s time, this technology might transform how patients are screened – and quite possibly the interventions too.
Richard Rosen, Professor of Ophthalmology at New York Eye and Ear Infirmary of Mount Sinai shares his experiences using the OcuMet Beacon for retinal metabolic analysis.

How did you get involved in the development of the Beacon?
I have been following its development for some time. I have a lot of experience studying prototype imaging devices and trying to identify useful parameters – for example I collaborated with Adrian Podoleanu and his team when developing the simultaneous OCT/SLO/ICG imaging system. At the same time, I'm primarily a clinician, so my main interest is getting these technologies into the clinic, to find out how I can use them to treat or monitor my patients. I had some mutual friends in the team that was working on the OcuMet Beacon, and I told them I was really interested. I'm now helping to gather data, but I'm not employed by them on a research or collaborative basis.

Why was it previously difficult to study?
The biggest problem was that many of the processes occurring in the mitochondria occur at fluorescence wavelengths that aren't readily accessible. Two-photon imaging has been explored, but as it currently stands, it's still far too phototoxic for clinical use. There was also the work done by Ralph Zuckerman, who used fluorescence anisotropy to look at changes in mitochondrial walls, but this never reached the clinic. With this device, you're looking at a very narrow bandwidth, so it's very targeted, and less harmful to the eye.

What have been your findings so far?
Flavoprotein fluorescence seems to give us a good indication of oxidative stress levels in the mitochondria, providing the potential for monitoring changes to cell metabolism that later result in structural changes to the eye. An indication that a drug or intervention is working, or improving overall tissue metabolism, before structural changes become apparent, would be fantastic. I think this truly could be the next big leap in diagnosing, monitoring and treating retinal disease.

As we are all aware, there are many spectacular new imaging devices out there, from the latest OCT instruments to adaptive optics. We've explored these extensively in our institute, and they're very helpful, but by and large, they simply can't give us this kind of early functional data. We need to explore this area further, in order to understand how these elevated levels of oxidative stress can be related to retinal health.

The technology is still in the relatively early stages, but we're finding that there's a huge interest in being able to monitor mitochondrial function, as it's becoming obvious from a lot of research that this dysfunction is likely to be central to many diseases.

What retinal diseases have you been focusing on?
We're both looking at normative changes, and some specific diseases, namely Leber hereditary optic neuropathy (LHON), diabetic macular edema (DME) and glaucoma.

LHON – a condition caused by mitochondrial DNA mutations – is one we’re very interested in. We have a cohort of patients we’re following in our neuroophthalmology group. Currently, there is no treatment for the disease. A number of pharmaceutical agents have been trialed, to try and bolster the electron transport mechanism in the mitochondria and thereby overcome the effects of the mutation, but these haven’t met with much success. However, there are a number of new agents currently being studied – for example, the group Stealth BioTherapeutics is doing some promising work in this area – and the effects of these therapies could be studied using retinal metabolic analysis.

In patients with diabetic eye disease, we want to observe the rate of change in oxidative stress, in terms of response to treatment. We've observed that patients treated with anti-VEGF agents for DME have also shown reduction in FPF levels. This suggests a possible re-normalization or improvement in function. But the correlation isn't perfect – it’s both challenging and incredibly interesting! Our next project in this area is to examine the effects of subthreshold laser treatments used to stimulate heat shock protein response – these are incredibly subtle treatments, which are not easily monitored, as they don't really cause structural changes.

Another exciting area is glaucoma. In a way, glaucoma is a particularly difficult disease, as current monitoring methods can only detect it very late in the process. You can look at the intraocular pressure (IOP) and watch to see how quickly the nerve disappears at a certain pressure, but we don't have any earlier indications. Interestingly, in one of our patients with high IOP, when we looked at mitochondrial dysfunction we found very high levels of FPF. When IOP was lowered to a more normal pressure, FPF levels also came down, close to what they would be for an age-matched control. Although we don't have a great normative database for glaucoma yet, we presented some of our preliminary research at ARVO 2015 (6). We have definitely showed that FPF levels are higher in glaucoma patients than in age-matched controls.
This information could potentially be used to ensure that patients are receiving optimal treatment. One of the issues glaucoma specialists face is that, although they may have a target pressure, it’s based on the nomogram of a large number of patients, and may not give the right target for individual patients. It’s hoped that in the future you could use retinal metabolic analysis as a means of monitoring – and minimizing – oxidative stress.

What are the challenges?
We need to distinguish age-related changes from the impact of a disease process, or the effect of a treatment or drug. Like any technology, it requires a lot of engineering and clinical experience to validate these things over time, because you’re dealing with very small signals, and there are a lot of sources of noise.

The physicist Ran Ziemer, who was involved in the development of a device called the retinal thickness analyzer, once said to me “the thing with any new technology is that you’re already caught in a bind – when it comes to what parameters you want to use, you only understand what you know already.”

And it’s true – the challenge with measuring a new parameter is figuring out where it fits in with the knowledge you already have, and what it adds.

How far is this technology from the clinic?
Well, right now we’re working with a laboratory model. As a reference database is built up, it’s going to be important in determining whether it will be possible to create a clinically viable device that isn’t prohibitively expensive. Right now, although the prototype is very promising, it’s detecting a very, very small signal, and requires a sensitive cooled EMCCD camera, which is not a cheap tool. Achieving this level of sensitivity in consumer electronics will take some work – but from what I’ve seen, I think the next generation will be a lot less costly.

The device will also need approval from regulatory agencies like the FDA, and we’ll need to wait and see what they’ll find acceptable in terms of reproducibility and consistency. I don’t have too much information on that side of things, but I do see good consistency in patients I’ve looked at, and I would guess that as more data is acquired, things will improve. It’s probably still a few years away, but I believe it’s getting there.

How can it help with disease management?
We’re very interested to see if we can spot earlier effects of drugs, rather than waiting for a structural change. That would be tremendous. I’m fortunate as a retina specialist that, if I treat patients with an anti-VEGF drug, I’ll generally get a quick and visible response. In glaucoma, you don’t get much of a
LUNCHTIME SYMPOSIUM
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Chair: SriniVas Sadda, MD (Doheny, UCLA USA)

SriniVas Sadda, MD – Doheny, UCLA USA
Retinal Imaging Hot Topics: Diabetic and Retinal Vein Occlusive Disease

Prof Paulo Stanga – Manchester Royal Eye Hospital, UK
Ultra-widefield Targeted Retinal Photocoagulation: A New Disease Treatment Paradigm

Tunde Peto, MD – Moorfield’s Hospital UK
Current and Emerging Strategies in diagnosis and treatment of Diabetic Retinopathy

Prithvi Mruthyunjaya, MD – Duke Eye Center USA
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Flavin fluorescence in human tissues is first reported.

1993
Measurements of NAD(P)H and flavoprotein fluorescence shows elevated levels in skeletal muscle fibers of patients with ophthalmoplegia.

Flavoprotein fluorescence studied in liver, skeletal muscle, kidney and brain tissue.

1997
Studies show flavoprotein is elevated in apoptosis-prone regions of ischemia-reperfusion injury in the brain.

2007
Fluorescence is used to view the mitochondria in detail in living corneal endothelial cells for the first time.

2008
Use of the OcuMet Beacon for measuring flavoprotein fluorescence and detecting ocular dysfunction is first described.

Non-invasive fluorescence anisotropy imaging for early detection of diabetic retinopathy is studied.

Association between increased retinal FPF and diabetes-induced retinal metabolic stress first reported.

2015
First study showing flavoprotein fluorescence increases in primary open angle glaucoma is presented at ARVO.

structural response after you’ve normalized IOP. Years ago it was shown that cupping actually improved in patients if you lowered pressure within a certain period of time. But by and large, this disease is relatively silent. If you had an additional index to monitor, you may be able to pick up very early changes, both during the disease process, and to see the effects of the pharmaceutical interventions you’re using. This type of monitoring could also offer a unique way to assess the effects of other interventions such as gene and stem cell therapies.

What about screening?
The potential is there. With many of the current imaging methods, as your demand for resolution increases, there are less patients you can screen — patients with significant cataract, or small pupils, or perhaps dry eye, become unsuitable candidates. We’ve been studying microvascular changes in diabetics with our adaptive optics system for years, and although you can see a lot, it’s not an ideal screening tool. Something like this is easily tolerated by most patients, it’s very fast, and it could give you an early signal that something’s wrong — by the time you’re observing anatomical changes, the problem has already been present for some time.

In particular, it could have a lot of utility in identifying “prediabetic” patients — we know there are patients who report that their vision is affected very early on, due to subtle lens changes. In patients with consistently high sugar levels, this will affect their levels of oxidative stress, and make it possible for the system to pick them up. So if we had a relatively inexpensive version of this device, it could be coming to the ophthalmologist’s office soon — but the goal would really be to get it into the hands of the hospital doctors, to identify disease as early as possible.

We have so many great imaging tools in ophthalmology, but I think, once it’s been developed and validated further, something like this could really bring ophthalmology to the masses, in terms of screening, and catching disease as early as possible.

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A Novel Avastin Injection Technique
Anti-VEGF agents have transformed how choroidal neovascularization is treated, but it does involve regular, often monthly, transscleral injections. Murad Sunalp and colleagues propose a different way of doing things.

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Beyond nutritional supplements, there’s no intervention that can be made that can affect the course of AMD – only in late diseases, when vision has been impaired. Three-nanosecond pulse laser therapy might change that…

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Analyzing the AMD Proteome
Proteomic analysis of the vitreous could help provide a better understanding of the pathophysiology of wet AMD at the molecular level, explains Michael Koss.
A Novel Avastin Injection Technique

Direct visualization delivery of bevacizumab in pseudophakic eyes for the treatment of subretinal neovascularization

By Murad Sunalp, Lindsey Buchbinder, Myhidin Shehu

The introduction of vascular endothelial growth factor (VEGF) inhibitors has revolutionized the treatment of many retinal disorders: wet age-related macular degeneration (AMD), diabetic macular edema (DME), and macular edema secondary to central or branch retinal vein occlusions. However, that treatment comes at a cost: monthly intravitreal injections by a retinal specialist for the rest of that patient’s life.

The standard approach involves injection of approximately 50 μL of drug (in this case, bevacizumab) solution via a needle inserted through the pre-anesthetized conjunctiva and sclera, placing the needle approximately 3.5–4.0 mm posterior to the limbus, while avoiding the horizontal meridian and aiming toward the center of the globe. The injection volume is delivered slowly and the needle removed slowly to ensure that all solution has been injected (see Figure 1). Complications are rare – but they tend to be serious, and include retinal detachment, retinal pigment epithelial laceration and retinal hemorrhage – among others.

To avoid some of the adverse complications associated with intravitreal drug delivery, we have developed a novel technique to deliver VEGF inhibitor therapy into the posterior chamber in pseudophakic eyes. Crucially, our method (see Box) avoids contact with the sclera or retina.

“This procedure can be safely performed by ophthalmologists who aren’t retinal specialists.
In Practice

By accessing the posterior chamber using the perilimbic route, we avoid injury to the sclera and the retina, although possibility of corneal endothelial damage remains. We have performed this procedure over 400 individuals and to date have had no cases of endophthalmitis and no retinal detachment. In addition, by following endothelial cell count we have observed no evidence of corneal endothelial damage.

VEGF inhibitors can be introduced into the pseudophakic eye safely using a perilimbic approach – and potentially even with phakic eyes too. This method avoids scleral and retinal injury, reduces the risk of endophthalmitis and central retinal vein occlusion, and can be safely performed by ophthalmologists who aren’t retinal specialists.

Murad Sunalp is President of Sunalp Laser Vision, Tulare, CA, USA. Lindsey Buchbinder is a medical student at St. George’s University, True Blue, Grenada. Myhidin Shehu is the Medical Director of Sunalp Laser Vision.

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The Perilimbic Intravitreal Injection Procedure

- After instilling a mydriatics agent (Mydriacyl 0.5%, Alcon, Dallas, TX, USA), the eyelids are scrubbed with 1% povidone iodine. A drop of povidone iodine is instilled into the eye, followed by a drop of the local anesthetic 0.5% tetracaine hydrochloride (Alcon Laboratories, Dallas, TX USA). The eye is draped with Tegaderm dressing (3M, St. Paul, MN, USA), a lid speculum is placed and the patient is placed supine under the operating microscope with light off.
- A Mastel ring light and fixation light are used to fixate the eye. Using an Alcon single use ophthalmic 15° angled knife, a 0.4 mm paracentesis is made at the limbus at 11 o’clock.
- A 30-gauge irrigating, 5 mm angled cannula, attached to a 1.0 ml syringe is fitted into the paracentesis incision and advanced through the limbus, over the iris, across the edge of the intraocular lens into the anterior vitreous in between the zonules – at this point it can be visualized within the posterior chamber.
- Next, 0.05 cc of bevacizumab is injected into the posterior chamber behind the IOL (Figure 1b), and the cannula is removed immediately so as not to chafe the iris.
- After delivery of the bevacizumab, the paracentesis site is hydrated and the fundus examined by indirect ophthalmoscopy to insure normal central artery perfusion.

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Figure 1. The standard (a) transscleral and our perilimbic (b) approaches to intravitreal anti-VEGF agent administration.
Taking the Heat out of Retinal Laser Therapy

There’s currently an unmet need for effective interventions in early-stage retinal degenerative diseases – before vision is lost. Can three-nanosecond pulse laser therapy meet that need?

By Wilson Heriot

Typically, laser-based treatment of retinal diseases uses conventional retinal laser photocoagulation with pulse durations of between 100 and 200 milliseconds, with an “endpoint” of tissue whitening. In the case of diabetic retinopathy, retinal laser photocoagulation has been considered standard of care for decades. The resulting lesions, however, routinely affect the retinal pigment epithelium (RPE) and the outer retina including the photoreceptors and the inner nuclear layer. These lesions cause permanent scarring which creates central visual scotomas, reducing patients’ visual function and adversely affecting color and night vision (1,2). Additionally, current retinal laser photocoagulation can be associated with glare and occasional pain.

Further, reports from the Diabetic Retinopathy Clinical Research Network (DRCR.net) have highlighted that treatment outcomes for macular edema are significantly worse with retinal laser photocoagulation alone, as compared with a combination treatment of photocoagulation and anti-VEGF therapy (3,4). The role of retinal photocoagulation in preventing disease progression in age-related macular degeneration (AMD) has also been limited, addressing the late “wet” stage of the disease only.

Despite the advent of various anti-VEGF therapies for patients with wet AMD, there are currently no treatments available to limit disease progression from the early stages of the disease. Consequently, patients with early AMD are recommended nutritional supplements, namely the formulation assessed in the Age-Related Eye Disease Study (AREDS), and advised to report to their physician promptly should their vision begin to deteriorate. Unsurprisingly, the search is on for a viable and effective solution for early-stage patients.

Compared with convention…

And this might be in the form of a non-thermal, three-nanosecond pulse retinal laser therapy, 2RT (Ellex, Adelaide, Australia). It has been labelled ‘Retinal Rejuvenation Therapy’ by the manufacturing company, which has high hopes for it to become the world’s first treatment for early AMD. Why is it different from conventional laser photocoagulation? The short green (532 nm) YAG laser pulse duration limits thermal spread outside the RPE and offers protection to the neural retina by removing the threat of thermal tissue damage, which is intrinsic to conventional laser treatment.

To put the three-nanosecond pulse of 2RT into perspective, we can compare its process and outcomes with those of conventional photocoagulation lasers. Conventional laser photocoagulation generates a thermal reaction because the laser energy is absorbed by the melanosomes in the pigment epithelium, heating the local region. This heat can be likened to the effects of poaching an egg, where the proteins are denatured instantly. On average, most clinicians set the power pulse duration at around 100 milliseconds when performing retinal photocoagulation. This timescale allows propagation of heat well beyond the pigment epithelium alone, potentially causing extensive damage to the surrounding retina, Bruch’s membrane and choroid. In contrast, the three-nanosecond pulse of 2RT, set at the therapeutic power range, localizes its injury insult to the RPE cells only, while causing no thermal damage to the underlying Bruch’s membrane and overlying photoreceptors (Figures 1 and 2) (5). With this approach it is possible to eliminate the thermal extension intrinsic to retinal photocoagulation while maintaining the efficacy of treatment with pinpoint accuracy. Essentially, it is a unique approach of lethally injuring a small, targeted monolayer: the RPE cells and allowing the adjacent RPE cells to subsequently recreate a normally functioning pigment epithelial layer. This triggering of a natural healing process is why it is called rejuvenation. It is comparable to skin rejuvenation, where cryotherapy causes damage to the more sensitive cells in the epidermis, while preserving the dermis. The epidermis is consequently repopulated from the surrounding dermis.

Essentially, 2RT involves the repopulation of new cells from the adjacent healthy cells. The treatment effect stimulates a natural process of cell turnover and tissue restoration without causing any more injury than is needed. The effect of the three-nanosecond laser pulse should therefore be a healthy and rejuvenated cell...
layer surrounded by undamaged cells and membrane layers, which all contribute to preserving patients’ visual function.

What I have found, when comparing the microperimetry assessments of patients with early AMD before and after 2RT treatment, is that 2RT treatment was associated with large improvements in contrast sensitivity. By comparison, contrast sensitivity outcomes following standard thermal photocoagulation are weaker, owing to the blind spot caused by the thermal injury and the subsequent lack of functional improvement.

The 2RT effect can be adjusted according to the individual patient’s requirements. This is particularly important because the RPE pigment density increases closer to the fovea, resulting in a more intense reaction. The macular degeneration prevention strategy assessed in the 2RT pilot study achieved the effect from treatment near the major vascular arcades (6), in contrast to the exposure of conventional thermal photocoagulation for drusen to reduce neovascularization, which was nearer to the fovea. During the mid-1980s, studies had shown conventional lasers to induce the regression of drusen, but there appeared to be a high incidence of choroidal neovascularization, causing this method of treatment to be abandoned (7). Subsequent reviews of those results suggest that the rate of choroidal neovascularization was in keeping with the natural history cohort so that there was no greater risk with the laser, but no reduction in the risk either (5).

From experience

How is it used in practice? Based on my experience, 2RT takes between five and 10 minutes to perform. Following a local anesthetic and contact lens insertion, the laser power levels are brought up to threshold as defined by a slight opalescence at the RPE level. In the 2RT multi-center, randomized, sham-controlled LEAD trial (8), the treatment has been limited to six spots above and below the fovea, near to the major arcades. With this method, the therapeutic endpoint is a sub-threshold effect. After the application, the treated area is observed closely and it is important to wait a minute or two to assess the effect. The slight whitening or opacification of the epithelium which occurs over a few minutes is very different to the instant whitening observed in standard continuous wave retinal photocoagulation. Once the threshold has been determined, the power level is reduced, and you cannot observe any physical changes. Then, it is simply a matter of making 12 rapid applications of the laser treatment: six along the superior vascular arcade and six near the inferior one.
For the early AMD protocol, the ideal patient is defined as having drusen greater than 125 µm and functional disability. However, the candidate’s visual acuity should be 6/12 or better, before a more severe onset of visual loss occurs. Finally, ideal patients should not have dense cataracts, due to the difficulty of achieving a therapeutic endpoint.

Evaluating the impact
Much of our understanding of the outcomes of 2RT therapy can be gleaned from the 12- and 24-month pilot study data published by Robyn Guymer and colleagues, in which the changes in drusen area of 50 patients treated with 2RT were compared against a natural history cohort (5). Their results showed drusen reductions at 12 and 24 months of 40 percent and 35 percent, respectively, compared with 11 percent in the natural history cohort. An improvement in flicker threshold within the central three degrees at the third postoperative month was also observed in the 12-month data set. Seven of the 11 eyes at greatest risk of progression (where the flicker defect was greater than 15 dB) improved to the high-risk category. Subsequent vast improvements in macular appearance and function were observed, which sustained themselves over 24 months. These findings provide circumstantial evidence that it is possible to delay the progression of AMD before it develops into its advanced “wet” form. Longer-term studies are required, however, to corroborate these observations. As part of a multicenter LEAD trial, we are now looking to evaluate the three-year outcomes, which will enable us to understand the longer-term effects of 2RT in the treatment of early AMD patients.

We have high hopes for a game-changer with this approach. Conventional AMD treatments, such as ongoing intraocular injections of anti-VEGF medications, address late-stage complications associated with AMD. In contrast, 2RT appears to offer the potential to apply treatment earlier in the disease process and to intervene at the level of the underlying pathology, preventing neovascularization and the progression to wet AMD.

Erica Fletcher and her colleagues at the University of Melbourne have demonstrated the effects of the three-nanosecond pulse 2RT in a mouse model (5), showing that the photoreceptors and retinal neurons are preserved and undamaged following 2RT. A healthy reaction is induced among the microglia, which sends down the pseudopodia to clear the debris, including the drusen-like material. Within an hour, the microglial changes that we can see are spectacular, demonstrating the efficacy of the healing response induced in the RPE. The process of improving hydraulic conductivity through the thinning of Bruch’s membrane is demonstrated over the entire retina rather than being confined to the lesion area on available animal models. Since a microglial reaction is induced, it is also upregulated in the fellow eye, so that drusen regression may also occur in the fellow untreated eye. The results show that while drusen was reduced in 44 percent of treated eyes, it was also reduced in 22 percent of untreated fellow eyes. Additionally, retinal structure was preserved over the treated area in comparison with the untreated area. It is important to note the widespread effect on the microglial activation and Bruch’s membrane structural changes despite the limited application areas.

These results have also been observed in human retina explants, where two enucleated eyes were examined following the application of 2RT at clinical and supra-threshold energy levels (5). Imaging which was conducted prior to and post collection of the enucleated eyes, demonstrated that there were enlarged RPE cells on the lesion boundary, with some cells extending into the lesion site. One month after treatment, enlarged RPE cells completely occupied the lesion site. In both cases, the application of 2RT had no effect on the structure of the retina. The endogenous retinal microglial processes extending through the outer nuclear layer towards the lesion site exhibited normal microglial responses in the retina.

In another context, 2RT has been shown to have a beneficial effect in reducing cystoid macula edema secondary to diabetic retinopathy. The treatment parameters are similar to those for early AMD, ideally with sub-threshold intensity, but these parameters are not as well defined at the moment. The potential advantage of 2RT is in the absence of photoreceptor damage or significant pigment epithelial destruction close to the fovea, where the fovea is an area that is not amenable to standard thermal laser treatment. Currently, anti-VEGF therapy is the only sight-preserving therapy available for perifoveal diabetic macula edema.
Delaying degeneration without photocoagulation

Naturally, AMD will continue to progress eventually, but this kind of rejuvenating treatment appears to delay the degeneration significantly. We still need to continue long-term studies to see the broader effects over time, but since we know that the treatment injures select, individual RPE cells while preserving surrounding cells and Bruch’s membrane, we can expect that the daughter cells will successfully slide in, being phenotypically and functionally normal. It is this sense of normality that sets 2RT apart from virtually every other form of retinal laser treatment, in my opinion, where the surrounding tissue is damaged by heat in the process. With 2RT we have a procedure that is minimally invasive, can be performed in-office within minutes, and with almost no risk of infection. It can therefore potentially revolutionize AMD management, particularly because it allows us to treat patients in the early stages of AMD rather than waiting until the disease has progressed into its “wet” form.

Wilson Heriot is a principal at Eye Surgery Associates, Melbourne, Australia, and chair of the Oceania Retina Association and board a member of the Macular Degeneration Foundation.

References
Analyzing the AMD Proteome

Looking at vitreous samples allows us to determine which proteins are involved in the disease process, and to what degree

By Michael Koss

To gain a better understanding of the pathophysiology of wet AMD, we analyzed the proteomes of 88 vitreous samples (73 from patients with AMD and 15 patients with idiopathic floaters serving as controls) (1). After vitreous sampling, we used mass spectrometry to detect, sequence and identify the proteins present.

Statistical analysis revealed 19 proteins (Figure 1) with significantly increased abundance in AMD. Most of these proteins are secreted, with functions that include biological transport, fatty acid binding, protease inhibition and processes involving hydrogen peroxide. They form part of a densely interconnected network that includes an immunoglobulin cluster (suggesting a role in inflammatory responses), and processes including cell adhesion, lipid metabolism, apoptosis prevention and regulation of proteolysis.

Michael Koss is currently the head of the retina unit of the Department of Ophthalmology at the oldest German university in Heidelberg.

Reference

Figure 1. Results of a comparison of the vitreous proteomes of patients with and without wet AMD. The area of each circle reflects the n-fold increase in vitreal protein abundance in patients with AMD relative to control patients.
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Benchmarking AMD

We present a clinical trials registry analysis: all clinical trials that involved AMD therapies or interventions present on clinicaltrials.gov. Who are the big players? Where is the focus? What proportion has been published? It’s all there…
AMD Clinical Trials

By Mark Hillen and Roisin McGuigan

AMD is the leading cause of blindness in developed countries, and the third-leading cause in developing countries. Globally, between 20 and 25 million people are affected by AMD, and the World Health Organization (WHO) estimates that eight million people have severe blindness as a direct result of the disease: it is projected that the number of people with some form of AMD will double between now and 2050 (1).

Tools to treat AMD are limited. Wet AMD is addressed reasonably effectively with anti-VEGF therapy, lasers and even low-voltage x-ray therapy, but it accounts for only 10 percent of all AMD cases. Very little can be done today to treat the 90 percent of patients with dry AMD, beyond a recommendation to take high doses of vitamin supplements and antioxidants (2).

The practical implications of the rise in AMD patient numbers are being felt everywhere. Retina clinics are massively oversubscribed, with specialists often working far longer than their allotted hours to get through the case loads, in part because intravitreal ranibizumab or aflibercept injections are time-consuming, and in many cases, need to be administered monthly.

Improved ways of treating wet AMD that involves fewer clinic visits are needed, whereas novel approaches for dry AMD are therefore a desperate requirement in the near future. To gain an insight into where research into therapies for AMD have been, and where they are going, we decided to analyze clinicaltrials.gov (Box).

We searched clinicaltrials.gov for: (“AMD” OR “age-related macular degeneration”), and exported the entire dataset as tab-separated values, for import into and analysis within Microsoft Excel 2013. Inappropriate records (mostly related to an oncology drug, plerixafor, which has the company name AMD3100) were removed, and the full text of each record examined for additional details to be recorded into the spreadsheet.

Top 10 Keywords

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AMD – The Modern Marathon
It is a long road to effective AMD therapies, and it’s a journey that requires toil and teamwork between clinicians and scientists to triumph.
AMD – The Modern Marathon

The path to truly effective AMD therapies is long and requires us to recognize that it’s not a single disease entity: toil and teamwork are needed to triumph

By Tiarnán Keenan

In Ancient Greece, life was indeed short in comparison with the enduring art of medicine. However, longevity presents new challenges. For many of us, life is now long – perhaps too long for our eyes. Owing to a combination of genetic and environmental factors, people now often outlive their maculae (Figure 1). Despite anti-VEGF drugs, age-related macular degeneration (AMD) remains the leading cause of blindness in developed countries. Indeed, our aging population means that many thousands of people will continue to lose their vision and independence unless we can develop new treatments that target the underlying disease processes in AMD.

Opportunity is fleeting
While the anti-VEGF era has seen a tremendous advance in our approach to AMD, the window of opportunity for initiating this therapy is very short. In some senses, anti-VEGF therapy is palliative medicine. We observe patients until they have the most advanced form of AMD before injecting an eye with drugs that fail to target the underlying disease process. Significant tissue damage and visual loss may have already taken place and, further, some patients respond poorly to these treatments. We still have no treatments in routine use for geographic atrophy, which is thought to affect over 8 million people worldwide. Ideally, future treatments should target the underlying disease process, preferably during early-stage AMD, and be personalized to patient genotype.

To make this a reality, we need a refined understanding of AMD pathogenesis, and specifically one that is predicated on our knowledge of its genetic basis. The progress in our grasp of AMD genetics has been a fantastic success story over the past decade. It is now 10 years since four papers reported a strong association between the Y402H polymorphism in the Complement Factor H (CFH) gene on chromosome 1; a second strong association with a locus in ARMS2/HTRA1 on chromosome 10 was demonstrated soon after. However, we have perhaps been slow to discover the precise biochemical mechanisms of disease related to each of these loci.

Following clinical training in ophthalmology and a PhD studying the biochemistry of aging changes in the human macula, I spent a year as a Fulbright Fight for Sight Scholar doing research at the Center for Translational Medicine in the Moran Eye Center (University of Utah). This work was with Gregory Hageman, who has been a pioneer in demonstrating that AMD may represent at least two partially distinct biological diseases: one driven by the complement system through risk at chromosome 1 (the CFH locus) and the other associated with risk at chromosome 10 (the ARMS2/HTRA1 locus). Many of our patients with AMD will have risk variants at both these loci but studying those individuals with risk at only one locus or the other has been pivotal in examining these subtypes of AMD in their purest forms. The main message is that patients with ‘pure 1 disease’ have a greater tendency towards formation of large drusen in the central macula and development of geographic atrophy, though they do also develop neovascular disease; patients with ‘pure 10 disease’, by contrast, exhibit relatively few macular drusen but are strongly predisposed towards neovascular disease, with a high incidence of retinal angiomatous proliferative (RAP) lesions (1).

Understanding AMD in this way has important implications. It helps explain some marked geographical differences in disease phenotypes and appearance, since chromosome 1 disease is more common in Caucasian populations and chromosome 10 disease more prevalent in Asian populations. It also means that we have two sets of biological pathways...
to unravel in order to understand AMD pathogenesis fully. Most importantly, it means that we will need at least two, genotype-dependent, sets of therapies for patients with AMD. In the interim, it certainly means that we need to select patients very carefully (on the basis of genotype as well as phenotype) for inclusion in clinical trials, depending on whether the drugs being evaluated target AMD related to chromosome 1 or chromosome 10.

Experience is perilous
The use of animal models in an attempt to replicate AMD has significant limitations and may mislead. In addition, the complement system is notoriously difficult to study in vitro. For a truer understanding of the disease, it is essential to study genetic and biochemical changes at the site of disease formation in the species of interest. I therefore feel that it is vital to use human ocular tissue in order to understand AMD pathogenesis. I have been lucky enough to work at the Moran Eye Center and the University of Manchester, both of which have superb access to large banks of human macular tissue. In fact, through the generosity of many donors (including those with AMD), Gregory Hageman has, over the past 20 years, been able to create a repository of over 7,000 pairs of human eyes – the largest collection anywhere in the world. Crucially, each pair of eyes has extensive accompanying information about the donor, including AMD genotype, medical history, and even retinal imaging carried out clinically over many years prior to death.

At the Moran Eye Center, under the auspices of Gregory Hageman, I was able to perform the first published study of pure chromosome 1-directed AMD using human macular tissue (2). We demonstrated conclusively that, even before clinical AMD develops, individuals with genetic risk at chromosome 1 have significantly higher levels of complement activation at the macular RPE-choroid interface. We also showed that cigarette smokers have significantly increased complement activation, oxidative stress and inflammation at the same site, compared to non-smokers of the same genotype (Figure 2). Clearly, the mixture of genetic predisposition and smoking is a potent combination that over decades can prove too toxic for the vulnerable human macula. This work provides a compelling rationale for complement inhibitors in reducing AMD progression, particularly for geographic atrophy. Most importantly, it shows that the best candidates for clinical trials of these drugs will be patients with chromosome 1 disease.

A second vital question to address is how exactly genetic risk at chromosome 1 leads to increased complement activation. Funded by Fight for Sight, I spent my PhD years at the University of Manchester examining this question, together with Paul Bishop, Anthony Day, and Simon Clark. In fact, we discovered a new potential disease mechanism for AMD (3). In Bruch’s membrane, CFH is required in order to prevent excessive complement activation, which leads to inflammatory damage. In the human macula, CFH relies on
particular sugar chains called heparan sulfate to bind to Bruch’s membrane. Using human macular tissue, we made two very important observations: first, that the risk variant of the \textit{CFH} protein binds poorly to heparan sulfate (4) and, second, that levels of heparan sulfate in human macular Bruch’s membrane decline very substantially with age (3). This has very significant implications and may help explain why AMD takes decades to develop. It means that chromosome 1-directed AMD develops through a double hit of genetic risk at \textit{CFH} together with age-related changes in the human macula, leading to excessive complement activation and a downwards spiral to inflammation, macular damage and visual loss.

A ‘big data’ approach

Over the past decade, I have also worked closely with the professor of public health at the University of Oxford, Michael Goldacre, at the institution’s Unit of Health-Care Epidemiology. Our approach has been to bring ‘big data’ to bear on important questions related to AMD. We have used routinely collected data – information collected on all patients treated in the English National Health Service – and have published multiple studies, most of which have been the largest and longest studies of their kind in AMD research. Importantly, we have used record linkage with these datasets in order to trace individuals through multiple diagnoses over long time periods – an extremely powerful tool for association studies.

For example, we analyzed an AMD cohort of 66,000 people over a decade to demonstrate that neovascular AMD and Alzheimer’s disease are not associated in the English population (5). Our biggest study group so far has been an English osteoarthritis cohort of over 2 million people. We followed these individuals for over a decade and found that people with arthritis have a modestly increased risk of neovascular AMD (6). These studies were
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conducted on individuals with AMD associated with any genotype; the next step would be to perform association studies on groups of AMD patients with pure genotypes to see whether distinct disease associations may emerge.

We have been interested to examine these and other common conditions of aging to look for potential associations, and ‘big data’ have been extremely helpful in providing clear answers. These answers have sometimes been surprising. Since AMD and Alzheimer’s disease share many pathological features, it has often been assumed that they are associated in populations. The general conclusion we draw from these studies is that degenerative diseases of aging such as AMD, glaucoma, Alzheimer’s disease and osteoarthritis often share disease mechanisms like inflammation and complement activation, but the underlying ways in which these pathways are triggered may be distinct and dependent on the specific genetic basis of each condition. It is essential that we look to the genetics of each disease in order to understand the biochemical pathways involved and to develop effective treatments. This is particularly true for AMD, where genetics play such a strong role.

How far have we come?

It is vital to realize that that the wide umbrella of the common and debilitating condition of AMD comprises at least two partially distinct entities. Each of these has its own clinical features, biochemical pathways and potential therapies. For chromosome 1 disease, we have now established direct links between the major epidemiological risk factors for AMD – age, genetics and smoking – specific molecular features in human macular tissue. This paves the way for trials of complement inhibitors and other therapies. For these trials to succeed, however, we must select the best candidates prospectively on the basis of patient genotype as well as phenotype. Looking to the future, once we have effective drugs for both chromosome 1 and 10 disease, we can use personalized medicine to provide treatments that target the underlying disease processes and at a much earlier stage.

The art of medicine endures. However, the fields of medicine and biological science have become increasingly specialized, with individual groups often pursuing clinical research, genetics or biochemistry in splendid isolation from the other disciplines. To make significant progress towards treating a disease, I feel that we must pursue these approaches in parallel. Perhaps the Greek model of a trireme is useful (Figure 3). As the dominant warships in Ancient Greece, these fast and agile vessels were powered by three rows of oarsmen working in unison to achieve impressive speeds and distances. Could clinical researchers, geneticists and biochemists work in unison like this, with discoveries in epidemiology and genetics used to power and direct biochemical work, creating new therapies to take back to the clinic? In this craft, there may even be a place for the clinician-scientist as κυβερνήτης (helmsman), προφήτης (bow look-out) and occasional rower.

Tiarnán Keenan, is a clinical ophthalmologist and research scientist based at the University of Manchester, UK, with a special interest in age-related macular degeneration and retinal disease.

References

Figure 3. A Trireme (τριήρης; “three rower”), the fastest and most agile ship in the ancient maritime civilizations of the Mediterranean – and perhaps a model for future AMD research, bringing together epidemiology, genetics and biochemistry for a common purpose.
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The Long and Winding Road to VEGF

Sitting Down With...
Patricia A. D’Amore, Director, Howe Laboratory; Director of Research, Schepens EyeResearch Institute, and Charles L. Schepens Professor of Ophthalmology, Harvard Medical School, Massachusetts, USA.
How did you get into angiogenesis?
In the 1970s I was a student at a liberal arts college that was so small there was no research being conducted there. I was lucky and got a small summer fellowship studying hematology, looking at patients who had platelet defects. My supervisor pointed out to me that these people had vascular defects that were not obviously explained by the absence of platelets so I became interested in how the platelets might be “nourishing” or supporting the endothelial cells.

When I went to graduate school, I chose to study blood vessels, and then I did a post-doc at Johns Hopkins working on tumor angiogenesis. There, I was introduced to ophthalmology, and I realized how important angiogenesis was in the eye. So my path, although long and winding, was a fortuitous one.

You’ve been involved in the field for over 30 years – how has it changed?
The biggest changes that have moved the field forward are the technical ones. When I started, there was really no molecular biology, no restriction enzymes, no gene cloning. If you wanted to find a growth factor, you had to purify it from the tissue, and that was challenging! The introduction of restriction enzymes, gene cloning, and the ability to create gene knockout animals let us not only identify specific molecules, but to figure out their role in angiogenesis – these were huge steps.

Before that, the field was very descriptive – we didn’t have any molecules to blame, or even study!

The single biggest breakthrough is probably the identification of VEGF. People in the field spent a long time looking for an angiogenic factor that might be involved in pathology, so when VEGF was first identified in the late 1980s, and people began studying it, it became obvious that it was going to be important.

What’s your current research focus?
We’re looking at a few things beyond VEGF – the most relevant for ophthalmology is our work on dry AMD. There’s a lot of evidence that inflammation is involved, and reasonable evidence that lipids are involved. One major focus of my lab is understanding if lipids are involved in the pathogenesis of dry AMD, and if so, how?

“The biggest changes that have moved the field forward are the technical ones.”

How do you find a work-life balance?
Now that I am the director of research at Schepens and director of the Howe Lab at Mass. Eye and Ear, my lab is smaller than it was – in the old days my average lab size might have been eight or more, now it’s closer to four or five. That’s saved a lot of time, in terms of managing people, and writing grants to support them. Some people I’ve mentored previously have labs of their own, we share lab space, and our people collaborate. It’s great to have that internal support, and it means I can afford take on these other roles.

As for managing my time, I just do the best I can, and I try not to spend my time at work doing things that could be done elsewhere. I’m a very good multi-tasker – when you’re a mother and scientist you have to learn that quickly. Finally, I prioritize; I try to say no. I turn tasks over to people in my lab – they get good experience, and I don’t take on something I have no time for.

What is your management style?
I like the people in my lab to be independent. We’ll meet every few weeks and I’ll support them, but I’m not controlling. As director of research, I like consensus and compromise. I like solutions. I’m learning to go into meetings without a definite opinion on how I want things to go – I want to hear all the sides of the story and find a solution that suits everyone.

Describe a typical day
I probably have more of an average week. I’ll usually have a few meetings with other senior people – such as Joan Miller, who is chief of ophthalmology – as well as others in leadership during a week. I’ll attend some seminars. I’m involved in the medical school, so I’m probably over there once or twice a week to meet students and attend committee meetings. There’s some troubleshooting, dealing personnel issues, providing career advice, talking to faculty on strategy and finding funding. A lot of meetings, seminars, and talking.

What advice would you give Patricia D’Amore 20 years ago?
In terms of my career, I’m pretty happy with my progress. I don’t think there’s a lot I would change – I would definitely take a few more courses, especially on organization and management. I don’t think I’m bad at it, but as scientists, we are poorly prepared for management through education and training. I would probably spend some more time on myself, too, and set myself a personal policy to take more time off, as I don’t usually take a lot of vacations.
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References:

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Aflibercept in Europe: Setting New Standards in Retinal Disease Care

Strength and durability in the real world

Highlights from Bayer HealthCare’s Satellite Symposium ‘Aflibercept in Europe: Setting new standards in retinal disease care,’ held on June 7, 2015, at the European Society of Ophthalmology Congress, Vienna, Austria

This supplement is a write-up of a promotional meeting organized and funded by Bayer HealthCare. The speakers were paid honoraria toward this meeting. Bayer HealthCare checked the content for factual accuracy, to ensure it is fair and balanced, and that it complies with the ABPI Code of Practice. The views and opinions of the speakers are not necessarily those of Bayer HealthCare or the publisher. No part of this publication may be reproduced in any form without the permission of the publisher.

Prescribing information can be found on the back cover
Real World Data in Wet AMD: The National Aflibercept Audit

James Talks, Medical Retina Service, Royal Victoria Infirmary, Newcastle upon Tyne, UK

Since their introduction, anti-vascular endothelial growth factor (VEGF) drugs have transformed patients’ visual outcomes in diseases like wet age-related macular degeneration (AMD), branch or central retinal vein occlusion (BRVO and CRVO), and diabetic macular edema (DME). They’re also expensive, and that’s why you want real-world data that shows that the drug you’re using in your clinic works in your patients.

Several published real-world datasets exist, and all show that anti-VEGF therapy provides useful benefits, irrespective of the drug used. But real-world datasets have highlighted a disparity between the outcomes of clinical trials – where the best outcomes came from continuous treatment – and the real world. Many audits have shown that vision gains achieved in the clinic fail to live up to the trial results, as shown in a case with ranibizumab (1–3). Why? It seems clear to me that under-treatment is the main issue in real-world practice.

Across the UK (with some exceptions) we have largely followed a pro re nata (PRN) ranibizumab regimen (4). In Newcastle, we tried to review patients every four weeks, and treat them according to optical coherence tomography (OCT) findings. This is often a challenge, partly due to National Health Service (NHS) capacity issues, and the fact that many patients struggle to adhere to that schedule. So when the results from the aflibercept VIEW studies came out, which reported that you could get good visual outcomes when administering a 2 mg dose of aflibercept every eight weeks (2q8) – after three initial monthly injections (5,6) – several centers decided to implement this pathway. We hoped that such a regime would improve our outcomes, as we would be better able to provide the required appointments at the correct time intervals, less monitoring would be required, and patients should find it easier to attend. We have audited our own results and have then rolled this audit out to 16 centers in the UK. The data has been extracted from an electronic medical record that all centers used. So far multi center data is available for patients with one-year follow up and some second year data from our center. Overall, the audit showed that treatment-naïve patients experienced a mean increase of 5.4 letters from baseline; the proportion of eyes with >70 letters rose from 17.2 percent at baseline, to 35.7 percent after one year (Figure 1), and patients received a mean of seven injections over that period. This is very similar to the Newcastle data, but here there were 4,355 eyes at baseline, and 790 eyes after a year. Therefore, the baselines and outcomes are similar even with this much larger patient population, reinforcing and confirming the real-world efficacy of aflibercept.

In reality, a five-letter improvement in a single patient isn’t much of a gain and is within the margins of a test error, but for a large national audit group, it is more meaningful. You could argue that the primary aim of anti-VEGF treatment should therefore not be vision gain, but treating as many people as early as possible, to maintain their vision for as long as possible. As these data also show, regardless of the vision gain, on-label, bimonthly treatment does seem to maintain patients’ vision in the first year and to a similar extent in the second year. In terms of improvement in patients’ VA, about 50 percent gained ≥5 letters, and 25 percent gained ≥20 letters.

Figure 1. Percentage of eyes achieving over 70 letters in the UK National Aflibercept Audit.
letters from baseline, and about 35 percent gained >70 letters from baseline.

The multicenter dataset does contain some data on switch patients (3,181 eyes to begin with, and by 14 months, 1,021 eyes with a mean gain of 1.2 letters). These people had prior treatment for a number of years with different anti-VEGF drugs before changing to aflibercept therapy. The data show a slight VA decline in the year before switching and stabilization. It is not possible at this stage to say whether there is an improvement, but the data suggest that the decline is either slowed or arrested, consistent with most published reports on switching patients from other anti-VEGF agents to aflibercept (8–10).

So far we have looked at the first year of treatment, but what happens in the second year? Figure 2 is the proposed algorithm for the treatment of wet AMD with aflibercept after year one from the UK wAMD National Consensus Meeting.

This model recommends that in year two of treatment, patients can continue with aflibercept injections every two months, and our data show that this is effective. The model also suggests monitoring patients in the first year — but not at every visit — as it will provide information to help guide treatment in the second year. So, if patients still show signs of disease activity, you might consider continuing bimonthly injections, but if the retina is dry with infrequent activity, you might consider treat-and-extend. This helps address the issue of capacity, because it is difficult, if not impossible, to assess every patient at every visit. Ideally, at the end of the year we treat those with dry maculae, and extend their appointments by another couple of weeks, continuing this approach for as long as they remain dry. In some cases we stop treatment and observe if they have been stable and dry for some time.

In conclusion, the UK treatment registry data show that the on-label regimen: three monthly injections followed by bimonthly for a year produces useful VA improvements — and greater VA improvements than those achieved with other anti-VEGF agents in the real world (2,11). With switch patients, dramatic improvements are unlikely, but stabilization is certainly possible. Finally, I think this regimen allows us to at least make some effort toward managing capacity issues, which are a serious problem in many countries, not just in the UK.

Case Study: Royal Victoria Infirmary, Newcastle, UK

The Newcastle dataset contains one-year data on 200 eyes (188 patients) and two-year data on 76 patients receiving on-label aflibercept therapy.

Mean baseline visual acuity (VA) was 56.5 ETDRS letters (greater than the VIEW trials’ baseline of 53.6 letters [5]).

Our mean vision gain was 5.5 from baseline, which was slightly lower than the VIEW studies’ 8.4 [5], but of course, our baseline VA was higher.

In any event, the outcomes were identical by the end of the 12-month period, at 62.0 letters.

The percentage of patients with VA >70 letters was 41.5 percent (compared with 32.6 percent across the VIEW trials [5]), and the vast majority of patients maintained their VA, with 97.5 percent of Newcastle patients losing <15 letters from baseline, compared with 95.3 percent in the VIEW trials — very encouraging.

We maintained roughly the same visual improvement into the second year (mean VA at the end of year 2 was 61.8 letters), requiring a mean of 12 injections over the 2-year period, and the proportions of patients at the end of the second year of treatment with VA of ≥70, 55–69, 35–54, or <35 ETDRS letters were 38.3, 30.0, 26.7 and 5.0 percent, respectively.
Practical Benefits in Treatment Management

Sebastian Wolf, Department of Ophthalmology, Bern University Hospital, Bern, Switzerland

As ophthalmologists, we are all aware of the challenges of managing our patients’ anti-VEGF treatment regimens – irrespective of the approach we decide to use – in order to achieve the best possible patient outcomes. One thing is very clear to me: the advent of anti-VEGF drugs (aflibercept, ranibizumab and bevacizumab) has revolutionized the treatment of wet AMD, improving patient outcomes significantly.

Figure 3 charts data from a population-based, observational, Danish patient registry-based study that began in 2000 (12). The chart shows that there was a slow trend towards the reduction of the incidence of AMD-caused blindness between 2000 and 2006. This was then followed by a dramatic drop in incidence rates due to one thing: the introduction of anti-VEGF therapy. I have been fortunate enough to see 2014 data, which continues the downward trend.

When deciding between the various treatment regimens for AMD, we have several possibilities, including:

- a proactive, fixed dosing approach (monthly or bimonthly as per clinical trial data), and
- a reactive, flexible/PRN approach

Fixed proactive regimen

In my opinion, the VIEW studies (5) demonstrated that a fixed treatment regimen with bimonthly injections of aflibercept (after an initial period of three monthly injections) works well – patients experienced a significant visual gain in the first year of treatment. No other approach has shown better outcomes and this one is very straightforward, as monitoring may be necessary only every 3–6 months.

Fixed treatment does have disadvantages, as there is an increased risk of over- or under-treatment – an injection every three months may be too little, whereas monthly dosing might be too much and is also unpopular with both patients and doctors. Nevertheless, our own experience with monthly or bimonthly aflibercept dosing shows that it works; our clinic managed a treatment-naïve patient using this approach over a one-year period. From baseline to nine months, OCT imaging showed that the patient’s retina changed from having significant subretinal fluid at baseline to a normal-looking retinal anatomy, and VA improved from 68 to 80 letters.

Flexible PRN

In the VIEW studies, (5,6,13) treatment was fixed for the first year before changing to a flexible PRN regimen (modified quarterly dosing) with aflibercept. The results demonstrate that VA was relatively stable in the first year, but over the next two years there was gradual loss of 3.5 letters (13). This loss could be relevant for some patients, but let’s remember that they had fewer injections, so it’s a trade-off.

So, PRN regimens are both flexible and individualized, and there’s no likelihood of over-treating the disease. The main drawback is the significant risk of under-treatment, as demonstrated by the Bayer-sponsored AURA study (1) – a retrospective analysis of PRN treatments in Europe – which showed that most patients who lose their vision do so because of under-treatment. Another drawback is that the patient

Regimen Pros and Cons

Fixed Proactive

Regimen Advantages
- Best outcome
- Straightforward logistics
- Minimum monitoring
- No need for a specialist to administer the injections or monitor the patient

Disadvantages
- Risk of over- or under-treatment

Flexible PRN

Advantages
- Individualized treatment regime
- No over-treatment

Disadvantages
- Lots of clinic visits needed
- Complicated logistics
- Every visit, expert opinion necessary
- Risk of under-treatment
- Variable outcome

Treat-and-extend

Advantages
- Individualized treatment regime
- Certainty – treatment every visit
- Fewer clinic visits

Disadvantages
- Lack of data from large randomized controlled trials
- Risk of over-treatment
must see the ophthalmologist every month for assessment to decide whether an injection is necessary, complicating matters for the patient and the clinic staff.

Treat-and-extend
Per aflibercept’s approved posology (13), from the second year onwards, we can individualize treatment for patients according to their disease activity, and by doing so, we minimize the number of hospital visits required. This can mean a lot to patients and save their families and carers – many of whom transport patients to and from the clinic and care for them after the procedure – time, money, and schedule disruption.

In summary, I believe the main benefit of treat-and-extend for the retinal specialist after the appropriate fixed dosing period (4,13) gives us proactive control over the disease, instead of having to react to disease progression – and, at the same time, minimizes the chance of relapse. It also balances treatment, because there is a reduced risk of over-treatment – which is possible using a fixed regimen – and it reduces the risk of under-treatment inherent to reactive PRN regimens. I admit that we need to do more work, as we need more data from a large randomized control trial to provide a clearer view of its efficacy for a larger population. However, I feel that patient management and treatment regimens should always aim to maximize visual outcomes and reduce treatment burden to a manageable level. Therefore, treat-and-extend can help optimize the balance between achieving good vision outcomes and the burden of treatment on the patient.

“Patients experienced significant visual gains in the first year of treatment.”
Treating Visual Impairment Due to DME and Macular Edema Secondary to BRVO with Aflibercept: The Highlights

So far, you have read about the wonderful advances in treating wet AMD with aflibercept. But wet AMD is only one of aflibercept’s many indications. I would like to review some of the more recent Phase III aflibercept clinical trial data, namely the VIBRANT, VISTA and VIVID studies, to show how it has benefited patients with other conditions too.

Branch retinal vein occlusion

VIBRANT (14), was a Phase III, randomized, multicenter, double-masked study that compared aflibercept with grid laser photocoagulation in 183 treatment-naïve patients with BRVO. The aflibercept group received a 2 mg dose every 4 weeks (2q4) for the first 20 weeks, followed by a 2 mg dose every 8 weeks (2q8) from weeks 24 to 52 (13,14). The second group received grid laser photocoagulation at baseline (and a single grid laser rescue treatment, if needed, from weeks 12 through 20); from weeks 24 to 52, these patients received an aflibercept 2q8 regimen. The primary outcome was the proportion of patients displaying an improvement in BCVA of ≥15 ETDRS letters from baseline. Other efficacy assessments included mean BCVA and mean reduction in central retinal thickness (CRT) from baseline levels. The primary and secondary analyses were performed at weeks 24 and 52, respectively, and the results are summarized in Figure 4.

At 24 weeks, aflibercept-treated patients fared better than their laser-treated counterparts: a significantly greater proportion of these patients gained ≥15 ETDRS letters from baseline (52.7 vs. 26.7 percent, p=0.0003; Figure 4a). Furthermore, mean BCVA was greater (17.0 vs. 6.9 letters, p=0.0001; Figure 4b), in the aflibercept group, relative to the laser treatment group. The second period of the trial (where all patients received a bimonthly aflibercept regimen) were retained – and that patients switched to 2q8 aflibercept from laser therapy displayed dramatic improvements from baseline in BCVA and CRT, almost catching up with the patients originally randomized to receive aflibercept (Figures 4b and 4c).

Diabetic macular edema

Diabetes is the epidemic of the century, the complications from which include amputation, stroke, end stage kidney failure, and crucially, blindness. One form of diabetes-related blindness, DME, is particularly pernicious: unless detected by fundoscopy, patients are unaware of its presence until significant damage has occurred. It’s a bilateral condition, growing in prevalence, and a leading cause of legal blindness. It affects many people of working age, meaning the societal impact of DME-related vision loss is profound.

DME is multifactorial in origin, but it’s clear that a large part of the...
problem is local hyperglycemia-related inflammation, which damages the retinal microvasculature, often leading to edema. DME can be challenging to treat – over the years, we have seen variable responses to mainstay therapy, where, according to the current literature, about 40 percent seem to be resistant to the drug. Aflibercept is the most recent anti-VEGF agent brought to the market in the EU, gaining approval for "the treatment of visual impairment due to DME" on the basis of results from the Phase III VISTA and VIVID trials (15). VIVID and VISTA enrolled 872 patients who had DME with central involvement, and randomized them to receive either a 2q4 aflibercept regimen for the 52-week duration of the trial, a 2q8 aflibercept regimen (after five initial consecutive 4-weekly 2 mg doses) or laser photocoagulation at baseline. The primary outcome was the mean change in BCVA (in ETDRS letters) from baseline to week 52 (Figure 5).

At week 52, both aflibercept regimens resulted in significant vision gains compared with laser therapy. In VISTA, mean BCVA gains in the 2q4 and 2q8 were +12.5 and +10.7 letters from baseline, compared with +0.2 letters with laser photocoagulation (p<0.0001); in VIVID, these gains were +10.5, +10.7 and +1.2 letters from baseline, respectively (p<0.0001; Figure 6a). Likewise, at week 52, both aflibercept regimens resulted in significantly greater reductions in mean CRT from baseline levels (Figure 6b). Of note, the benefits achieved with both aflibercept regimens in the first year were maintained out to 100 weeks (16).

These are impressive results. However, there is another factor worth noting: aflibercept’s pharmacology (17-19). Designed as a cytokine trap, aflibercept is a soluble fusion protein that contains specific extracellular components of VEGF receptors 1 and 2, fused to the constant region of immunoglobulin G1. This results in a molecule with two identical arms, both capable of binding VEGF and, importantly, the pro-angiogenic cytokine placental growth factor (PIGF). Aflibercept, therefore, can uniquely bind both ends of activated, dimerized VEGF or PIGF between its arms, rendering them inert, and preventing it from binding to the native receptors or cross-linking – something that is possible with monoclonal antibodies and antibody fragments. PIGF inhibition may have additional benefits beyond inhibiting angiogenesis; PIGF production has been associated with localized inflammation (20) – as is the case in patients with diabetes (21).

Aflibercept’s unique pharmacology may help explain the favorable results seen in the aforementioned trials.
epithelial retinal detachment. Withhold treatment in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes; with retinal break and do not resume treatment until the break is adequately repaired. Withhold treatment and do not resume before next scheduled treatment if there is: decrease in best-corrected visual acuity of ≥30 letters compared with the last assessment; central foveal subretinal haemorrhage, or haemorrhage ≥50% of total lesion area. Do not treat in the 28 days prior to or following performed or planned intraocular surgery. Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk to the foetus. Women of childbearing potential should use effective contraception during treatment and for at least 3 months after the last intravitreal injection. Populations with limited data: There is limited experience of treatment with Eylea in patients with ischaemic, chronic RVO. In patients presenting with clinical signs of irreversible ischaemic vascular function loss, aflibercept therapy is not recommended. There is limited experience in DMO due to type 1 diabetes or in diabetic patients with an HbA1c of ≥12% or with proliferative diabetic retinopathy. Eylea has not been studied in patients with active systemic infections, concurrent eye conditions such as retinal detachment or macular hole, or in diabetic patients with uncontrolled hypertension. This lack of information should be considered when prescribing such patients. Interactions: Fertility, pregnancy & lactation: No recommended during pregnancy unless potential benefit outweighs potential risk to the foetus. No data available in pregnant women. Studies in animals have shown embryo-fetal toxicity. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last injection. Not recommended during breastfeeding. Excretion in human milk: unknown. Male and female fertility impairment seen in animal studies with high systemic exposure not expected after ocular administration with very low systemic exposure. Effects on ability to drive and use machines: Possible temporary visual disturbances. Patients should not drive or use machines if vision inadequate.

Undesirable effects: Very common: Conjunctival haemorrhage (phase III studies: increased incidence in patients receiving anti-VEGF agents), visual acuity reduced. Common: Retinal pigment epithelial tear, detachment of the retinal pigment epithelium, retinal degeneration, vitreous haemorrhage, cataract (nuclear or subcapsular), corneal abrasion or erosion, corneal oedema, increased intraocular pressure, blurred vision, vitreous floaters, vitreous detachment, injection site pain, eye pain, foreign body sensation in eyes, increased lacrimation, eyelid oedema, injection site haemorrhage, punctate keratitis, conjunctival or corneal ulceration. Uncommon: Injection site irritation, abnormal sensation in eye, eyelid irritation. Serious: If CIWSP^ -- in addition: blindness, endophthalmitis, cataract, transient increased intraocular pressure, vitreous detachment, retinal tear or detachment; hypersensitivity (incl. allergic reactions), vitreous haemorrhage, cortical cataract, limbal opacities, corneal epithelial defect/erosion, vitritis, uveitis, iritis, iridocyclitis, anterior chamber flare. Consult the SmPC in relation to other side effects.

Overdose: Monitor intraocular pressure and treat if required. Incompatibilities: Do not mix with other medicinal products. Special Precautions for Storage: Store in a refrigerator (2°C to 8°C). Do not freeze. Unopened vials may be kept at room temperature (below 25°C) for up to 24 hours before use. Legal Category: POM. Package Quantities & Basic NHS Costs: Single vial pack: £816.00. MA Number(s): EU/1/12/797/002. Further information available from: Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire, RG14 1JA, United Kingdom. Telephone: 01635 653600. Date of preparation: March 2015.

References