Past, Present & Future of Intravitreal Medications for Exudative AMD

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Some Dates Mean More

- 7 December 1941
- 22 November 1963
- 20 July 1969
- 15-17 August 1969
- 8 December 1980
- 11 September 2001
A Few of Many

- Pearl Harbour bombed
- John F. Kennedy assassinated
- Moon Landing
- Woodstock Music Festival
- John Lennon assassinated
- United States attacked by Islamic radicals
And another:

- 17 July 2005
Montreal ASRS Meeting

- Two presentations shook the retina world to its core, and treating exudative macular degeneration was transformed.

- First, it is worth a step back to see where we were, and why a fellow resident at Washington University in St. Louis asked me in 2003, when I said I had accepted a fellowship at the University of Wisconsin in medical retina, why I would ever go into such a depressing field.
Way Back When

- Macular degeneration wasn’t much of an issue:
  - 1900: US ALE 46.3 for males, 48.3 for females
  - 1940: US ALE 60.8 for males, 65.2 for females
- An uncommon disease. Just as well, for there no treatments.
- Postwar, the incidence began to creep up, as life expectancy grew, diet worsened, and smoking was epidemic
AMD

- Now it is the most common cause of moderate and severe vision loss in most developed countries.

- Untreated AMD is characterized by irreversible damage to the macula resulting in progressive loss of central vision.

- Two major forms exist: dry, which leads to atrophy of the outer retina and RPE, and wet, which is characterized by invasive neovascularization from the choroid.
Choroidal neovascular membranes are subdivided based on appearance on fluorescein angiography into occult, classic, and mixed (and polypoidal, but that’s a different talk).

Classic lesions progress most rapidly and induce scar formation faster than occult types.

Though the neovascular forms account for less than 20% of the cases, they account for 90% of blindness caused by the disease.
Exudative AMD

- Occurs when ischemic areas of retina send out biochemical signals, among them vascular endothelial growth factor (VEGF) to initiate the growth of new blood vessels in an attempt to improve oxygenation.

- Works great in heart muscle and skin.

- Not so much in the retina - the new blood vessel network disrupts the precise anatomy of the outer retina’s relationship to the retinal pigment epithelium (RPE) and choriocapillaris.
“Treatment”

- Until the 1980’s, treatment was counseling.
- If you live in the country, and there is no one to drive you or write your checks, sell your house and move into a city apartment. You’ll still need help.
- If you are fortunate to have a spouse or family to help, prepare for a seismic change in dependence.
- You probably won’t be able to work at your current job.
- You will become legally blind. You won’t drive.
The Macular Photocoagulation Trial (MPS) began in 1980, to investigate the efficacy of argon laser photocoagulation of neovascular lesions.

Two arms initially—extramacular and juxtafoveal, with subfoveal added later.

All eyes on average did better than the control arm (untreated).

This is what ‘better’ means: By 18 months, 24% of the treated group lost >6 lines vs. 41% of the control group
MPS

- High recurrence rates
- Vision at best stabilised and did not improve
- Immediate loss of vision for subfoveal group- try convincing someone that statistically, in an indeterminate number of months, the vision will be worse than the immediate effect after laser.
- Perverse tendency of treated lesions, if they recur, to grow toward the foveal centre.
SST

- The Submacular Surgery Trials aimed to determine if surgically removing the CNVM has a better visual outcome than laser.

- It did not show any significant difference in efficacy-though selected cases involving histoplasmosis (and other)-caused classic lesions in YOUNG people could have dramatic improvement in vision that was lasting.
PDT

Photodynamic therapy (PDT) seemed like the best thing possible when it was approved in 2001 for classic or predominantly classic lesions.

It was, because current therapies were generally not helpful, and it was less unhelpful. Plus, a few patients actually got better vision! That was exciting.
PDT Downsides

- Relatively few patients qualified for treatment; classic lesions are less common than occult lesions.
- The usual best outcome was stopping further damage; only a small percent overall achieved better vision.
- The treatment required temporary lifestyle changes.
- In many cases, it damaged both the lesion as well as the already-impaired RPE and caused a new form of atrophy, similar to, though not as complete, as end-stage geographic atrophy. Way to go!
A few trials investigated the use of external-beam radiation to treat CNVM due to AMD. They were based on small studies which showed promise in shrinking or obliterating CNVMs. No study has shown this modality to be efficacious.
Pegaptanib

- Pegaptanib (Macugen) was the first ant-VEGF drug approved, in December of 2004.

- It was considered a safer alternative to ranibizumab, about to start Phase 3 trials, as it bound to only one of five VEGF isoforms.

- VISION trial showed 0.3 mg injected every 6 weeks reduced the rate of visual loss. 70% of patients at one year lost less than 3 lines of vision vs. 55% in the control group.
Macugen Problems

- Only 5% of patients experienced moderate visual improvement.
- 1% of injections resulted in endophthalmitis, 1% had retinal detachments and 1% had traumatic cataracts.
- It came in a prefilled glass syringe with a needle about as sharp as my little finger. There was alarming indentation of the eyewall during those injections.
- Did I mention people still lost vision?
One of the two talks I mentioned earlier detailed the 1-year results of the Phase-3 MARINA trial, involving a new drug called ranibizumab. There were 3 arms, a sham injection, a .3 mg and a .5 mg injection.

Ranibizumab is derived from the Fab fragment of a previously developed molecule, called bevacizumab.

Both drugs were developed by Genentech.
MARINA

- The results were seismic: the patients treated with ranibizumab gained seven letters in the treated eye, versus a loss of 10.5 in the sham group. This was big, & the company would shortly apply for FDA approval.

- Especially impressive, the lesion type- occult, classic or a combination did not matter.

- It would be months before approval, and meanwhile patients were going blind as always.
Bevacizumab (Avastin)

The presentation that shook the retina world to its core was presented by Philip J. Rosenfeld, of Bascom Palmer Eye Institute in Miami. Presented prior to the MARINA talk, it deflated the important news of the MARINA trial by its unexpectedness, and by revealing that off-label use of a drug available NOW could wrest control of a universally disabling disease into the hands of the ophthalmologist.
Avastin

- The results presented were incredible, but not persuasive in the sense of large study-incredible. Only a few dozen patients had been treated.

- Still, there was unprecedented news: with the infusions, patients gained an average of 7 letters at one week and 13 at 24 weeks. The patients receiving the first intravitreal injections were being rescued from certain blindness.

- The MARINA presentation which followed had the wind knocked out of its sails.
Back in Time, Again

To trace how these doctors came to try bevacizumab as a rescue drug in AMD patients facing certain blindness, one has to go back to at least 2001, when the Stratus OCT (optical coherence tomography) machine was first used in the Phase ½ trials of ranibizumab which Dr. Rosenfeld and colleagues were participating in.

It was clear then that ranibizumab had a dramatic effect on the subretinal fluid (SRF) and macular edema, confirmed on the standard of the time, fluorescein angiography.
Dr. Rosenfeld had studied the molecular lineage of ranibizumab, and discovered it was derived from the same clones as bevacizumab. The cloned nucleic acid sequences used to create bevacizumab were mutated to create ranibizumab, a higher-affinity smaller molecule. This was done on the hypothesis that the larger molecule bevacizumab might not penetrate the retina. Subsequently (and clinically) this has not proven to be true, as rabbit studies have shown excellent retinal penetration of both molecules.
Rosenfeld concluded that despite the differences, both molecules should have close to identical anti-VEGF activity.
His conclusions were further substantiated by reading of the monoclonal mouse antibody (progenitor of bevacizumab) in 1990s monkey models prevented iris neovascularization.

This also led to the conclusion that even the non-humanized mouse antibody (bevacizumab precursor) did not cause ocular inflammation, even in a cross-species experiment (mouse Ab in monkey eye).

The molecule was humanized from mouse to human, but preserved the anti-VEGF binding domains.
Sorry about that
3 Critical Steps toward Using Bevacizumab for Wet AMD

- FDA approval 2/2004 for metastatic colorectal cancer, so it was available for use
- Phase 3 trials for ranibizumab were just starting and FDA approval would be at best 2+ years away
- The only approved wet AMD treatment was PDT which was only approved for predominantly classic CNVM lesion
Rosenfeld & colleagues approached Genentech in 2003 asking if they were interested in a clinical trial using intravenous bevacizumab for wet AMD.

Answer: No
Early Studies

- Rosenfeld got IRB approval in spring 2004 to treat patients with wet AMD who had no other treatment options. Study was funded by donations from patients.

- 3, then 2 treatments of 5/mg/kg infusions were given 2 weeks apart. 18 patients treated, followed for 6 months: ALL 18 patients either stabilized or improved vision and same OCT results as intravitreal ranibizumab with complete resolution of intra or sub retinal fluid resolving within a day. FA confirmed OCT findings.
Black Box Warning

- In August 2004 FDA issued a black box warning, declaring a 1% risk of thromboembolic events when bevacizumab was infused every 2 weeks in conjunction with chemotherapy in patients with metastatic colorectal cancer.

- No patients declined participation or withdrew from the ocular study.

- Of note, the intravenous dose was greater than 500 times the eventual intravitreal dose.
ARVO 2005

- Breakfast meeting at ARVO. Genentech refused to participate. 50 + retina specialists. Rosenfeld proposed multicenter prospective study for systemic bevacizumab for patients without other treatment options.

- Outcome: Negative. Overwhelming concern about potential thromboembolic risks. Pegapnatib sodium (Macugen) had been approved a few months earlier and (ultimately erroneously) is was portrayed as safer due to being a selective VEGF inhibitor.
Rosenfeld’s Eureka Moment

Driving home. Obsessing. Realizing bevacizumab had 25mg/ml in bottle and ranibizumab’s is 10 mg/ml and the molecular weight of bevacizumab is 3x ranibizumab so equal volumes of each drug will have same number of molecules. So if the same volumes of bevacizumab as ranibizumab was injected into the eye there would be the same number of molecules. The buffer solution of bevacizumab seemed to be safe for the eye. Plus, bevacizumab had two binding sites to one for ranibizumab. Huh!
Consults

- Serafin Gonzales, Pharmacy Director at Bascom Palmer. He said not only could he prepare the solution in individual syringes, but was legal: in compliance with Chapter 797 for Compounding Sterile Preparations.

- Carmen Puliafito, Chairman. Gave permission to use off-label bevacizumab as salvage therapy for patients who had failed standard approved clinical care for wet AMD.
The First Injection

- Mid-May, 2005, retired nurse.
- PDT treatment in one eye, now legally blind. Active wet AMD in other eye, losing vision with PDT, triamcinolone acetonide, and pegaplatatin sodium. Worsening vision with growing classic lesion. She signed detailed consent form, was injected with bevacizumab. The lesion’s growth was stopped, vision improved.
- Wow, to say the least.
Dr. Puliafito presented the first results at a meeting: Robert Avery, M.D. began using it with his patients, as did Edgar Thomas, M.D. with good results. They both became strong advocates.

Dr. Avery backed up his advocacy with rabbit studies, which proved the penetration of the drug into the retina as well as its safety.
A huge number of studies erupted worldwide, concurrent with off-label use of bevacizumab having unprecedented success in treating wet AMD and increasingly, edema from vein occlusions.

A unique convergence of events: OCT availability and the evidence provided, scientific rationale, convincing data of systemic bevacizumab, ranimizumab data, worldwide availability of bevacizumab, and its very low cost.
A Rational Approach to Choice of Anti-VEGF Therapy in Wet AMD
How Do I Choose?

- I have 3 great meds...where do I start?
- Various studies have given me guidance, and so has my own experience.
- I Consider:
  - Cost: to patient directly (often unknown at first)
  - Lesion type: my experience
  - Idea of how long therapy may last (this morphs)
Before Aflibercept

- CATT Trial: bevacizumab is non-inferior to ranibizumab when injected monthly
- IVAN: ranibizumab = bevacizumab
- MANTA: ranibizumab = bevacizumab PRN
After Aflibercept

- VIEW Trial:
- Both drugs equally efficacious
- Therefore, using the transitive property:
- Bevacizumab = Ranibizumab = Aflibercept
- So, can we assume they are all the same?
- Yeah, you guessed it...
Anti-VEGF Activity

- In the lab, and theoretically: aflibercept > ranibizumab > bevacizumab
- In vitro, aflibercept’s binding capacity 140 x ranibizumab’s
- Aflibercept’s 1 month binding capacity is much greater than ranibizumab and bevacizumab
CATT Data

- Despite statistical equivalency, CATT reports 1/3 more letters gained at 2 years, ranibizumab vs> bevacizumab.
Do The 3 Drugs Dry Equally?

- By OCT, ranibizumab dries better than bevacizumab.
- By OCT, aflibercept dries better than ranibizumab.

- Is more drying (by OCT data) better or does it matter?

- Visual data suggests drying is better, but there are concerns of increased atrophic changes.
Safety

- CATT suggests less geographic atrophy with bevacizumab, and less atrophy with either drug with PRN dosing
- No solid data with aflibercept: but there seems to be clear data that aflibercept is a stronger anti-VEGF agent than ranibizumab or bevacizumab, so one would expect regarding GA bevacizumab > ranibizumab > aflibercept
Safety

- Bevacizumab is compounded, so there is a theoretically higher risk of SAEs.

- In all trials there was a slightly higher risk of SAEs with bevacizumab, but not statistically significant. Does it have to do with half-life?

- Half-life: Ranibizumab: 6 hours
  - Aflibercept: 36 hours
  - Bevacizumab: 20 days
Cost

- Bevacizumab costs a LOT less than the others.
- Exclusive use of bevacizumab in the US for wet AMD would save 5 billion dollars a year.
- So with respect to cost:
  - Bevacizumab > ranibizumab > aflibercept
But wait...

- But aflibercept costs slightly less than ranibizumab, and it is used less frequently, so...

- Bevacizumab > aflibercept > ranibizumab

- VIEW Trial: significantly fewer treatments with aflibercept versus ranibizumab to get same VA outcome
Also in VIEW Trial:

- By 2\textsuperscript{nd} year when all dosing was PRN, there was no difference in number of doses to get same level of VA
Confused?

- A reasonable reaction to the data.
- Bevacizumab is orders of magnitude cheaper and has a statistically significant similar effect in general.
- But we have three excellent medications, and some work better for particular situations. I start with Avastin and may move on depending on the type of lesion and the response.
My General Plan

- Start with Avastin, usually
- For vascularized pigment epithelial detachments, I prefer ranibizumab. I like the small molecular size and have excellent results
- If it looks like this may be a long-term therapy, I switch to aflibercept, as most often it allows less-frequent dosing
What drug is he on?

- Results like the following are common in my clinic, and in early 2006 if they were repeated, the whispered question would be ‘what drug is he on?’

- Better-seeing eye is the wet AMD eye vs the dry eye.

- 20/20 vision after presenting at finger-counting.

- History of treated wet AMD OU, 20/25 OU, and no visible evidence on 90D exam at the slit lamp.

- Giant PED resolving after 1 treatment.
My first shot

Shortly after the 2005 ASRS meeting, I contacted Leiter Compounding Pharmacy in Santa Barbara to arrange the first delivery of Avastin to the UW-Madison Retina Clinic. The coalescing plan was to use it in patients who had failed standard therapy.

Before that could happen, a glaucoma patient with bilateral neovascular glaucoma presented. She had florid iris neovascularization and was to have surgery the next day. The surgeon was concerned about intraoperative bleeding.
My first shots

Consultation between the retina surgeons, the glaucoma surgeon and retina fellows led to the decision to try bevacizumab in this desperate case to shrink the iris neovascular vessels.

The retina surgeon who was to inject the drug had to leave for surgery, and I ended up injecting both eyes. Photographs of the neovascularized irises were taken before the injection.
The next day

- There was no visible iris neovascularization. Her green eyes, which had looked brown due to the blood vessels crawling over the surface, were green. Photos were taken. She went through surgery uneventfully, without bleeding complications.

- The collective response was (fill in the blank) or, Wow!

- We relatively quickly, as a community of specialists, began to ask ‘should we be using this first-line, instead of salvage therapy?’

- You know the answer.
The rest of 2005

UW retina doctors, like our colleagues worldwide, began to use Avastin first as rescue therapy, with profound results: rapid resolution of fluid and stabilized vision, sometimes a little better. But these eyes were already damaged by the existing therapies: PDT, pegaptanib and triamcinolone acetonide in combination with too much time with incompletely treated exudation.

The inevitable question: Should this be a first line treatment? Is that reasonable? Is it ethical?
Debates & Discussions

We debated this question among ourselves and in meetings, through emails, and interactions with patients. I don’t remember exactly how the transformation took place, but I do remember, in September, convincing my attending physician to let me treat a patient who presented for the first time with wet macular neovascularization, with bevacizumab. It helped that she had a large occult lesion, with a foveal-threatening bleed, a lesion PDT was not approved for and pegaptanib had been most unimpressive in treating.
Her vision was in the 20/80-100 range. She was maybe 75, vital, a former health professional who was now a visual artist in retirement.

She and I had a discussion I’ll never forget. I did the doctor thing, going over the risks and potential benefits and emphasizing the experimental nature of the drug and its delivery into the eye. She got it and moved right past me folding all I said into her perspective: “I don’t see what I have to lose with Avastin, and I do see what I will lose with the other treatments.”
I was more nervous that she. The injection went fine.

Three days later (we always brought patients back then to check for complications) her vision was 20/50 and OCT showed most of the fluid gone.

At six weeks, 20/40. Another injection.

At 12 weeks, 20/25, at 18 weeks 20/20, no fluid.

This was the beginning of a new approach to treating a once-invincible disease.
Now we are spoiled, comparatively.

If a patient with new-onset wet AMD comes in, we expect a good result, as in a return to baseline.

If any patient does not gain any vision back, we wonder how we can do better.

But still, and Kim hears this all the time, I still exclaim to my patients, with wonder and joy, how incredible it is that this awful disease can be forced into submission.

When you’ve been there from the beginning, it never gets old.