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# Ranibizumab—Retinal Care for All Ages:

## RIVAL (nAMD) to RAINBOW (ROP)

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This supplement features summaries of presentations from a Novartis-sponsored symposium held at the 2019 EURETINA meeting in Paris.

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- A New Horizon in ROP: The RAINBOW Study
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- Clinical Perspectives on Ranibizumab as a Therapy for All Ages
  *Moderated by Ramin Tadayoni*


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# Ranibizumab—Retinal Care for All Ages:
## RIVAL (nAMD) to RAINBOW (ROP)

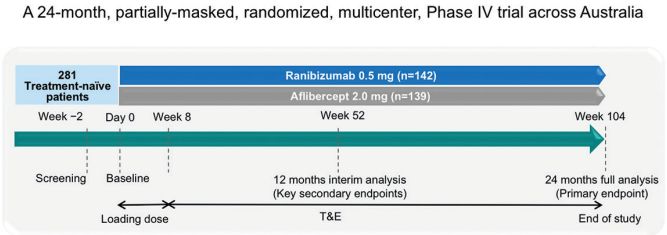
### Clinical Value of Treat-and-Extend Regimen and the RIVAL Study

**Patricio Schlottmann**

In early clinical trials of ranibizumab in neovascular age-related macular degeneration (nAMD), such as ANCHOR and HARBOR, patients achieved impressive mean gains in vision with monthly dosing (11.3 and 10.1 letters, respectively, at 12 months).[1,2] Patients in the 2007 PrONTO study achieved a similar mean gain of 9.3 letters with 5.6 injections given according to a prn regimen.[3] These outcomes appear superior to the mean gain at 12 months of 6.2 letters with 8.7 injections reported in the 2018 TREND study of ranibizumab given according to a treat-and-extend (T&E) regimen.[4] However, these results should be considered in light of the fact that the profile of patients enrolled into nAMD clinical trials has evolved since anti-VEGF agents first became widely available, with the average patient now having considerably better vision at baseline.

Patients in ANCHOR, HARBOR, and PrONTO had mean baseline VAs of 47.1, 54.5, and 56.2 letters, respectively, compared with 60.7 letters in TREND, meaning patients in the earlier trials had greater scope for improvement upon treatment.[1-4] Indeed, comparing the absolute mean VA scores at 12 months in ANCHOR, HARBOR, PrONTO, and TREND (58.4, 62.7, 65.5, and 68.6), it can be seen that the best final mean VA score was seen with the T&E regimen in TREND.[1-4] "It's difficult to tell what matters the most," said Prof. Patricio Schlottmann.

## Study design




nAMD, neovascular age-related macular degeneration; n, number of patients; T&E, treat and extend

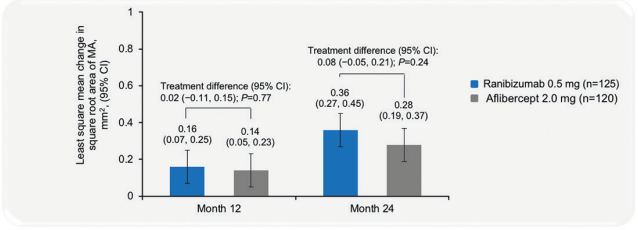
Figure 1. RIVAL study design.

"Is it the number of letters gained, or is it the final vision that the patient achieved? Baseline VA may confuse the comparison between trials."

In a meta-analysis of 42 real-world observational studies of ranibizumab for nAMD published between 2007 and 2015, patients treated according to a T&E regimen achieved mean VA gains at 12 months of 8.8 letters, compared with 3.5 letters for prn.[5] This was with a greater mean number of injections (7.3 vs 5.4), but fewer clinic visits (7.8 vs 8.6).[5] More evidence for the benefits of T&E over prn dosing comes from a retrospective study of treatment-naive patients switching from a prn to a T&E regimen during routine clinical practice. A decrease in mean BCVA during prn maintenance therapy was reported following a gain achieved in the initial loading stage, followed by a sustained improvement in mean BCVA following the switch to T&E.[6] In addition, greater variability was seen in intraindividual BCVA during prn treatment versus T&E. The mean number of visits was significantly higher during the prn phase ($P < .001$).[6] "This evidence shows that T&E leads to a lower number of injections, greater comfort for the patient, and less burden for the clinician, for the system, and for the patient," said Prof. Schlottmann.

The RIVAL study is the first randomized clinical trial to compare the two anti-VEGF agents ranibizumab and aflibercept using identical T&E regimens (Figure 1).[7,8] This was a 24-month, partially masked, randomized, multicenter, phase 4 trial performed in Australia, with the primary objective being to discover whether a difference exists in the development of macular atrophy between the two agents in terms of growth in macular atrophy area over

**No statistical difference between ranibizumab and aflibercept in change in square root area of MA**



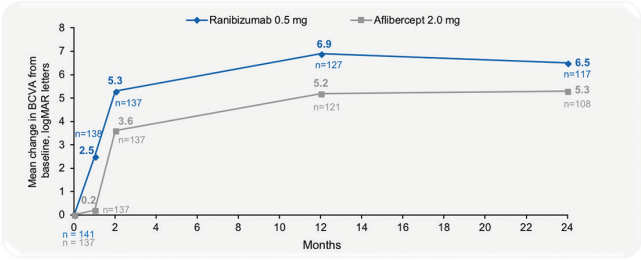

Full analysis set; Least square means=estimated change in area of MA from baseline; Mixed model analysis adjusting for baseline area of MA (Primary analysis); Results were similar when applying LOCF method. CI, confidence interval; MA, macular atrophy; LOCF, last observation carried forward

Figure 2. RIVAL primary endpoint: change in square root area of macular atrophy.

24 months. Key secondary outcomes included number of injections and change in BCVA at month 12.[7,8]

The T&E regimen used in RIVAL mandated three monthly loading injections before entering the T&E phase. During the T&E phase, the treatment interval was reduced by 2 weeks if one out of three prespecified disease activity criterion was present (out of loss of ≥ 5 letters from the best VA recorded since treatment started, new retinal hemorrhage, or the presence of any intra- or subretinal fluid on spectral domain-OCT), or to a 4-week interval if two or more of these criteria were present.[7,8] "An important point is that the presence of fluid was detected by the reading center which was fully masked to the randomization of the patients, removing the possibility of bias," said Prof. Schlottmann.

## Similar gains in BCVA with ranibizumab and aflibercept at Month 24




Full analysis set; Observed data at nominal visit window from CRF i.e. fixed visits included (baseline, Week 4, Week 8, Month 12, Month 24)
BCVA, best-corrected visual acuity; CRF, case report form; logMAR, logarithm of minimum angle or resolution

Figure 3. Mean BCVA change from baseline to 24 months in RIVAL.

The 24-month results of RIVAL are now available, and they reveal no statistical difference between ranibizumab and aflibercept in terms of the primary endpoint, change in square root area of macular atrophy ($P = 0.24$; Figure 2).[8] Longer term studies would be required to investigate the long-term effects of anti-VEGF on the development of macular atrophy.

Gains in BCVA with ranibizumab and aflibercept at month 24 were similar: 6.5 letters and 5.3 letters, respectively (Figure 3).[8] There was some evidence that patients in the aflibercept arm took slightly longer to initially achieve their vision gains, which could not be accounted for by factors such as differences in baseline characteristics or clusters of slow gainers at particular study sites, implying treatment errors.

The mean numbers of injections were very similar between arms, with patients in the ranibizumab group receiving 17.7 over 24 months and those in the aflibercept group receiving 17. A return to monthly dosing at any time over the 24 months was triggered in 64% of the ranibizumab group and 59% of the aflibercept group. The mean injection interval over 24 months was 6.1 in both arms, and the distribution of maximum injection intervals was similar between groups (Figure 4).[8] "If there was a myth of extra durability for one agent over the other, these results appear to dispel it: there is no difference between agents in terms of injection frequency," said Prof. Schlottmann. Safety results showed similar rates of ocular and non-ocular serious adverse events in both groups.[8]

## Highlights

- A T&E regimen provides better VA gains with a reduced number of injections compared with prn.[4]
- RIVAL is the first prospective randomized controlled trial comparing ranibizumab 0.5 mg and aflibercept 2.0 mg using a T&E regimen.[7,8]
- RIVAL found no statistical difference between ranibizumab and aflibercept in terms of development of macular atrophy in nAMD patients treated over 24 months. Number of injections, VA improvements, and safety profiles were also comparable between agents.[8]

**Similar distribution of maximum injection interval over 24 months in both groups**

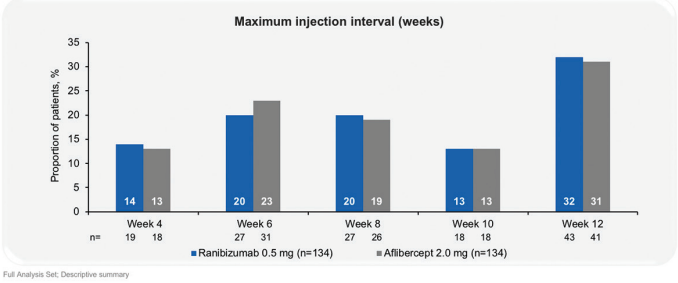



Figure 4. Maximum injection intervals over 24 months in RIVAL.

## Changing Clinical Paradigm in Diabetic Retinopathy

Adrian Koh

Diabetes is a growing worldwide epidemic, affecting the working age population. The number of individuals affected with diabetes is expected to increase by around 48% between 2017 and 2045.[9] A common microvascular complication of diabetes, diabetic retinopathy (DR) is the leading cause of blindness in working-age adults in the developed world.[10,11] The advanced, vision-threatening stages of DR are proliferative DR (PDR) and diabetic macular edema (DME).[10,11]

In clinical trials of DR, the Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity scale (DRSS) is used to grade the stage of DR and monitor change over time.[12] The scale can also be used in clinical practice. "The DRSS gives us all the opportunity to carefully study and accurately record changes in the stages and severity of retinopathy," said Prof. Adrian Koh. The DRSS ranges from level 10 (normal) to level 85 (advanced PDR) in 12 steps (Figure 5).

The DRSS is a clinically relevant measure that correlates with functional anatomical outcomes, including change in VA and retinal thickness.[13] An increase in DRSS level is associated with an increased risk of developing vision-threatening PDR or DME, and reduction in DRSS level is associated with improved VA and DME resolution.[13] A two-step change on the DRSS is considered to be clinically relevant. In the ETDRS study, patients with two or more steps of progression over the first 4 years were 5.8 times more likely to develop PDR than those without.[12]

Patients with eyes at DRSS levels 47 and 53 are on the threshold between PDR and non-proliferative DR (NPDR) and are at high risk of developing PDR. In eyes with DRSS scores of 47 and 53 at baseline, 66 and 80%, respectively, will progress to PDR in 5 years without treatment.[12,14]

Historically, clinical approaches to managing DR have consisted of risk factor control to manage blood glucose and blood pressure in patients with NPDR[15] and panretinal photocoagulation (PRP) in patients with PDR.[16] These aimed to prevent the development or progression of DR/DME and prevent further loss of vision. Restoring diminished VA was not a realistic treatment goal.[17]

However, evidence from an increasing number of clinical trials now supports a disease-modifying effect for ranibizumab in DR. "On reflection, improvement in retinopathy severity at the same time as improvement of DME upon treatment with ranibizumab makes sense, because, after all, PDR is mediated by an upregulation and surge of VEGF," said Prof. Koh. In the RISE and RIDE studies, over 75% of ranibizumab-treated patients with DRSS scores of 47 to 53 at baseline had a ≥ two-step improvement in DR up to 36 months (Figure 6).[18] These patients were also three times less likely than patients treated with sham to have experienced a new PDR event by month 36 (11.9% versus 35.2%).[18] "This includes vitreous hemorrhage, pre-retinal hemorrhage, and tractional retinal detachment. This is not something trivial," said Prof. Koh. "There is a real and consistent effect." Overall, compared with patients in the sham arm, those treated with ranibizumab were significantly more likely to improve by ≥ 2 (5.4 vs 35.9%) or ≥ 3 (1.3 vs 14.5%) steps on the DRSS (both $P < .001$ vs sham).[19]

**Diabetic retinopathy severity scale**

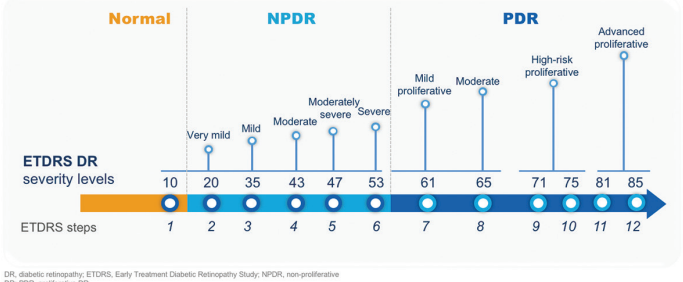
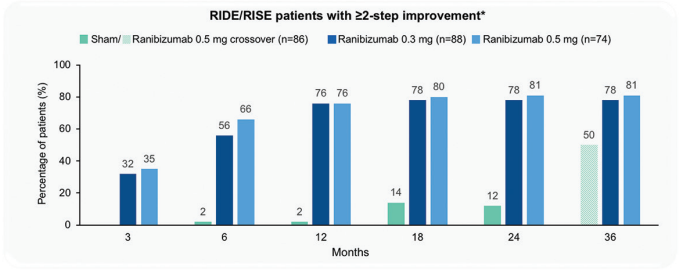



Figure 5. The DRSS.

**>75% of ranibizumab treated patients with DRSS 47–53 had ≥2-step DR improvement**




Primary endpoint data. *All sham vs ranibizumab comparisons for ≥2-step improvement. P<0.0001.
DR, diabetic retinopathy; DRSS, diabetic retinopathy severity scale

Figure 6. Patients with DRSS 47 to 53 with a ≥ two-step DR improvement in RISE and RIDE.

In the DRCR.net Protocol S study, patients with PDR treated with ranibizumab had lower rates of developing vision-impairing DME and less visual field loss at 5 years than those treated with PRP. In eyes without DME at baseline, 22% of patients treated with ranibizumab had developed DME at 5 years, compared with 38% of patients treated with PRP (Figure 7).[20] PDR eyes both with and without DME at baseline achieved VA gains at 2 years with ranibizumab: 7.9 and 1.8 letters, respectively, compared with 1.9 and -0.5 letters for PRP.[21]

The DRCR.net Protocol I study demonstrated that ranibizumab treatment is associated with a reduced risk of DR worsening at 3 years compared with laser in eyes with or without PDR at baseline. This difference was significant in eyes without PDR at baseline ($P$ = .01).[22] Most recently, the PRIDE study compared ranibizumab alone or in combination with PRP with PRP alone in patients with PDR. At 12 months, patients treated with ranibizumab alone had a greater reduction in the area of neovascularization compared with those in the combination or PRP arms (Figure 8).[23,24] In addition, more patients in the ranibizumab arm demonstrated complete regression of leakage from neovascularization at month 12 (28 vs 8% for PRP and 18% for combination).[23,24]

"There is compelling evidence across all trials for a disease-modifying effect of ranibizumab in DR. I believe that this marks the start of a paradigm shift in our approach to the management of PDR," said Prof. Koh.

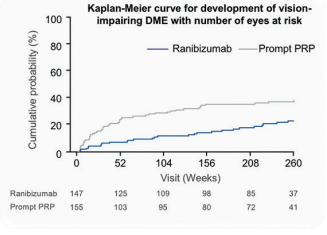
**Lower rates of development of DME compared with PRP**

Eyes without DME at baseline

Clinically relevant endpoints (5-year results)

Kaplan-Meier Estimate

| Treatment Group | 1-year | 2-year | 3-year | 4-year | 5-year |
|---|---|---|---|---|---|
| Ranibizumab | 6% | 11% | 14% | 17% | 22% |
| Prompt PRP | 24% | 29% | 35% | 35% | 38% |



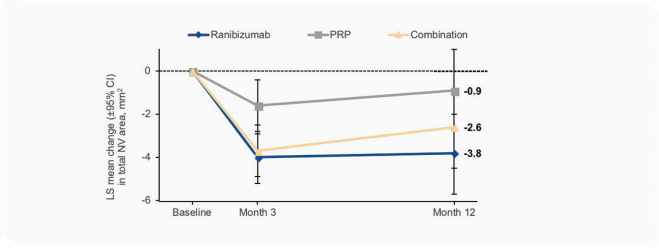

Secondary endpoint data. P<0.001 for treatment group comparison from marginal Cox proportional hazards model, with adjustment for baseline OCT CST, laterality, and correlation between two study eyes of the same patient. CST, central subfield thickness; DME, diabetic macular edema; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; OCT, optical coherence tomography

Figure 7. Development of DME in eyes without DME at baseline in Protocol S.

## Highlights

- Ranibizumab treatment results in significant improvement of ≥ 2 or ≥ 3 DRSS steps in patients with DR and a reduced risk of DR worsening in eyes with or without PDR.[19]
- Better VA outcomes are achieved with ranibizumab monotherapy versus PRP in patients with and without DME.[21]
- Ranibizumab treatment consistently shows disease modifying activity in patients with DR.[19-24]

**Greater reduction in neovascularization area with ranibizumab* at Month 12**




Primary endpoint data; *ranibizumab vs PRP and combination arms
CI, confidence interval; LS, least square; NV, neovascularization; PRP, panretinal photocoagulation; VA, visual acuity

Figure 8. Reduction in neovascularization area at 12 months in PRIDE.

## A New Horizon in ROP: The RAINBOW Study

Nicole Eter

Retinopathy of prematurity (ROP) is one of the most common complications of premature infants.[25] It affects around 15 to 20% of all babies born preterm each year.[26] "The incidence of ROP has increased in recent years as a result of advances in neonatal care resulting in increases in the numbers of premature births,"[26,27] said Prof. Nicole Eter. ROP can be caused by a number of factors, including hypoxemia, postnatal oxygen supply, postnatal hyperglycemia, neonatal infections, and hypercarbia.[28,29] Dysregulation of VEGF plays an important role in the development of ROP,[30] leading to the hypothesis that anti-VEGF agents could be used in the treatment of ROP.

Clinical evidence for anti-VEGF therapy in ROP includes BEAT ROP, a study comparing bevacizumab with laser in 150 infants in the United States,[31] and CARE ROP, a small study of 19 patients treated with 0.12 mg or 0.2 mg ranibizumab in Germany.[32] Most recently, the international RAINBOW study compared ranibizumab 0.2 mg and 0.1 mg with laser in 225 patients with ROP.[33,34]

RAINBOW was a randomized, multicenter, open-label, parallel-group clinical trial to compare ranibizumab with laser therapy in premature infants with ROP (Figure 9).[33,34] The primary objective was to demonstrate superior efficacy of ranibizumab 0.2 mg to

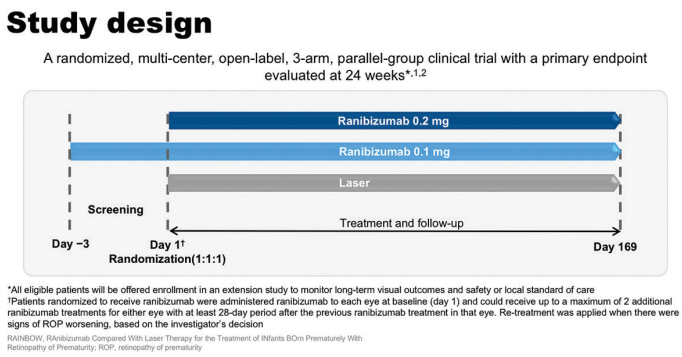



Figure 9. RAINBOW study design.

laser as measured by treatment success at week 24. Treatment success was defined as the absence of the following criteria: death; the need for intervention for ROP with a treatment other than the assigned therapy; active ROP in either eye at week 24; and unfavorable structural outcomes (retrolental membrane obscuring the view of the posterior pole, substantial temporal retinal vessel dragging causing abnormal structural features/macular ectopia, or posterior retinal fold or retinal detachment involving the macula).[33,34] Key secondary outcomes included demonstrating superior efficacy of ranibizumab 0.1 mg to laser and superior efficacy of ranibizumab 0.2 mg to ranibizumab 0.1 mg. Patients were male or female, with a birth weight of less than 1500 g and with bilateral ROP with one of the following categories of ROP in each eye: zone I, stage 1+, 2+, 3, or 3+ disease; zone II, stage 3+ disease; aggressive posterior ROP.[33,34]

Of the 225 infants enrolled, 218 infants completed the study at week 24, including over 98% in each of the ranibizumab arms (Figure 10). Baseline characteristics were well balanced among the study groups, although the ranibizumab 0.2 mg group had the lowest mean birth weight (791 g vs 831 g in the laser arm). At baseline, most infants had zone II stage 3+ disease.[33,34]

On the primary outcome measure of treatment success at week 24, 80% of the infants achieved treatment success with ranibizumab 0.2 mg vs 66.2% with laser (odd ratio, 2.19; 95% CI, 0.99-4.82; one sided $P = .0254$; Figure 11).[33,34] "Infants treated with ranibizumab 0.2 mg were twice as likely to achieve treatment success versus laser, which we consider to be clinically relevant," said Prof. Eter. Higher treatment success was observed in

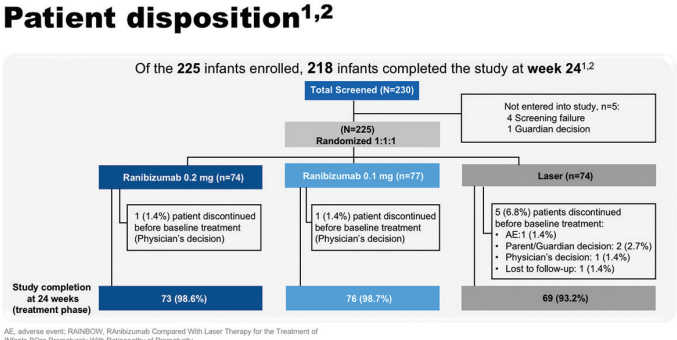



Figure 10. RAINBOW patient disposition.

patients with zone II ROP (88.1 vs 67.9% for zone II versus zone I in patients in the ranibizumab 0.2 mg group). The incidence of unfavorable structural outcomes was lowest in the ranibizumab 0.2 mg treatment group, with only one occurring during the course of the study, compared with seven in the laser arm.[33,34]

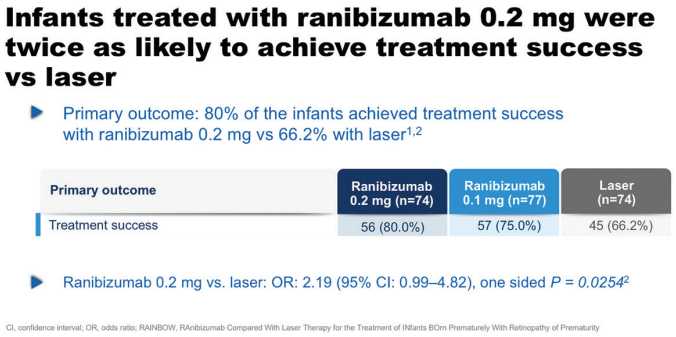



Figure 11. Primary outcome results in RAINBOW.

RAINBOW was the first study to report pharmacokinetic and systemic VEGF data in ROP. Serum ranibizumab levels were tested at day 1, 15, and 29, and the median concentration at day 29 was seven-fold lower compared with day 1 in the ranibizumab 0.2 mg group (a reduction from 7,820 pg/mL to 1,070 pg/mL). Systemic VEGF levels were tested on the same schedule, and across treatment groups there was a trend for a reduction in systemic VEGF concentrations between day 1 and 15, with return toward baseline by day 29.[33,34]

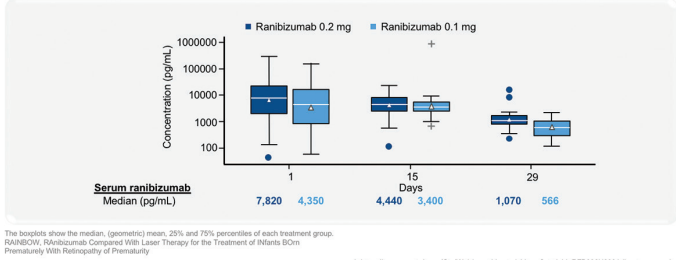



Figure 12. Serum ranibizumab levels in RAINBOW.

The frequency of ocular serious adverse events was low across all three groups. Non-ocular serious adverse events occurred in around one-third of patients, but this frequency was similar across groups and as expected in a preterm population.[33,34]

Based on the results of the RAINBOW study, on September 4, 2019, ranibizumab received approval from the European Commission for the treatment of ROP (zone I, stage 1+, 2+, 3, or 3+; zone II, stage 3+; or aggressive posterior ROP). "These are really exciting times for the youngest patients on ranibizumab treatment, the ROP babies," said Prof. Eter.

## Highlights

- ROP is one of the most common avoidable causes of blindness, which is increasing in incidence with advances in neonatal care.[25]
- Approximately 15 to 20% of the estimated 15 million babies born preterm every year are affected with ROP, of whom up to 45,600 are diagnosed with irreversible visual impairment.[26]
- In the RAINBOW study, infants treated with ranibizumab 0.2 mg were twice as likely to achieve clinically relevant treatment success compared with those treated with laser.[33,34]
- Ranibizumab is now approved for the treatment of ROP in premature infants in Europe.

## Clinical Perspectives on Ranibizumab as a Therapy for All Ages

### Moderated by Ramin Tadayoni

Prof. Ramin Tadayoni leads a discussion about the clinical management of patients with nAMD, DR, and ROP treated with ranibizumab.

**In ROP, is there still room for laser treatment, and what is the maximum number of anti-VEGF injections that can be given?**

**Prof. Eter:** In my practice I prefer not to apply laser treatment in ROP babies. However, if a clinician finds that anti-VEGF treatment is not enough, of course peripheral laser can be added if necessary. In terms of the number of anti-VEGF injections, usually one is enough, but according to the protocol there could be two repeat injections.

**In light of the recent approval of ranibizumab for ROP, what practical information can you provide on administering ranibizumab to ROP babies?**

**Prof. Eter:** A different syringe is used to administer ranibizumab to babies compared with adult patients, and the dose is reduced. The injection is performed under general anesthesia, with RetCam (Natus Medical Incorporated) imaging performed before injection. If both eyes are affected, we perform bilateral injections in the same session. Follow-up occurs every 4 days. If treatment is effective, the results are usually apparent within a few days. However, if active disease remains, then another injection is given after about 3 to 4 weeks.

**In nAMD, are there any studies showing a benefit of one anti-VEGF agent over another?**

**Prof. Schlottmann:** If you look at the results of the VIEW 1 and 2 studies[35] and those of RIVAL,[7,8] we see no differences whatsoever regarding VA outcomes, number of injections, development of macular atrophy, safety, or any other major endpoint that you may want to look at. When I discuss this issue with colleagues who tell me that they have seen a difference in the clinic, I tell them that what is statistically significant in a clinical trial can be invisible in clinical practice, and what appears significant in individual clinical practice is often proved to be an anomaly in a large clinical trial.

**What is your preferred regimen for treating a patient with nAMD with anti-VEGF therapy?**

**Prof. Schlottmann:** My preferred regimen would be T&E, but it depends on the region the patient comes from since sometimes the payors will not reimburse treatment without an OCT image showing disease activity. That means I have to use a prn regimen in those patients.

**Prof. Koh:** T&E is also probably my favored regimen. However, not every patient needs such proactive treatment. I usually provide three initial injections if possible, then wait 2 months without treatment. If there is early recurrence of activity, the patient is immediately moved to T&E. If there is no disease recurrence, I give the patient the option of prn but with the proviso that they must be prepared to return every month for review. Most patients can't or don't wish to do this, so they choose T&E.

**Prof. Eter:** In cases of bilateral disease, we use prn, but if it's just one eye that is being treated, then I prefer T&E.

**In DR, are you concerned that injecting an anti-VEGF agent may lead to detachment of the macula?**

**Prof. Koh:** I think there's always a risk of acceleration of fibrosis and traction, so patients must be counselled appropriately. If anti-VEGF is given, it should be done in the knowledge that the macula may detach and that the patient might require vitrectomy. However, while I wouldn't say that there is no risk, I do think the risk has been overstated. In the Protocol S study, for example, the rate of tractional retinal detachment was just 5%.[21]

**Could combining anti-VEGF injections with PRP decrease the number of injections required to treat PDR?**

**Prof. Koh:** The results of the PRIDE study suggest that there is no added advantage to combining PRP with anti-VEGF therapy.[23,24] In addition, I think it's wrong to assume that once PRP

is done you never have to repeat it again. These patients must still be watched for recurrence of PDR in the future, in the same way that you cannot be complacent after treating PDR with anti-VEGF therapy and say that the disease is gone for good. However, if patients are unable to come back frequently for repeated injections, PRP could potentially be useful—it's always good to have more than one option. ■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## Conclusions: Ramin Tadayoni

In summary, ranibizumab has been proven to be an effective therapy for retinal diseases across all ages. In babies with retinopathy of prematurity, the RAINBOW study showed that infants treated with ranibizumab 0.2 mg were twice as likely to achieve treatment success versus those treated with laser. In patients of working age, ranibizumab treatment in DR is associated with a reduced risk of DR worsening in eyes with or without PDR. Finally, in older patients with nAMD, the RIVAL study demonstrated comparable clinical outcomes between ranibizumab 0.5 mg and aflibercept 2.0 mg in a T&E regimen. "The wealth of scientific evidence available for ranibizumab has led to seven approved indications and the flexibility in the product label to enable us to meet our patients' needs, whatever their ages," said Prof. Tadayoni.


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