Supplement to November/December 2016

Advancing the Management of Retinal Diseases:
Current Perspectives and Beyond

Sponsored by Novartis Pharma AG
This supplement features summaries of two Novartis-supported symposia held in conjunction with the 2016 Euretina Meeting in Copenhagen, Denmark. The speakers for each symposium represent retina experts from around the globe discussing important clinical aspects of major retinal diseases, and the current and future directions in the management of these diseases.

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The design. The decade. The difference.

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Age-related macular degeneration is the most frequent cause of legal blindness, affecting 25 to 30 million people worldwide. The major cohort studies have confirmed prevalence increases with age, and it is likely we will see a substantial increase in the number of people affected in the next 25 years. Treatments have progressed from laser photocoagulation (prominent in the 1970s) to photodynamic therapy, and in today’s world anti-VEGF drugs are the predominant treatment regimen, said Prof. Nicole Eter, MD. The anti-VEGF agent ranibizumab was first approved in Europe in 2007 for neovascular AMD, and is now also approved for diabetic macular edema (DME), retinal vein occlusion (RVO), and pathologic myopia (Figure 1).

There are three VEGF receptors, and it is well known that the soluble forms of VEGF-1 and VEGF-2 are the most critical in ophthalmology.

“In general, there are different possibilities to inhibit VEGF,” Prof. Eter said. “You can use antibodies, antibody fragments, soluble VEGF receptors, aptamers or antibodies against the VEGF receptor.”

Currently, three anti-VEGF therapies are commercially available. Two—ranibizumab and aflibercept—are indicated for the treatment of various retinal disorders. A third, bevacizumab, is approved to treat a number of cancers, but is used off-label for retinal diseases. However, only ranibizumab has a unique molecular design that specifically binds VEGF-A in all isoforms.

Ranibizumab was specifically designed for use in ophthalmology, and underwent a series of systematic modifications from a full-length antibody to ensure it had a profile that was suitable for use in ophthalmic indications.

“Ranibizumab was specifically designed for use in ophthalmology, and underwent a series of systematic modifications from a full-length antibody to ensure it had a profile that was suitable for use in ophthalmic indications.”
—Prof. Nicole Eter

There is a much higher affinity than the full antibody (Figure 2), she said.

“The minimal concentration to neutralize VEGF is much lower in ranibizumab compared to bevacizumab. There are also huge differences in vitreal half-life and systemic half-life,” Prof. Eter said. “There is a much slower systemic appearance of bevacizumab due to the complete antibody structure and the Fc recycling.”

Ranibizumab was first investigated for the treatment of neovascular AMD, beginning with monthly doses and then incorporating studies that evaluated variable dosing. The EXTEND studies conducted in Asia concentrated on choroidal neovascularization secondary to AMD. Other studies evaluated ranibizumab and vetoporphin for the treatment of CNV in AMD.

Figure 3 shows results from MARINA, ANCHOR (both dosing ranibizumab monthly), PIER (dosing with ranibizumab every 3 months after a dose-loading phase) and PRONTO (the first study to use an as-needed [PRN] scheme). In all cases, dosing with ranibizum-
ab resulted in improved vision, and PIER helped to confirm monthly dosing is necessary.11

“The SUSTAIN13 study which was actually the first multicenter trial to introduce PRN as treatment scheme. And so now we know that there are different response groups. There are gainers and maintainers. There are gainers that do not maintain. And there are primary non-responders. In addition, no correlation between visual results and morphological results can be found (Figure 4),” Prof. Eter said.

There have been a multitude of clinical trials that confirm the safety and efficacy of ranibizumab in AMD and DME, Prof. Eter said. The recently published COMRADE-C14 study compared ranibizumab and dexamethasone for the treatment of RVO, and Figure 5 shows the “huge difference starting from month 2 where the ranibizumab group still maintained visual acuity and the dexamethasone group lost visual acuity again.”

—Prof. Nicole Eter

If left untreated, there is a “dismal natural history” of vision decline for people with age-related macular degeneration (AMD),1 said Prof. Adrian Koh, MBBS, MMed (Ophth).

“The question really is—are the treatments that offer so much promise, such as ranibizumab, delivering on those promises?” he asked. “Has the performance matched the promise?” Ranibizumab has been key to the start of the anti-VEGF treatment regimen for the past 10 years.

“In the past our main goal in managing patients with wet AMD was to give them bad news and to tell them that they would not go...
completely blind, but it is likely they would lose quite a bit of their vision,” Prof. Koh said. Wong and colleagues showed over the course of 3 years, patients could be expected to lose up to 4 lines of vision.

“But we have moved from halting progression in the last century, to preventing further visual loss in the early 2000s. With the introduction of the anti-VEGF agents like ranibizumab, we were able—for the first time—to improve vision previously unseen in other treatment modalities (Figure 1),” he said.

Ranibizumab was the first treatment for choroidal neovascularization (CNV) proven to improve visual acuity in patients with AMD, Prof. Koh said, and since its introduction in 2006 numerous pivotal trials have continued to validate those findings. MARINA² looked at the minimally classic and occult CNV in more than 700 patients. ANCHOR³,⁴ showed a response of predominantly classic CNV to ranibizumab that was significantly better than the control arm (photodynamic therapy, or PDT [Figure 2]).

“These studies, followed by PIER,⁵ EXCITE,⁶ SUSTAIN,⁷ and SAILOR,⁸ were all robust and included large numbers of patients,” Prof. Koh said.

Results from MARINA² and ANCHOR,³,⁴ “show that on a monthly basis, patients receiving ranibizumab over 24 months had a net gain of at least 20 letters between treatment arms and the control arm,” Prof. Koh said. In MARINA, the control arm was sham and in ANCHOR the control arm was verteporfin PDT.

“These are very impressive results. We could now tell our patients they would avoid moderate vision loss, but more significantly, the improvement in vision might mean the difference between an ability to drive or ability to read or discriminate faces,” he said. “A third of patients treated with ranibizumab in the MARINA trial doubled their visual acuity.”

CATT and VIEW directly compared ranibizumab to other treatments. In CATT,⁹ ranibizumab was compared to bevacizumab in two treatment regimens, continuous (monthly treatment) and the discontinuous (as needed therapy). CATT clearly showed very similar results between the agents, “and ranibizumab was successful in maintaining initial visual acuities with both monthly and in as-needed regimens,” Prof. Koh said. “There were significantly fewer injections at the end of 2 years in the PRN groups, ranibizumab versus PRN bevacizumab.” During its second year, the CATT protocol meant at least three monthly injections of all the agents and PRN treatment.

**“Ranibizumab has been key to the start of the anti-VEGF treatment regimen for the past 10 years.”**

—Prof. Adrian Koh

VIEW¹⁰ used four treatment arms, ranibizumab 0.5 mg administered every 4 weeks compared to 2 mg of aflibercept every 8 weeks (2q8), every 4 weeks (2q4), and then 0.5 mg aflibercept arm every 4 weeks (0.5q4).

“At the primary endpoint at month 12 aflibercept 2mg every 8 weeks was noninferior to ranibizumab given every 4 weeks,” Prof. Koh said. “There were slight losses at week 96, but probably not clinically meaningful. There was a slight drop in the 2q4 arm from 9.3 letters down to 7.6 letters and the ranibizumab arm from 8.7 letters to 7.9 letters. These two drugs are really, very, very similar in outcomes and the differences are not significant (Figure 3).”

In VIEW,¹⁰ the two agents were also similar in their ability to dry the macula, with 68% of the patients in the 2q8 aflibercept arm dry at week 52 compared with 62% in the ranibizumab arm. At week 96, 46% of the ranibizumab arm and 50% of the 2q8 aflibercept arm were dry,” Prof. Koh said.

VIEW was somewhat unique in that it used a “capped PRN” injection regimen, Prof. Koh said, where each arm mandated three initial

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**Figure 1. Treatment landscape in nAMD.**

**Figure 2. Improvement of vision with ranibizumab in nAMD.**

**Figure 3. VIEW (1 & 2) studies in nAMD.**

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**Milestones in therapy for neovascular AMD**

Laser photocoagulation

MPS reports

1980

PTD with verteporfin

TAP reports

2000

Submacular surgery

VIP reports

2006

Anti-VEGF therapy

VIM

2012

MARINA

SST

VISION

ANCHOR

CATT

VIEW

HALT PROGRESSION

IMPROVE VISION

TO RETINA TODAY
monthly injections. Through weeks 52 to 96, the ranibizumab arm received a mean of 4.7 injections compared with a mean of 4.2 injections in the aflibercept arm.

Proportions of eyes maintaining BCVA across treatments were 94.4% to 96.1% at week 52, and 91.5% to 92.4% at week 96. Mean BCVA gains were 8.3 to 9.3 letters at week 52 and 6.6 to 7.9 letters at week 96 (Figure 4).

“In terms of pigment epithelial detachments (PEDs), in VIEW there was really no significant difference between agents of the three regimens,” Prof. Koh said. “There was a broad overlap whether the intraretinal fluid was present or absent, regardless of subtype: occult, classic, PED, or polypoidal choroidal vasculopathy (PCV).”

This becomes particularly relevant as CNV is not the only subtype of neovascular AMD.

“In Asia close to 40% of patients with wet AMD might have an underlying PCV, compared to only 15% in Europe,” Prof. Koh said.

The PEARL study showed that ranibizumab monotherapy “improved vision and could resolve hemorrhage very efficiently,” Prof. Koh said. “In the PEARL study, about 38% of patients had complete polyp regression. The remainder had at least persistent polyps right out to month 12. Visual acuity was very good because ranibizumab was efficient at drying out the macula.”

Similar results have been seen with aflibercept, Prof. Koh added, with high rates of regression of polyps, “perhaps as high as 75%.”

EVEREST was the first randomized controlled trial to evaluate ranibizumab and verteporfin PDT on various subtypes of AMD. EVEREST was really targeted as combination therapy for PCV,” Prof. Koh said. “This was an exploratory pilot trial, but it was a breakthrough for researchers and practitioners.”

EVEREST was a randomized, double-masked trial 6 months long, evaluating a combination of ranibizumab 0.5 mg with standard fluorescence of verteporfin PDT compared with verteporfin monotherapy and ranibizumab 0.5 mg monotherapy. All three treatment arms had “significant and appreciable gains in visual acuity gains from month 6. There was no statistical difference between the treatment arms (Figure 5),” Prof. Koh said.

Although the pilot study was not powered to show differences, “all three agents ended up with good vision. In the primary outcome of complete closure of polyps, PDT monotherapy and PDT in combination with ranibizumab had significantly higher rates of polyp closure, close to 80%. This is really a validation of our clinical observation and our own clinical experience. In addition, the combination arm seemed to help in terms of reducing the treatment burden,” he said.

In non-AMD CNV, ranibizumab works equally well. Wolf and colleagues showed between a 9- and 14-letter gain in patients with myopic CNV, with very few injections.

“This is a much different story than we are used to in AMD-related CNV. It is comforting that in any situation where CNV affects vision, we can use an anti-VEGF agent such as ranibizumab for safety and great efficacy,” Prof. Koh said.

Anti-VEGF treatment is not perfect; CATT showed by year 5 a decline in vision back to baseline after the initial gains.

“I believe some of that regression is related to the natural history of the disease, not because of the failure of the drug treating it,” Prof. Koh said.

Anti-VEGFs have had an “immense global impact on blindness, and this is really the true test of any treatment,” Prof. Koh said. “For example, in Denmark there was a 50% reduction in blindness associated with AMD after the introduction of ranibizumab in 2006. Similarly, in Scotland there has been a 60% reduction in legal blindness due to AMD. Neil Bressler, MD, noted that ranibizumab given monthly would reduce the incidence of legal blindness in 2 years by 72%.”

Ranibizumab “has definitely delivered on its promise and continues to do so,” Prof. Koh said. “It has given us excellent results and safety in CNV treatment. The introduction of anti-VEGF agents such as ranibizumab has led to a significant decline in blindness and visual impairment due to AMD,” he said. “But I believe that we are only on the cusp of the beginning of a long road in our ongoing fight against AMD.”

“These are very impressive results. We could now tell our patients they would avoid moderate vision loss, but more significantly, the improvement in vision might mean the difference between an ability to drive or ability to read or discriminate faces.”

—Prof. Adrian Koh
When the Diabetic Retinopathy Clinical Research Network published the results of its Protocol T trial,1 “it impacted the way we decide which drug we are going to use to treat our patients with diabetic macular edema,” said Patricio Schlottmann, MD. But the study was US-funded, and only enrolled US patients; 0.3-mg ranibizumab is approved for monthly treatment of diabetic macular edema (DME) in the United States; outside that country, the 0.5-mg dose is approved to treat DME.

“The treatment protocol was not the typical PRN that is commonly practiced,” he said. “Protocol T used a computer-based decision-making process based on visual acuity and variable thickness of the retina on optical coherence tomography.” The first year results found all three anti-VEGF agents to be similar, “but these are patients with really good visual acuity —20/32 to 20/40. In several places in the world these patients may not be treated,” he said.

When the results were qualified by patients with 20/50 or worse vision, however, the difference is greater for aflibercept over the 0.3-mg ranibizumab. However, these visual acuity differences are skewed by a small group of 37, 29, and 32 patients that have very poor vision,” Dr. Schlottmann said. “These patients with poor vision do not do very well when you treat them with 0.3-mg ranibizumab that is used in the United States.”

“Results continued to improve with ranibizumab in the second year [of Protocol T], whereas they began to decline with aflibercept, regardless of baseline vision.”

—Dr. Patricio Schlottmann

Protocol T Year 2 results have been recently published,2 and the differences between the aflibercept and ranibizumab groups disappeared. Results continued to improve with ranibizumab in the second year [of Protocol T], whereas they began to decline with aflibercept, regardless of baseline vision (Figure 1).

“Some may say that we should use the drug that provides earlier results, but that is not a valid argument any more than suggesting that after the first year, patients will start losing vision in one drug and gaining vision in the other drug. Neither assumption is very solid,” he said. Further, the average number of injections was similar between the two groups (14.8 injections in the ranibizumab group and 14.2 in the aflibercept group), so “claims about durability did not transpire,” Dr. Schlottmann said.

Protocol T used the 0.3 mg ranibizumab that is approved in the United States, but RISE and RIDE evaluated both the 0.3-mg and the 0.5-mg versions and found essentially the same outcomes.3,4

RISE and RIDE essentially compared either 0.3 mg ranibizumab to sham treatment or 0.5 mg ranibizumab to sham treatment. In the RISE study at both 24 and 36 months, the 0.3-mg arm fared slightly better than the 0.5-mg arm, but this has been the only study with such results.3,4

The single most important factor in determining potential visual gains is baseline visual acuity, Dr. Schlottmann said. “If baseline visual acuity is very good (20/32), at most patients might gain 5 letters. But if the baseline vision is quite poor (20/100), patients can easily gain 25 or 30 letters. The baseline vision for the RIDE4 study was about 57 letters in each arm. But for RISE, the baseline vision was 57 letters in the sham arm, 54.7 in the 0.3mg ranibizumab arm, and 57 letters in the 0.5mg ranibizumab arm,” Dr. Schlottmann said. “The reason the 0.3-mg ranibizumab arm fared better in RISE4 is the poorer baseline visual acuity—17% had 20/200 or worse baseline vision—and the increased need for laser rescue therapy (Figure 2).”

RISE and RIDE “confirm what we have seen in Protocol T—that a small group of patients with poor vision do not do well if they are treated with 0.3-mg ranibizumab,” Dr. Schlottmann said. This is reconfirmed in RISE and RIDE by the percentage of patients who needed rescue laser therapy (Figure 3)—30% more in the 0.3-mg
ranibizumab arm than in the 0.5-mg ranibizumab arm.\textsuperscript{4,5} RISE and RIDE found no safety difference between the two arms of ranibizumab.\textsuperscript{4,5} In RIDE and RISE, visual acuity gains tended to be better with ranibizumab 0.5 mg in patients with poor baseline vision (Figure 4).

The visual acuity results at 12 months reported in Protocol T are inconsistent with other published studies,\textsuperscript{1-4,6-12} Dr. Schlottmann said. There is also potential bias with Protocol T, he said because “the principle investigators, study coordinators, and visual acuity testers were aware of treatment assignments and that leaves the data open to the possibility of bias. When you conduct a trial without masking, results can be overestimated. It is that potential for bias that may have affected the outcomes presented in Protocol T,” he said.

“When we make our clinical decisions and must choose between one drug or another, we should all look at the entire range of evidence that is published, and not put so much emphasis on one study over the rest,” Dr. Schlottmann said.

With the introduction of the anti-VEGF agents came an increased treatment burden, which has led to some clinicians implementing a “treat and extend” protocol.

“We are still determining if there are preferable treatment regimens, especially in light of real-world evidence,” said Asso. Prof. Francesco Boscia, MD.

The clinical trials discussed earlier in this supplement have shown monthly intravitreal injections of ranibizumab effectively improve visual acuity in both neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME).\textsuperscript{1-4}

“There has been an issue with compliance for both the patient and the physician since almost the beginning,” Asso. Prof. Boscia said. The question became whether extending treatment beyond a monthly injection (after the dose-loading phase) could achieve similar outcomes.

“The PIER\textsuperscript{5} and EXCITE\textsuperscript{6} studies found there was a benefit from injecting patients with AMD-related subfoveal choroidal neovascularization (CNV) quarterly after the dose-loading phase, but EXCITE did find a higher gain in patients who had monthly doses versus quarterly,” Asso. Prof. Boscia said.

These neovascular conditions all have continuous chronic VEGF levels; “while we though initially that ranibizumab had the capability to suppress VEGF for 30 days, studies have shown more than half the patients receive VEGF suppression that lasts, on average, 34 to 37 days, with some receiving VEGF suppression for more than 41 days,” Asso. Prof. Boscia said.

The decreased ability of the anti-VEGF drug to continue suppression after a set period of time, which is another way to say “disease reactivation,” is the driving force behind why the PRN regimen was introduced. The SUSTAIN, IVAN, and HARBOR studies incorporated a PRN arm, and in SUSTAIN,\textsuperscript{7} 20% of patients required no additional treatments following the dose-loading phase and HARBOR confirmed a large variation in the number of injections needed when using a PRN protocol (Figures 1 and 2).\textsuperscript{10} In both studies, Asso. Prof. Boscia noted the PRN arm “compared favorably with the monthly treatment.” In IVAN,\textsuperscript{11,12} vision outcomes were similar between monthly dosing and the PRN arm.
However, "two other large randomized controlled trials, CATT"¹³ and VIEW,"¹⁴ showed that as soon as the regimen was changed from monthly to the PRN, there was a drop in visual acuity," Asso. Prof. Boscia said. "The optical coherence tomography (OCT) monitoring is applied in a less vigorous manner in PRN, meaning we lack the sensitivity and robust biomarkers needed for OCT-based re-treatment."

In AURA,"¹⁵ PRN dosing led to less robust results than monthly dosing; the mean number of injections was 9 in the United Kingdom and 5.2 in Italy over the course of 2 years. "Less frequent monitoring and (therefore) fewer injections are associated with poorer outcomes," Asso. Prof. Boscia said.

In 2007 the treat-and-extend regimen (TER) was introduced,"¹⁶ "with the real assumption of merging a scheduled treatment with the flexibility of treatment interval," Asso. Prof. Boscia said. "The purpose was to extend visits and treatments as soon as the neovascular disease was stabilized."¹⁷,¹⁸

The TER algorithm is used for evaluating patients for monthly injections until a maximal clinical response is observed (frequently determined by OCT), followed by increasing intervals between injections (and evaluations) depending on disease activity."¹⁹

There is support for a TER regimen from the TREX trial, where patients with neovascular AMD were randomized to either TER or monthly dosing."²⁰ The mean number of injections through month 12 was 13 in the monthly cohort and 10 in the TER cohort, which was statistically significant; visual function was within a letter between the two groups (Figure 3).

"What we learned from this trial is that more than 25% of patients need an injection every 3 months, and only 20% of patients needing an injection monthly," Asso. Prof. Boscia said.

The LUCAS study had similar results."²¹ This study compared bevacizumab to ranibizumab in a TER and found "there was a good preservation of the visual acuity improvement achieved during the enrollment phase through 2 years," Asso. Prof. Boscia said. "There is also some evidence for DME that this regimen is effective."

The RETAIN"²² study compared ranibizumab plus or minus laser in a TER regimen or a ranibizumab PRN regimen based on an individualized criteria for TER, Asso. Prof. Boscia said.

"Both groups had a similar functional improvement, and there were no significant differences across the treatment groups at months 12 and 24 (Figure 4)," Asso. Prof. Boscia said. TER provided "an approximate 40% reduction in the number of patient visits, and about 70% of patients on the TER regimen had monitoring intervals longer than 2 months."

Retina specialists across Europe are faced with capacity issues, Asso. Prof. Boscia said. In the United Kingdom, a new "observe-and-plan" or "monitor-and-extend" regimen is taking hold; in this treatment regimen, following the loading phase physicians inject only when the disease is active and extend monitoring intervals in patients with disease stability."²³ Two-year results indicate visual function is preserved with fewer injections (averaging 2.2 months per treatment in year 2).²⁴,²⁵

Two new studies, BRIGHTER and CRYSTAL, evaluated if a PRN regimen is superior based on BCVA stability.
“BRIGHTER\textsuperscript{26} assessed the superiority of an individualized stabilization-criteria-driven PRN regimen of ranibizumab with or without laser versus laser alone for 6 months. CRYSTAL\textsuperscript{27} is also an efficacy study which involved PRN regimen of ranibizumab,” Asso. Prof. Boscia said. “Both studies included a large number of ischemic patients to specifically evaluate the effect of macular ischemia on visual acuity gains. Ischemia was graded as mild, moderate, or severe according to a grading scale. The outcome of this study was somehow surprising.”

BRIGHTER found the severity of ischemia did not affect the visual acuity over 6 months (Figure 5), Asso. Prof. Boscia noted. In CRYSTAL the presence of ischemia and the severity of ischemia at baseline “did not affect the BCVA over time (Figure 6),” he said.

There is a growing body of literature to support individualized treatments and reduce the overall treatment and injection burden for patients and clinicians, Asso. Prof. Boscia said.

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**Figure 4.** RETAIN study in DME.

**Figure 5.** BRIGHTER study in BRVO.

**Figure 6.** CRYSTAL study in CRVO.
Age-related macular degeneration (AMD) is a disorder of the macula that affects older people, said Prof. Usha Chakravarthy, MD, PhD, University of Belfast, Royal Victoria Hospital, Belfast, UK.

“We have a range of manifestations of AMD ranging from early macular degeneration which has almost no impact on function, to severe sight loss that comes with late stage manifestations,” she said. It is these later stages that are most disconcerting to retina specialists. In the later stages, the disease may develop into either geographic atrophy (GA) or neovascular AMD, Prof. Chakravarthy said, and the two are not mutually exclusive. Both early AMD and GA are sometimes referred to as dry AMD.

Neovascular AMD—sometimes called wet AMD—involves retinal hemorrhage and exudation in the macula, all of which leads to full receptor obstruction, adversely impacting vision.

“In the United Kingdom, there is a marked increase of neovascular AMD in older age groups, with prevalences of 4.8% aged in people at least 65 years old, but 12.2% in those older than 80 years. There is a difference between men and women,” she said. The gender differences may be because women live longer, but there may be a slight increase in susceptibility to AMD in women. The natural history of the disease includes “a great reduction within a few months, with most people ending up with massive reduction in visual function, even within a period of 2 years.”

In randomized clinical trials, it is common to use the Early Treatment of Diabetic Retinopathy Study (ETDRS) letter chart to monitor vision changes.

“A moderate change in vision equates to a drop of vision by about 15 letters, which is a 3-line change on this chart (Figure 1),” Prof. Chakravarthy said. A marked change would be 30 letters, or about 6 lines.

The ANCHOR study marked the first time researchers were able to show improvements in visual acuity in people with neovascular AMD, she said.

“But what does this actually mean in terms of what we observe in our patients?” she asked. “The natural history of AMD suggests most patients will end up only being able to see the top line of the ETDRS chart with their affected eye. After photodynamic therapy, the average improvement was a 1-line change on the ETDRS chart, or about 5 letters better. After Macugen (pegaptanib), vision improved by about 10 letters compared to natural history. After ranibizumab was introduced, we now had patients gaining 3 or more lines (Figure 1).”

Unfortunately, she said, normal vision (20/20 or better) has not been achievable in any clinical trial to date. There are, however, three known macular morphology factors that contribute to the poor visual acuity in neovascular AMD: retinal pigment epithelium (RPE) tear, fibrosis, and atrophy.

“In RPE tears, the RPE has curled up and torn away, leaving a denuded area, and this type of appearance is completely inconsistent with any level of good vision,” Prof. Chakravarthy said. “Figure 2 shows an escalating range of fibrosis, with the gradient of vision going from very good vision to poor vision. This was first described in 2003.”
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When we looked at the RPE lesion components that influence visual function in AMD.”

With the introduction of the anti-VEGF agents, “we are limiting fibrosis somewhat, but are we also limiting atrophy?” Prof. Chakravarthy asked. Figure 3 again illustrates an escalation in atrophy, “and all of these eyes received anti-VEGF therapy,” she said. “When there is no fibrosis or atrophy, the visual acuity remains good, but when there is atrophy—even in the absence of fibrosis—there is poor visual acuity.”

Toth and colleagues found the use of anti-VEGF “even in eyes with low visual acuity, particularly when fibrosis and atrophy are absent” can be beneficial.

“So, why are we disappointed with our outcomes? First, we may not be preventing certain types of pathology developing in the macula,” Prof. Chakravarthy said. “We often measure BCVA, but that may not reflect the true state of function. There are also some unrealistic expectations relating to clinical trial inclusion criteria.”

For example, Prof. Chakravarthy described a patient with improvement in vision to 58 letters after treatment with anti-VEGF from a baseline of 48 letters, and a recurrence of the disease in between visits 2 and 3 —yet visual acuity remained unchanged.

“There remains an inconsistency or disparity between visual acuity outcomes and what we observe on retina morphology,” she said.

“What really matters to patients, however, is their ability to read, their ability to maintain independence.”

— Prof. Usha Chakravarthy

“Based on both function and morphology, about one-third of the eyes we treat daily in clinical practice would not meet inclusion criteria for these randomized clinical trials. We cannot say to these patients that they will get the same sort of outcomes that has been observed in clinical trials.”

What really matters to patients, however, is their ability to read, their ability to maintain independence, “and in this particular age group, which are elderly patients, the ability to self-care and care for others,” Prof. Chakravarthy said.

A cross-sectional study Prof. Chakravarthy and colleagues undertook in 2004 evaluated “around 200 participants with either wet AMD or GA in at least one eye,” she said. “We measured their BCVA, near acuity and contrast. We asked about the self-reported ability to care for eyes themselves or others, and how they managed to do various daily living tasks. We assigned them to three levels of vision.

“Those people who could not look after themselves were assigned to care level 1. Those who could look after themselves were assigned to care level 2. And those who could look after both themselves and someone else were assigned to level 3,” she continued.

Figure 4 illustrates the key findings of the study: there is a gradient with those who cannot care for themselves having the worst function in distance, near acuity, and contrast, and those who can care for themselves and others having the best function in the three visual outcomes.

Figure 4.

“To summarize, visual function is a critically important physiological measure that is necessary for us to live our normal lives, and maintaining visual health is an important part of healthy aging,” Prof. Chakravarthy said.

Extension: Improving Outcomes With Anti-VEGFs

The potential visual outcomes for patients with retinal disorders is far superior to what likely outcomes were even a mere 15 years ago, but “how can we improve today and how can we improve outcomes tomorrow?” asked Prof. Ramin Tadayoni, MD, PhD, chairman, Hopital Lariboisiere and professor of ophthalmology, Sorbonne Paris Cité University, Paris, France.
First, he said, let us determine what is meant by “improvement.” “For the patient it is very clear. The single most important factor for patients is their vision, and it is the actual value of the vision and not necessarily a gain in letters,” he said. Vision increases (or improves) when patients with diabetic macular edema (DME) or neovascular age-related macular degeneration (AMD) are treated with the anti-VEGF drugs because the extra fluid and edema are being removed; when fluid and edema exist, vision decreases.

“We know that only a small proportion of patients will have vision better than 20/40—part of the retina is destroyed and we cannot repair that,” Prof. Tadayoni said. “This is likely the reason why we get different results with the same treatment in different patients.” In the VIEW studies, for example, only 33% to 39% of the 2,419 patients receiving an anti-VEGF drug achieved 20/40 or better vision at 52 weeks.1

“While we can control to some extent the macular edema and we treat that earlier to achieve better results in patients with DME, in AMD the baseline criteria is not as easy to control,” Prof. Tadayoni said. “Some patients have type 1 neovascularization, others have type 2, some are central, others are not, and these characteristics cannot be altered. Since we cannot act to change those parameters, what can be done?”

The PIER study showed 34% of patients had no initial response to treatment, and of those that did respond, 60% did not maintain that vision gain in the first 12 months.2 HORIZON showed that by 5 years, most patients had returned to baseline vision.3 SEVEN-UP looked at 65 patients who had been enrolled in the MARINA and ANCHOR studies, all of whom had been in the treatment arms, and found at 7 years the mean vision had fallen to worse than baseline.4

“These outcomes are across the whole range of anti-VEGFs,” Prof. Tadayoni said, but emphasized that while vision does slowly decline after improving with the anti-VEGF treatments, “compared to the natural history of the disease, we are doing much, much better,” he said. In HORIZON, for example, patients who received treatment lost a mean 0.1 letters at year 5, compared to a mean loss of 16.1 letters in the non-treated group.3

“Can we have better vision and maintain those gains? Prof. Chakravarthy explained (see article on page 11) the numerous factors that result in disease progression—fibrosis, atrophy, and hemorrhage,” Prof. Tadayoni said. “If you look at studies evaluating patients on a fixed regimen, that seems to be the way to retain good vision (Figure 1).5 So, the diagnosis of AMD is not a vision fatality. Anti-VEGF treatment can control those aspects of disease to give the patient better vision.”

Patients in different countries will also respond differently to the same drug.6 In France, for example, Prof. Tadayoni noted mean visual acuity fell below baseline around Day 570, but in the UK, visual acuity was still around +5 letters at the same time point (Figure 2).

“We know from SEVEN-UP that eyes that were consistently injected fared much better than those with variable injection schedules,” he said. Eyes with more than 11 injections between years 4 and 7 had the best final visual acuity: +3.9 letters.4

Switching from strict monthly treatment to a PRN dosing regimen may not be advantageous in this disease, Prof. Tadayoni said.
to us 12 times per year. Before switching to the short path, they had around 6 to 7 visits per year. After switching to the ‘short pathway’ in which we guarantee the patient that will come once a month and stay less than 2 hours, it increased naturally to 11 visits (Figure 4),” Prof. Tadayoni said.

“We are not the only group evaluating how to change the delivery of care,” he said. Konstantinos and colleagues7 evaluated the concept of virtual clinics to monitor patients with AMD and found improved adherence, improved visual acuity, and little difference in injection rates. However, Markun and colleagues found a chronic care model did not improve visual acuity outcomes.8

“We have good drugs, we have a lot of good treatment regimens, and we have to customize this care delivery to have the patient

Figure 3.

Figure 4.

Expansion: New Pathways

“...It is important to choose a treatment regimen that works for each patient while not overburdening the clinic.”
— Prof. Ramin Tadayoni

“We are on the precipice of a change in how we treat neovascular age-related macular degeneration.”
—Dr. Pravin Dugel

a 70-year-old patient, living independently, was doing fine until she had fibrosis and loss of vision.

“When she came to see me her vision was 20/200. I treated her for many years with bevacizumab because of insurance reasons, and this patient’s vision improved to 20/40,” Dr. Dugel said. “She continued to be treated and although the optical coherence tomography (OCT) was dry, she gradually lost vision. Prof. Chakravarthy alluded to some of those reasons—scarring and fibrosis. Switching among the approved anti-VEGF agents that we have now does not seem to matter all that much.”
In his real-world data from a US-based electronic medical record (EMR) database, “treatment burden is not decreased whether you start with aflibercept and switch to ranibizumab or vice versa,” he said. “And it does not seem to alter the long-term vision outcomes or short-term gains.”

Even after the data was subdivided into patients with good vision (<69 letters) or poor vision (≥69 letters), “there was not much of a difference at all. There just did not seem to be a benefit in switching (Figures 1 and 2),” Dr. Dugel said.

And even when we sub-divided this into patients who did not see well versus patients who did see well, there seemed really to be not much of a difference at all. When we sub-divided the patients further, to see if there is any group that might benefit from one or the other, there did not seem to be a benefit.

While there is no definitive answer just yet, Dr. Dugel said there may be some on the horizon.

“We know neovascularization is a complex process. We also know that VEGFs are integral to the process,” he said, “so one obvious solution is to block VEGF even better.”

Among the potential solutions: RTH 258, or brolucizumab, a small, single chain antibody fragment, that is about half the size of ranibizumab, Dr. Dugel said.

“The idea is that a single-strand antibody can better penetrate tissue, directing more drug at the target and possibly lowering the systemic exposure,” he said. Early phase studies “show brolucizumab might decrease the central subfoveal thickness a little more than ranibizumab. Other early phase studies showed brolucizumab may provide a little more visual acuity gain. In a head-to-head analysis and follow-up extension analysis, brolucizumab required fewer rescue treatments. Duration also may be longer (Data on file, Alcon).” About half the patients treated with brolucizumab were successfully extended to every 12 weeks.

DARPinS are another burgeoning area of research, Dr. Dugel said.

“Abicipar pegol is a naturally occurring Ankyrin protein. These proteins can be constructed to last as long or as little as one needs,” Dr. Dugel said. “DARPin has a longer half-life and a good binding capacity, so presumably it may last longer than current anti-VEGF treatments.”

The early phase REACH study (Clinicaltrials.gov NCT01397409; Data on file, Allergan) had encouraging results, culminating in the phase 3 SEQUOIA and CEDAR studies, currently underway and expected to enroll up to 900 patients each.

“Unfortunately, in this area, the news has been a little bit disappointing recently,” he said.

Two companies were evaluating genetic therapies—Genzyme through intravitreal injections and Avalanche through subretinal injections—but disappointing results halted further investigation.

“Neurotech is developing encapsulated technology to deliver an anti-VEGF-A drug that you could presumably insert and remove at will,” he said. “Unfortunately, the study has been stopped because it was found to be ineffective in patients with neovascular AMD.”

Ongoing studies on a “very sophisticated pump, the Replenish pump, that consists of a series of micro-pumps that can be precisely programmed,” he said. Genentech’s port delivery system uses a refillable subconjunctival port to administer therapeutics.
Combination therapies, however, “are perhaps the most exciting strategy,” Dr. Dugel said.

RG-7716, co-developed by Genentech and Roche, is “a very elegantly designed molecule. A proprietary Cross Mab technology allows for the creation of an anti-VEGF-A arm and an anti-ANG2 arm in a single molecule. By binding to or inhibiting Ang2, there is some evidence of vessel stabilization,” Dr. Dugel said. “The FC site is tailor made for ophthalmology. A phase 1 study on RG-7716 met an endpoint of demonstrating safety as well as demonstrating a biological signal. In the single dose study there was a 7+ letter improvement. In the multiple-dose study (Data on file, Roche/Genentech) the 6-mg arm, there was a 7.5+ letter improvement as well as a decrease in the central subfield thickness over 100 microns.”

Squalamine lactate “has a very broad spectrum action and is a topical solution,” Dr. Dugel said. “It is isolated from the dogfish shark and seems to be broad acting in inhibiting VEGF, platelet-derived growth factor (PDGF), and basic fibroblast growth factor. The IMPACT phase 2 study suggested squalamine may have a positive effect if there is a limited amount of occult characterization of the vessel and more of the classic type vessel.”

OPT-302 is under evaluation to determine if pan-VEGF inhibition may help patients who are refractory to the VEGF-A inhibition,” Dr. Dugel said. “When we inhibit VEGF-A, we upregulate VEGF-C and VEGF-D. OPT-302 may target these incomplete responders by inhibiting VEGF-C as well as VEGF-D.” A phase 2b study should start in 2017.

Pegpleranib is the furthest along in development, and “we are learning how neovascularization occurs. There are specific tip cells that upregulate PDGF, which then recruit and mature pericytes to back cover the neovascular complex, like a protective armour against anti-VEGF drugs. This may be the source of some of the resistance that we are seeing,” Dr. Dugel said. “With dual inhibition, chemically these pericytes will be stripped, exposing the endothelial complex, allowing for the anti-VEGF-A to be more effective.”

Pegpleranib is an aptamer that may end up being disease modifying, according to Dr. Dugel: “It may modify the disease by chemically stripping these pericytes and exposing endothelial cells. The largest phase 2b study in retina shows that there was a 4.1 letter (62%) improvement with combination therapy the highest dose versus ranibizumab alone2 (Figure 4).”

Pegpleranib also had a classic dose response curve; at month 6 “the curves were divergent, suggesting that further improvement may occur.” The phase 3 registration trial has just finished recruitment.

“In conclusion then, I think we have reached a ceiling effect of our current anti-VEGF-A monotherapy treatment, both logistically and physiologically,” Dr. Dugel said. “Potential new strategies include a better anti-VEGF-A, a drug delivery system, or combination therapy.”

Figure 4.

Exploration: New Horizons in Ophthalmology

Age-related macular degeneration (AMD) “is really one of the best understood late-onset multifactorial complex diseases,” said Prof. Frank G. Holz, MD. “There has been enormous progress in understanding the genetic and biological factors through the convergence of basic science and clinical data, and that understanding is paving the way for new targets for new drug developments.”

And so, “despite the increasingly sophisticated diagnostic tools and imaging devices, and despite the tremendous advances we have heard about throughout this symposia, there are still unmet medical needs in this disease,” Prof. Holz said. Among the outstanding challenges: finding solutions for non- and poor responders, decreasing the treatment burden, finding treatments for other subtypes of AMD, including polypoidal choroidal vasculopathy (PCV), retinal angiomatous proliferation (RAP), and dormant CNV in intermediate AMD—the phenotypes of AMD that respond differently from classic or chronic CNV.

“We have heard from Dr. Dugel (see article on page 14) on what we need to do about fibrosis, atrophy, and hemorrhages. In the end,
we look at the Holy Grail of AMD therapy: to intervene in early and intermediate AMD to prevent the late stages,” Prof. Holz said.

One means to detect disease earlier is to use the imaging devices currently available. Figure 1 is typical of how “we not only see response to anti-VEGF, but how we base our treatment decision on what we see on optical coherence tomography (OCT), although interpretation can be challenging at times,” he said. “Figure 1 shows typical reticular pseudodrusen that we have all seen. But OCT can help confirm the reticular sitting on the wrong side of the retinal pigment epithelium (RPE). These classical drusen are under the RPE and in Figure 1, it is on top.”

Figure 1.

When clinicians were first able to image the abnormality, it was thought to be benign, but “we have learned that this is toxic material. We do not yet have the solution to clear the retina of this toxic adversarial material. And this has an impact,” Prof. Holz said.

As the imaging modalities increase in resolution, clinicians are now able to clearly identify the dysfunction in the retina.

“OCT-angiography may replace the more invasive fluorescein indocyanine angiography (FAF), and I believe we will begin using OCT-angiography to diagnose a large proportion of wet AMD patients,” Prof. Holz said. Figure 2 illustrates just how detailed the imaging has now become, “where we see exudation, we may not need additional information on the leakage. Look at the difference in detail between the FAF image and the OCT-angiography.”

Figure 2.

But better imaging also leads to more questions—“should we treat the new vessels above Bruch’s membrane? Are they friend or foe? They may nourish the retina in a better way and maybe increase retinal nerve fiber layer survival,” Prof. Holz said. OCT-angiography is noninvasive, which may also help relegate fluorescein and indocyanine green angiography to a secondary modality.

Adaptive optics scanning laser ophthalmoscope is, in essence, “single-cell psychophysics,” Prof. Holz said. “You can see not only the individual photoreceptors but you can stimulate them individually. So this would lend in future to much earlier diagnosis of disease and testing interventions at a much earlier stage before we see morphological damage on OCT. But again, this is still a work in progress.”

Ultimately, he said, molecular imaging would allow for even earlier disease detection and therapy monitoring.

“Ophthalmology is again at the forefront of this compared to other medical fields. We have an almost perfect optic situation—we do not need to go through hair or internal organs,” he said. Molecular in vivo imaging would allow for monitoring intraocular vascular endothelial growth factor (VEGF) molecules “in order to measure VEGF upregulation before it cause exudation,” Prof. Holz said. “We may treat our patients in a much more individualized manner in the future—before we see morphological changes. This may result in better visual outcomes.

“As we heard earlier, even if we successfully treat our patients and eliminate the macular edema, if atrophy develops the patient will lose vision despite the successful anti-exudative therapy,” Prof. Holz said. “CATT, IVAN, and HARBOR all showed that by month 24, approximately 30% of patients will develop atrophy despite monthly treatment. We just do not know which patients (Figure 3).”

Also unknown is whether treating with anti-VEGF injections trigger the onset of geographic atrophy (GA). Foveal-sparing treatments

“There are still unmet medical needs in this disease.”
—Prof. Frank G. Holz
are “of utmost importance” in GA, he said. “This feeds into studies trying to slow (and ideally halt) the process.”

“There is an ongoing search for innovative therapies to target newly identified pathophysiological pathways identified in GA,” Prof. Holz said. “Dr. Dugel pointed out several new compounds in development, some with high potential, others have already failed,” he said. For late-stage AMD or GA, however, one of the more promising compounds is lampalizumab, Prof. Holz said. This complement factor D inhibits the initiation/amplification of an alternative pathway.

With no approved treatment available, finding treatments for GA are “a first priority for many,” Prof. Holz said.

The phase 2 MAHALO study (Data on file, Genentech) confirmed a differential treatment response by lampalizumab. There was a biological signal of efficacy at month 18 for monthly lampalizumab versus sham. Larger phase 3 studies are under way that will hopefully provide definitive answers about the viability of lampalizumab over the long term.

“We are still in our infancy when it comes to finding treatments for AMD.”

—Prof. Frank G. Holz

“We may also need to vary how we select our patients in the future,” Prof. Holz said. “Early studies with lampalizumab found it was more successful in patients with a certain genetic profile.”

Atrophy is not restricted to the macula; “in the end AMD is not a macular disease. It is a pan-retinal disease,” Prof. Holz said. Figure 4 describes just some of the drug delivery devices and treatments being evaluated for AMD.

“We are still in our infancy when it comes to finding treatments for AMD,” Prof. Holz said. “Stem cell therapy may prove beneficial, but it is still in the early days of discovery. Until we find a way to use stem cells to directly replicate RPE photoreceptors and be able to introduce them back into the eye, it is likely a distant future development.”

The improvements in diagnostics, in understanding AMD and its treatment therapies, and the increasing interest in developing new treatment modalities are benefiting patients today, and will continue to improve treatments down the road.

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TRANSFORMING RETINAL DISEASES: THE DESIGN. THE DECADE. THE DIFFERENCE.

DEVELOPMENT WITH AN EYE ON DESIGN


DELIVERING PERFORMANCE IN CHOROIDAL NEOVASCULARISATION TREATMENT

THE NEED FOR CONTINUOUS INNOVATION IN RETINAL CARE

UNMET MEDICAL NEEDS


EXTENSION: IMPROVING OUTCOMES WITH ANTI-VEGF


EXPANSION: NEW PATHWAYS


The safety and efficacy of ranibizumab in children and adolescents below 18 years of age have not been established.

Contraindications:
Hypersensitivity to ranibizumab or any of the excipients, patients with active or suspected ocular or periocular infections, patients with active severe intraocular inflammation.

Warnings:
Intravitreous injections have been associated with endophthalmitis, intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors. Due to limited data in patients with prior history of stroke or transient ischaemic attacks, caution should be exercised when treating patients with DME, RVO and CNV due to PM. Should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus.

Precautions/Interactions:
Serious adverse reactions include: vitritis, vitreous detachment, retinal haemorrhage, visual disturbances, eye pain, vitreous floaters,conjunctival hyperaemia, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritus, intraocular pressure increased, nasopharyngitis, headache, arthralgia, conjunctivitis, conjunctival hyperaemia, iritis, keratitis, anterior chamber flare, vision blurred, posterior capsule opacification, punctuate keratopathy, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photophobia, dry eye, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia, urinary tract infection,

Common adverse reactions are:
blindness, endophthalmitis, hypopyon, hyperaemia, keratopathy, iris adhesions, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eye irritation, eyelid edema, eyelid erythema, eyelid pain, conjunctival hyperaemia, urinary tract infection, anaemia, hypertension, anxiety, cough, nausea, allergic reactions (rash, pruritus, urticaria, erythema), Uncommon adverse reactions are: blindness, endophthalmitis, hypopyon, hyperaemia, keratopathy, iris adhesions, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation, serious adverse reactions include endophthalmitis, blindness, retinal detachment, retinal tear and intravitreal traumatic cataract Products-class-related adverse reactions: there is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the LUCENTIS® clinical trials in patients with AMD, DME, RVO and PM and there were no major differences between the groups treated with ranibizumab compared to control.

Note: Before prescribing, consult full prescribing information.

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