Perspective

Treatment options for the wet form of age-related macular degeneration—a perspective

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Provenance: This is a Guest Perspective commissioned by Section Editor Yi Sun, MD (Department of Ophthalmology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China).

Comment on: Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group., Maguire MG, Martin DF, *et al*. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. Ophthalmology 2016;123:1751-61.

Abstract: Treatment of the wet form of age-related macular degeneration (wet AMD) has been revolutionized a decade ago with the introduction of vascular endothelial growth factor (VEGF) blockers that reduce neovascularization and macular edema. Two approved drugs are marketed for the treatment of wet AMD—ranibizumab and aflibercept, but there is a third drug, bevacizumab, which is widely used off-label; a cancer drug that also blocks VEGF but was never tested in pivotal trials and never approved for ophthalmic indications including wet AMD. Similarity of bevacizumab to ranibizumab led to off-label use and even to government-sponsored studies comparison the approved ranibizumab head-to-head to the off-label cancer drug bevacizumab in wet AMD, like the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) study, discussed in this perspective paper. Recent publication of 5-year follow-up from the initial 2-year CATT study provided the occasion to discuss the similarities and differences between these two drugs and the lessons learned from the last decade of anti-VEGF therapy for wet AMD. Clinical efficacy is comparable, with an advantage for ranibizumab. Likewise, safety finding favor ranibizumab over bevacizumab in some aspects. The latest addition of approved anti-VEGF drugs for wet AMD, aflibercept, may provide even more benefit to patients. In this perspective we discuss results of CATT and other long-term follow-up and comparative studies. While all demonstrate clinical benefit of anti-VEGF, all reveal that most patients' loose visual acuity (VA) in real-life situations over 5–7 years. This loss is based on—what we believe—significant under-treatment of wet AMD patients, due to economic or practical limitations and overestimation of perceived risks as geographic atrophy. We compare own data that showed more intensive treatment (more than twice the CATT-follow-up injections) with ranibizumab or aflibercept can maintain a sustained gain in VA in wet AMD patients after 6 years. We encourage retina specialists to treat wet AMD patients more aggressively and frequently in order to provide the maximum benefit for their patients.

Keywords: Wet form of age-related macular degeneration (wet AMD); Comparison of Age-related Macular Degeneration Treatments Trials (CATT); ranibizumab; bevacizumab

Submitted Oct 05, 2016. Accepted for publication Oct 09, 2016.
doi: 10.3978/j.issn.1000-4432.2016.12.12
View this article at: http://dx.doi.org/10.3978/j.issn.1000-4432.2016.12.12

Clinical therapy for a (former-) leading cause of blindness in particular in developed countries, the wet form of age-related macular degeneration (wet AMD) is a very interesting topic from many angles, the science, the clinical management and benefit but also from the commercial and regulatory side. In this regard, we would like to provide a perspective on the recently published five-year outcome of the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) (1). This CATT trial compared two blocking antibodies to vascular endothelial growth factor (VEGF), ranibizumab and bevacizumab.

We summarize in the following the thoughts and personal opinions and perspectives from both authors: a clinical ophthalmologist, an investigator in many of the past anti-VEGF studies and closely involved in the image/OCT analysis of many of the previous and ongoing anti-VEGF studies in different indication. The other side of the perspective stems from a former executive at the two leading global companies that developed and market the two (approved) anti VEGF treatments; a view from the inside from leading positions in global clinical studies that led to approval of the anti-VEGF treatments ranibizumab and aflibercept.

Anti-VEGF has become the mainstay of wet AMD therapy, with ranibizumab (Lucentis®, Genentech/Roche/Novartis) being the first approved in 2006, and aflibercept (Eylea®, Regeneron/Bayer) approved a few years later. In addition to these two approved drugs, indicated for the treatment of wet AMD, the anticancer agent bevacizumab (Avastin®, Genentech/Roche) is widely used for the treatment of wet AMD, despite no official pivotal study was conducted in ophthalmology and so the drug is used off-label, despite the legal risk of such an off-label use.

The use of these three anti-VEGF agents to treat retina diseases including wet AMD is one of the most interesting (textbook-ready) examples of drug development strategy and reimbursement potential from the pharma but also from the government/reimbursement point of view.

While on the one hand, health authorities around the world impose countless regulations on drug companies that develop new drugs, with numerous safety measures and highly demanding thresholds for primary and secondary study end points and for additional data demonstrating efficacy and safety—with the US FDA one of the global leading agencies in this regard, on the other hand, state agencies as the National Eye Institute (NEI) or NIH in the US support clinical studies like the here discussed CATT study that test the use of off-label drugs which have never been approved, never have undergone any of the year-long safety-tests that are usually required for a drug to be approved, and never have demonstrated their safety and efficacy in any phase 1/2/3 randomized, double-masked, parallel-group controlled study…

So the ranibizumab/bevacizumab example and all studies involving these two drugs present a very fascinating and impressive example of how to establishing rules only to break them (due to mostly financial constrains in health-care systems around the globe). In this regard, many payers in different countries around the world request and support/prefer the use of the non-approved off-label bevacizumab over the approved and well tested ranibizumab for the treatment of wet AMD.

There are not much examples of such a widespread off-label use despite highly effective, safe and approved therapies (ranibizumab and aflibercept) than in the retina field with wet AMD. Drugs are usually used off-label only where no approved or no sufficient therapy exists as in many oncology indications but one would not expect this in wet AMD, where two highly efficient and safe drugs (aflibercept and ranibizumab) are approved and marketed. In absence of any clinical benefit for the patient when treated with the off-label bevacizumab over the approved drugs—one key driver for the off-label use dominates: the price per treatment. In the US, the difference between bevacizumab and ranibizumab (the two drugs tested in the CATT trial) is around 40-fold. The anti-cancer agent bevacizumab is delivered in large volume vials, compounding pharmacies or the treating ophthalmologists can take just a tiny 50 µL out of the vial for the intravitreal injection—and so the cost for this 50 µL injection ranges at around 50 USD. On the other side—the approved ranibizumab has a price tag of about 2,000 USD—for the same 50 µL injection volume. So price pressure and socioeconomic factors, absence of reimbursement or insurance and other factors related to the drug costs drive ophthalmologist to use a non-approved drug. Even more interestingly, government organization as NEI sponsor trials like the CATT study where the approved treatments ranibizumab is directly compared to the non-approved bevacizumab. Similar head-to-head studies have been run in other countries around the world as well. This studies obviously supported the massive use of off-label bevacizumab, thereby invalidating the FDA's (and other health-authority)—imposed very stringent safety and efficacy data requirement normally requested from pharma companies before a drug can be marketed and used in patients.

The CATT trial

The CATT enrolled 1,185 neovascular (wet-) AMD patients between 2008 and end of 2009. Patients were randomized to one of four treatment groups with different dosing regimens (monthly versus as needed) and the two different drugs ranibizumab (0.5 mg) or bevacizumab (1.25 mg). All patients were reviewed/treated monthly (2). Overall, the trial showed a similar clinical outcome for all four groups at two years, but it became clear that monthly dosing is significantly better for the patient's VA improvement than as-needed dosing, with almost 4-letter difference between ranibizumab monthly and bevacizumab as needed.

In the now published (and here discussed) CATT 5-year follow-up study, patients were recalled for examination at five years and VA was obtained for 71% (647 of 914) living patients with an average follow-up of 5.5 years. Overall, vision gains during the first 2 years of the study were not maintained at 5 years. However, 50% of eyes had a VA of 20/40 or better, demonstrating a significant long-term benefit of anti-VEGF treatment, but also 20% of the patients had a VA of 20/200 or worse.

Disappointingly, as the mean 5.5 years follow-up of the 71% survivors from the CATT study revealed, the frequency of real-life treatment was insufficient to maintain vision. The mean VA declined to three letters worse than at baseline and 11 letters worse than at 2 years (i.e., the end of the intensive treatment phase). This decrease in vision was accompanied by expansion of the size of the total neovascular complex, scarring, and atrophy. One may even speculate: due to incomplete data, the VA results may even be biased to the better outcome as only 71% of the living patients were included, significant data were missing with 14% of the patients having no OCT and 28% no FA. Patients with better VA at baseline and after treatment usually are more motivated (or able) to participate in further study visits and therefore this bias to patients with higher VA scores may have shifted overall results to the better.

Alarmingly, of all wet AMD patients that were released from the study at 2 years, 14%/15.7% (from previous ranibizumab/bevacizumab groups) received no treatment at all during the following three or so years. Patients were seen an average of 25.3±13.3 times during the 3 years follow up—but were treated only an average of 15.4±12.5 times, with 4.8±4.0 injections in year 3, 4.5±3.8 injections in year 4, and 4.0±3.6 injections in year 5.

There is no much doubt that bevacizumab is almost as effective as the approved ranibizumab, based on the here presented CATT data and supported by other head to head studies as the IVAN trial (3). There were better VA/CRT values seen with ranibizumab but in clinical practice, those slight differences may not be very significant.

But what may be significant, is some demonstrated difference in safety. The 2-year CATT data revealed a significant higher proportion of patients with one or more systemic serious adverse events in the bevacizumab group versus the ranibizumab group (39.9% *vs.* 31.7%; adjusted risk ratio, 1.30; 95% CI, 1.07–1.57; P=0.009). In contrast to this difference, the rates of death and arteriothrombotic events were similar for both drugs (P>0.60) (2). Overall though, after a decade of treatment of hundred thousands of patients with both drugs and several direct head-to-head trials, combined safety data led to the reduction of concerns around the safety differences between ranibizumab and bevacizumab for the treatment of wet AMD. These safety concerns have further been limited by two previous compelling Cochrane meta-analysis (4,5) but still, a legal risk remains when injecting a cancer drug off-label in to the eye of wet AMD patients when two approved drugs are available.

All long-term follow-up studies, as this 5-year CATT data (2), the seven-up study (6) and many others, however, revealed that the biggest issue in today's patient care in AMD lies simply not in the insufficient efficacy of any of these three drugs used in wet AMD. The explanation for VA loss after years of treatment often is way simpler: Most patients are significantly undertreated, most patients do not receive the treatment frequency they need and almost no ophthalmologist is following the pivotal-studies-based and health-authority approved labels (for ranibizumab and/or aflibercept). The marginal statistical significant or non-significant differences between the different anti-VEGF drugs, as detected in large, controlled clinical trials seem to have limited to no relevance in daily clinical practice. The 5-year CATT real-life data for long-term treatment of wet AMD patients revealed that around four anti-VEGF injections are given per year in wet AMD patients (2). Other, earlier paper as a real-life study with more than 2,000 wet AMD patients from Canada, France, Germany and others revealed five injections in the first year but only 2.2 injections in the second year (7). This is in contrast to the approved label (for ranibizumab) which even recommend up to monthly (i.e., 12 times a year) treatment. That under-treatment is the most concerning finding in all these comparison/long-term studies.

As the drug label-recommendations for frequent and regular injections are followed only occasionally, other attempts to patient care have been established and vigorously studied, with PRN (pro re nata, "as needed") and treat and extent are currently the most widespread treatment regimens used in anti-VEGF therapy in AMD. Interestingly on the long term the treat and extend regimen seems to result in a higher number of administered injections. A median of five injections per year were reported from year 2 to year 5 in a recent publication which evaluated the visual outcomes and treatment frequencies in patients tracked by the Flight Retinal Blindness registry; all patients from Australia, New Zealand and Switzerland, mainly treated according to the treat and extend regimen (8). Also recent data on the Luminous trial with ranibizumab, presented at EURETINA (Copenhagen, 2016 P. Lanzetta. A comprehensive look back on the real-world: The LUMINOUS registry) revealed that patients treated according to the treat and extent regimen usually receive more injections and show a better clinical outcome compared to patients treated according to the PRN regimen. So it seems there are easy ways to optimize the treatment and benefit for the patient, aside from the choice of the drug.

So how can the treatment outcome be optimized? A careful analysis of the OCT images from the CATT study by a reading center demonstrated intraretinal, subretinal, or sub-retinal pigment epithelium fluid in more than 70% of eyes. Despite elimination of fluid is a goal of anti-VEGF therapy, most patients were not treated at every visit (mean of 25 visits, only 15 anti-VEGF treatments between year 2 and 5). The location of fluid may also be an important determinant for the individual treatment need and functional outcome. While SRF seems to be a positive predictive factor and is correlated with good visual function, the presence of intraretinal fluid often in combination with a PED, may be a poor prognostic factor and may reveal the need of frequent aggressive treatment.

Again, VA decreased by three letters below baseline in the 5-year CATT patients, not a bad value and way better compared to what could be achieved or even dreamed of 20 years ago. Others found way worse VA outcome, i.e., the seven-up study, evaluation patients after they left the pivotal trials for ranibizumab (ANCHOR; MARINA and HORIZON). While the patients received a mean of 6.8 anti-VEGF injection during the mean 3.4 years follow-up interval, this treatment frequency still resulted in a very significant loss of 8.6 letters compared to baseline (6), so even worse than the here discussed 5-year CATT outcome.

The authors of the CATT study report conclude in discussing the 5-year data that this declines "highlights an unmet need for further therapeutic advances" (2). While a need for better drugs and scientific advantages can't be denied and better, more efficient drug are highly welcome, we think, the presented data primarily highlight the need of more aggressive and frequent treatment, based on morphologic facts such as fluid in OCT. In our clinic in Bern, Switzerland, we collected data from 49 eyes with wet AMD which were treated over a mean period of 6.2 years with anti VEGF (mainly ranibizumab as this was approved earlier: 11 eyes with aflibercept, non with bevacizumab as in Switzerland off-label use of bevacizumab is usually not supported). Those 49 eyes were treated with a mean of 48±13 anti VEGF injections—a mean number of 8±2.1 per year. So a way more intensive therapy as in this CATT 5-year follow-up and more intense compared to most global, published long-term studies (we treated about 2 times more frequently than in the CATT 5-year follow-up per year). With our intensive anti-VEGF therapy—patients still resented with an increase in VA by three letters compared to baseline after 6 years. Our data proof (with all caveats as limited patient numbers etc.): intensive treatment with the approved anti-VEGF drugs is able to maintain a VA gain for 6 years.

And as reassurance and final note: in our opinion, there is no bad thing in treating patients more frequently. Many recent discussions and publications deal with the development of macular atrophy (MA) and the concern that long-term blocking of the "essential" growth factor VEGF can do harm. Accordingly, to add to the perceived concern, here the proportion of MA increased from 20% at year 2 to 41% at 5 years in the 5-year CATT follow-up study. Well, it seems to be proven that eyes treated with anti-VEGF develop MA. Eyes with monthly treatment may develop more MA than eyes with PRN (i.e., less frequent) treatment (seen in CATT and IVAN). However, undertreated or non-treated eyes with neovascular AMD may show even higher progression rates. But: what is the impact and is MA development really correlated with VA loss? Although fovea involving MA is associated with VA decrease, MA is mainly found within the original CNV lesion, an area where RPE and photoreceptor destruction already has happened (9). When comparing the MA growth in untreated wet AMD eyes with treated AMD eyes—as done in an excellent recent publication from the "*Seven-up*" study, it became clear that the MA

growth rate is more pronounced in the initially untreated (fellow-) eyes. The authors concluded that "*In patients with bilateral exudative AMD at baseline, final vision at year 7 was significantly better in study eyes (i.e., that were intensively treated with ranibizumab) than in fellow eyes, and MA was less severe. MA area correlated with final visual outcomes, determined inter-eye vision differences, and was not attributable to high-frequency ranibizumab therapy*." (10). Thus, it is more important to suppress wet AMD disease activity early and efficient and rather optimize (i.e., intensify) anti-VEGF treatment than be too much concerned of MA.

The future will bring more data on the existing therapies and how to use them best to the benefit of the patients. Even more, new and emerging therapies with combinations of different antibodies to target pathways beyond VEGF and/or more efficient topical therapies are emerging and hopefully can help to further increase the clinical benefit for our patients. New therapies for retinal diseases like wet AMD that can be applied at home such as eye drops, intravitreal slow release devices or new antibodies may reduce the need for frequent office visits and re-treatments and the treatment burden for ophthalmologists as well as for patients. This may finally result in a better clinical outcome for the patients.

Conclusions

We believe, approved drugs that have undergone stringent testing in controlled, randomized clinical trials and have shown safety and clinical benefit to treat wet AMD should be used whenever possible. However, obviously the off-label use of bevacizumab is standard for wet AMD for many patients and in many part of the world and large studies, as the CATT study, have shown that the use of bevacizumab is safe and results in a comparable (but usually a bit lower) efficacy than the approved ranibizumab (or aflibercept).

The most important lesson learned from all those real-life data, comparisons and long-term treatment trials in wet AMD, irrespective if they studied ranibizumab, aflibercept or bevacizumab is: most patients are undertreated. Most patients do not receive the care and number of anti-VEGF injections needed to maintain their initial benefit in VA—may it be due to cost, limited capacity, or implicit/explicit expressed preference of the patient to receive no intravitreal anti-VEGF injection. While monthly treatments may not be needed for the majority of wet AMD patients, more attention should be paid to the morphologic and functional status of wet AMD, and (re-) treatment decisions should be taken earlier and more aggressive in order to deliver the best possible clinical benefit for the patients.

So maybe the stage is still open to identify the good, the bad (and the ugly) in the quest for the best wet AMD therapy—but current evidence suggest—it is not the drug, it's the treating physician who decides the battle for optimal treatment and sustained benefit for the patient.

Acknowledgements

None.

Footnote

Conflicts of Interest: MR Munk received consulting and lecturer fees and travel support from Bayer, Allergan and Novartis. R Rückert is a shareholder in companies discussed, including Bayer, Novartis and Roche.

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Cite this article as: Munk MR, Rückert R. Treatment options for the wet form of age-related macular degeneration—a perspective. Yan Ke Xue Bao 2016;31(4):266-271. doi: 10.3978/j.issn.1000-4432.2016.12.12

