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Ranibizumab for Visual Impairment in DME: An Overview of The Evidence

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Ranibizumab for Visual Impairment in DME: An Overview of The Evidence


BY PROF. CHRISTIAN PRÜNTE AND PROF. NICOLE ETER

Diabetes is a growing worldwide epidemic, with an estimated global prevalence of 425 million in 2017, which is expected to rise by 48% to 629 million by 2045 (Figure 1).[1] Diabetic retinopathy is a common microvascular complication of diabetes,[2] which can progress to include diabetic macular edema (DME), the accumulation of fluid within the layers of the macula.[3] DME is the leading cause of vision loss in working-age people,[4] with the average age at diagnosis being just 50 years.[5] This supplement provides an overview of the key clinical trial and real-world evidence currently available for ranibizumab (Lucentis, Novartis) in the treatment of visual impairment due to DME.

The views expressed here are those of the authors and not of Novartis Pharma AG. Any information on competitor product(s) is based on publicly available material.

INTRODUCTION

Vascular endothelial growth factor (VEGF)-A is a key driver of DME pathogenesis.[6,7] Sustained hyperglycemia in diabetes leads to a marked upregulation of VEGF-A in the blood–retinal barrier, which in turn leads to blood vessel leakage, blood–retinal barrier breakdown, and local inflammation. "VEGF-A is a pro-inflammatory molecule and one of the major causes of vessel leakage; therefore, the inhibition of VEGF in DME is one of the best and preferred treatment options for macular edema," said Prof. Nicole Eter.

Ranibizumab was approved for the treatment of visual impairment due to DME in Europe in 2011 and in the United States in 2012.[8] Ranibizumab is an anti-VEGF agent that was specifically designed for use in the eye,[7] and it potently and selectively blocks VEGF-A signalling, thus helping to control macular edema and improve visual acuity.[6] "The approval of ranibizumab for DME was a major step forward as it was the first approved treatment where we could achieve improvement in vision in the majority of our patients," said Prof. Christian Prünte. Following an extensive series of Phase III clinical trials in addition to several large real-world studies, a wealth of evidence is now available to support the safety and efficacy of anti-VEGF therapy in DME (Figure 2).[9-28] In particular, ranibizumab has been studied in eight randomized controlled clinical trials including over 3,000 patients (over 1,800 of whom received ranibizumab 0.5 mg) and lasting for up to 5 years.[9-20]

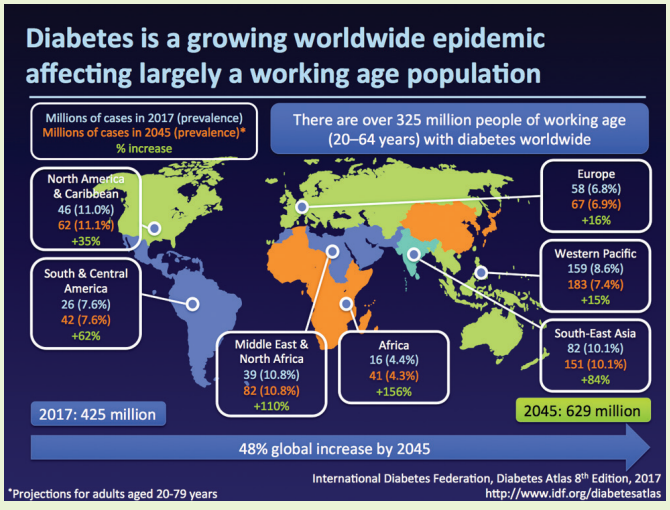

Figure 1. Global epidemic of diabetes.

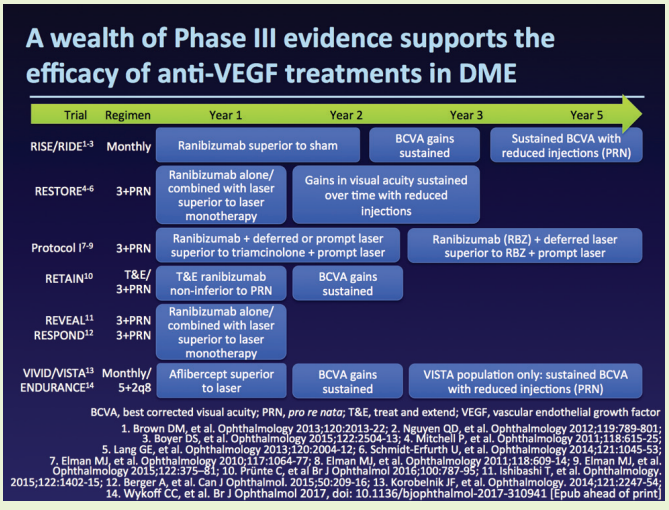

Figure 2. Phase III evidence for anti-VEGF therapy in DME.

EVIDENCE FOR RANIBIZUMAB IN PATIENTS WITH DME

Long-term clinical trial evidence for ranibizumab in DME

RESTORE was the first pivotal trial of ranibizumab in DME. The core study was a 12-month, double-masked, randomized controlled trial comparing ranibizumab 0.5 mg *pro re nata* (PRN, as needed) as monotherapy or combined with laser versus laser monotherapy in 345 patients with DME.[9] Patients treated with ranibizumab monotherapy achieved a mean gain of 6.8 letters at 12 months.[9,10] No benefit of adding laser therapy was seen; patients who were treated with combination therapy achieved a mean gain of 6.4 letters at 12 months, and those treated with laser monotherapy had a significantly lower mean gain of 0.9 letters.[9] At 12 months, patients completing the core study were eligible to enter a 24-month, open-label extension study in which patients received ranibizumab as needed.[10] The visual gains achieved by the patients treated with ranibizumab monotherapy were maintained over time, with a mean gain at 36 months of 8.0 letters (Figure 3).[10]

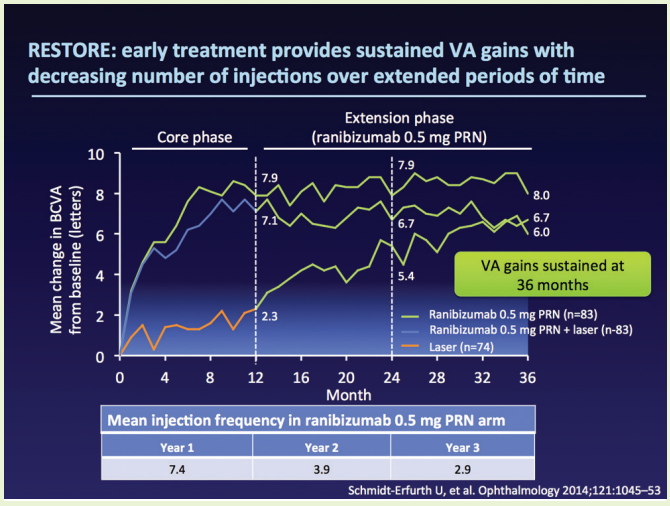

Figure 3. The RESTORE study.

The other pivotal trials of ranibizumab in DME were RISE and RIDE, two parallel, identically designed, double-masked, randomized controlled studies, in which a total of 759 patients were randomized to monthly ranibizumab (0.5 mg or 0.3 mg), or sham.[11,12] Following the primary endpoint at 24 months, patients in the sham arm were eligible to cross over to ranibizumab 0.5 mg in the third year.[12] Patients completing 36 months could then enter a long-term open-label extension where they received ranibizumab 0.5 mg as needed.[13] At 24 months, patients in the ranibizumab 0.5 mg arm achieved gains of 11.9 and 12.0 letters, respectively, compared with 2.6 and 2.3 letters for patients in the sham arm,[11] and these gains were maintained to 36 months.[12] In the open-label extension of RISE and RIDE, around 25% of patients required no further injections during the extension period of up to 54 months, whilst continuing to maintain vision (Figure 4).[13]

The longest duration dataset for ranibizumab in DME is provided by the independent Protocol I study, performed by the

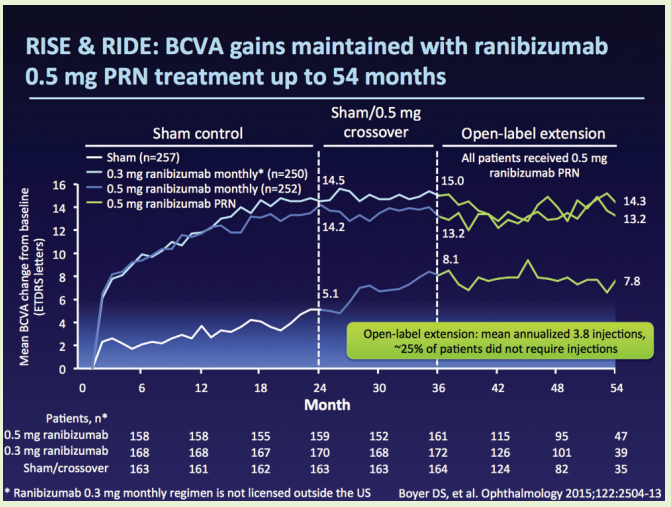

Figure 4. The RISE and RIDE studies.

Diabetic Retinopathy Clinical Research Network (DRCR.net).[14-16] In this randomized controlled study, 854 eyes from 691 patients were assigned to ranibizumab 0.5 mg plus prompt laser (within 3 to 10 days of injection), ranibizumab 0.5 mg plus deferred laser (at least 24 weeks from injection), sham plus prompt laser or triamcinolone plus prompt laser. Retreatment was given as needed, according to an algorithm.[14]

In the ranibizumab 0.5 mg with deferred laser arm, rapid, clinically meaningful visual acuity gains of approximately 7 letters were achieved within 2 months, and a mean vision gain of 9 letters was observed at 12 months ($P<0.001$ vs sham plus prompt laser).[14] These results were maintained to the end of the study at 3 years, and throughout a 2-year extension study, with a mean gain at 5 years of 9.8 letters (Figure 5, page 4).[15]

In comparison, patients receiving triamcinolone plus prompt laser in the Protocol I study gained 4 letters at 12 months (not significant compared with sham plus prompt laser).[14] Following analysis of the 1-year outcomes, patients in the sham plus prompt laser and triamcinolone plus prompt laser arms were eligible to receive ranibizumab, and 57% and 62%, respectively, of patients in these arms who entered the extension phase of the trial received ranibizumab. At 5 years, patients who were originally assigned to triamcinolone had a mean gain of 7 letters versus baseline.[16] "The Protocol I study taught us that treating with ranibizumab as a monotherapy is extremely successful," said Prof. Prünte. "The gain in vision was superior to what was seen with triamcinolone, and there were few side effects with ranibizumab, whereas with triamcinolone increased IOP and cataract formation were common. Also, importantly, and in contrast to what we see in neovascular age-related macular degeneration (AMD), in DME it appears that ranibizumab treatment may only be required for 2 or 3 years."

The long-term data from Protocol I demonstrate a marked reduction in injection requirements over time: patients in the ranibizumab plus deferred laser arm received a median of nine injections in year 1, but only one in year 4 , and zero in year 5,

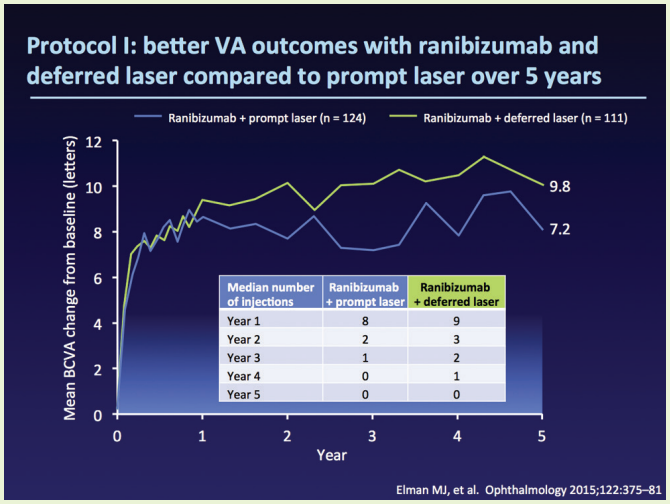

Figure 5. The DRCR.net Protocol I study.

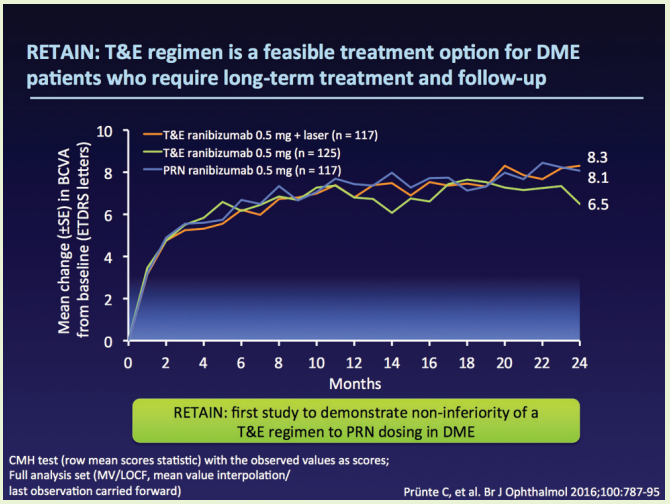

Figure 6. The RETAIN study.

which may be indicative of a disease-modifying effect with ranibizumab.[15] "These diabetic patients tend to have a very high clinic burden due to having to see other doctors as well as the ophthalmologist for their secondary diabetic problems, so a reduction in injection visits over time is extremely beneficial to them," said Prof. Eter.

Ranibizumab for DME given according to a treat-and-extend regimen

"The treat-and-extend regimen is of particular interest to me because I really believe that it can make therapy easier for the patient," said Prof. Prünte. "There are two key factors — that the number of clinic visits are reduced for the patient, and that the patient always knows in advance exactly what is going to happen at their subsequent visits in terms of having their diagnostic workup and their injection. What makes treat-and-extend different in DME compared with neovascular AMD is that treatment is usually only needed for about 2 to 3 years, and longer treatment intervals can often be achieved."

The RETAIN study provides clinical trial evidence on the use of the treat-and-extend regimen in DME.[18] RETAIN was a 24-month, single-masked study in which patients were randomized to ranibizumab given according to a treat-and-extend regimen plus laser (T&E+laser, n=121), ranibizumab treat-and-extend regimen without laser (T&E, n=128), or ranibizumab given according to PRN regimen (PRN, n=123).[18] On the primary endpoint of mean average change in BCVA from baseline to months 1 to 12, results in both the T&E+laser and the T&E groups were noninferior to those in the PRN group. After 24 months, mean change in BCVA from baseline was similar between the three groups (+8.3, +6.5, and +8.1 letters for the T&E+laser, T&E, and PRN groups, respectively; Figure 6), achieved with 12.4, 12.8, and 10.7 injections. Although the number of injections was slightly higher in the T&E+laser and T&E groups, these groups had a 46% reduction in the number of clinic visits compared with the PRN group.[18] Over 80% of patients in the T&E+laser and T&E groups achieved treatment intervals of ≥2 months, with 44% of patients in both groups achieving intervals of 3 months (at which the interval was capped according to the protocol).[18]

The RETAIN study demonstrates that ranibizumab given according to a treat-and-extend regimen in DME can provide improvement in visual acuity, and the maintenance of those improvements over 24 months, whilst reducing clinic visit burden.

Ranibizumab in PDR

Proliferative diabetic retinopathy (PDR), with or without associated DME, is an important cause of vision loss in patients with diabetes.[29] While there is a significant amount of long-term clinical evidence for ranibizumab in DME, as discussed above, it is

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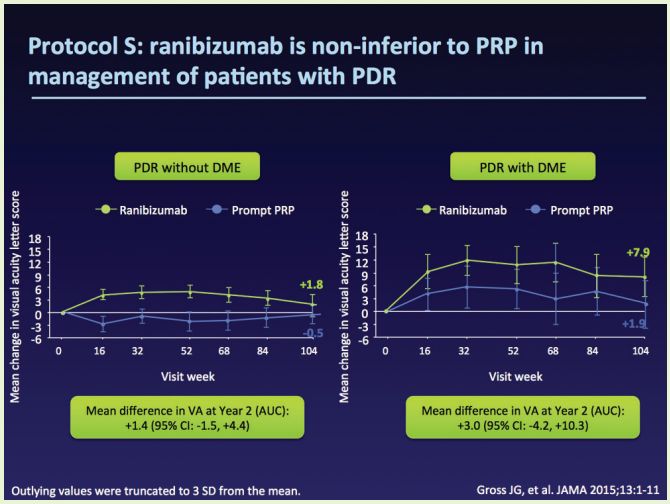

Figure 7. The DRCR.net Protocol S study.

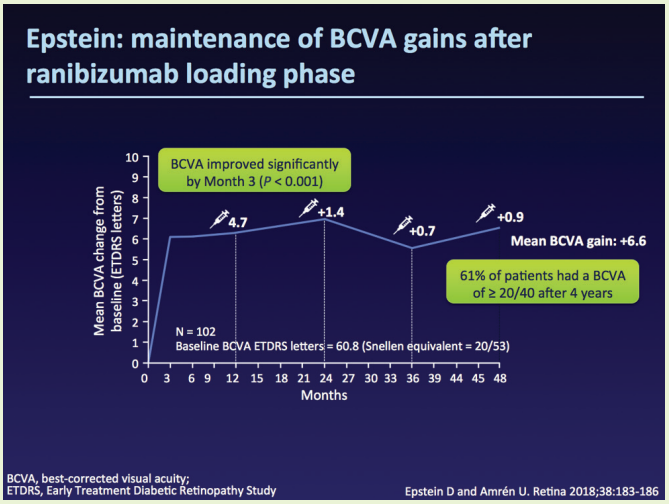

Figure 8. Long-term study by Epstein and Amrén.

only more recently that it has begun to be investigated for use in patients with PDR.[17] "For the first time, we looked not only at DME but also at the diabetic retinopathy itself, and at what ranibizumab can do in the periphery," said Prof. Eter. The Protocol S study was a 2-year, randomized, multicenter clinical trial carried out in the United States that assessed the noninferiority of ranibizumab compared with panretinal photocoagulation (PRP) in terms of visual outcomes in 394 study eyes with PDR, with or without DME. Patients were randomized to ranibizumab as needed (with PRP in case of treatment failure; n=191), or to PRP (with ranibizumab as needed for DME treatment; n=203).[17]

In the ranibizumab group, eyes without DME at baseline received a median of 10 injections over 2 years, seven of which were in the first year, while those with DME at baseline received a median of 14 injections over 2 years, nine of which were in the first year. Twelve eyes received PRP. In the PRP group, 35% of eyes received ranibizumab for DME at baseline and an additional 18% received ranibizumab by the end of the study.[17]

At 2 years, mean gain in visual acuity from baseline was 2.8 letters in the ranibizumab group and 0.2 letters in the PRP group (a mean treatment group difference of 2.2 letters; 95% confidence interval [CI], −0.5 to 5.0; noninferiority $P<0.001$). This result met the pre-specified study criteria for noninferiority. In eyes with DME at baseline, the mean gain in visual acuity from baseline at 2 years was 7.9 in the ranibizumab group and 1.9 letters in the PRP group (a mean treatment group difference of 3.0 letters; 95% CI, −4.2 to 10.3; Figure 7).[17] "The Protocol S study shows that treatment with ranibizumab is limiting proliferative disease, so it's really a disease-modifying treatment. This means that PRP can be postponed and may not even be needed at all in the future," said Prof. Prünte.

Real-world evidence for ranibizumab in DME

The clinical trial evidence for ranibizumab in DME is reflected by real-world evidence from clinical practice.[22-26] "It is difficult to compare randomized clinical studies with real-world evidence, and the outcomes of treatment in the real world are often disappointing compared with the results from randomized controlled trials," said Prof. Eter. "However, there are increasing numbers of real-world studies in DME showing that good visual results are absolutely feasible and can be achieved even outside a clinical trial program." Patients in the ranibizumab arm of RESTORE, the pivotal study of ranibizumab in DME, achieved a mean visual acuity gain of 6.8 letters with seven injections at 12 months.[9] Since then, several real-world studies have reported similar outcomes over the same follow-up period. Patients in the ETOILE study gained a mean gain of 5.3 letters with 5.8 injections,[22] while those in the BOREAL-DME study achieved a mean gain of 7.4 letters with 5.1 injections.[23] In a study by Patrao and colleagues, patients had a mean gain of 7.2 letters with 6.6 injections,[24] and the EMR Users Group reported a mean gain of 5.0 letters with 3.3. injections.[25] A recent real-world study performed in Sweden by Epstein and Amrén demonstrates that these 12-month gains can be maintained over the long

Safety findings from clinical trials of ranibizumab in DME report a lower incidence of ocular safety events such as increased IOP and cataract than steroids, and similar rates of systemic adverse events compared with steroids or laser. These findings are reflected by real-world evidence in patients with DME treated with ranibizumab in clinical practice.

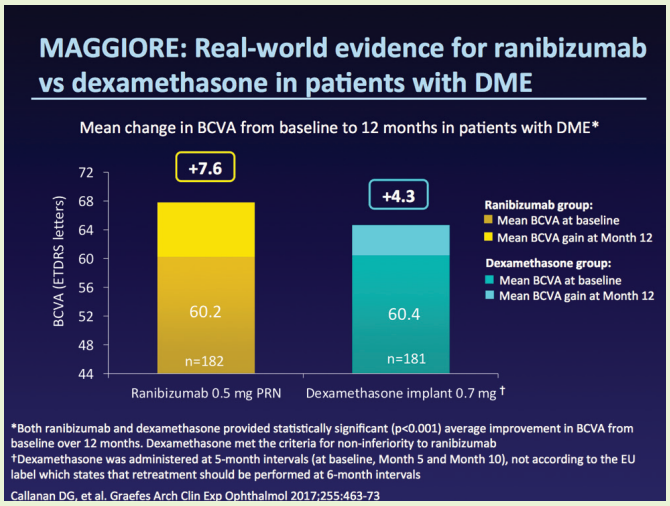

Figure 9. The real-world MAGGIORE study.

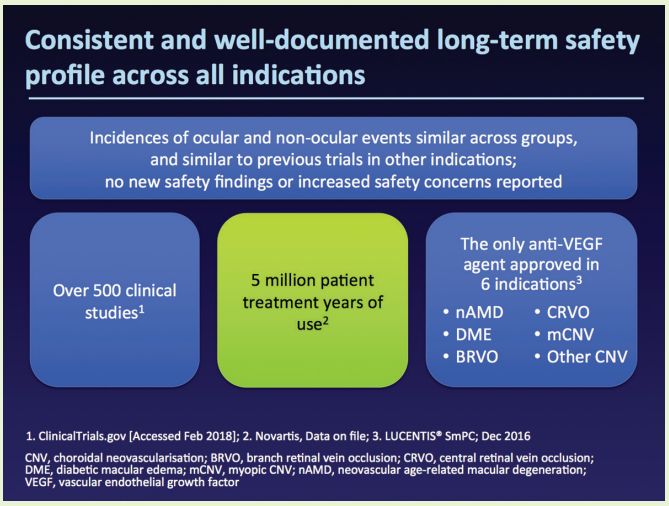

Figure 10. Consistent and well-documented safety profile of ranibizumab.

term, with follow-up to 4 years.[26] Patients had a mean gain of 6.6 letters at 4 years with 7.7 injections (Figure 8, page 5). From a mean baseline BCVA of 60.8 letters (Snellen equivalent 20/53), 61% of patients with DME treated with ranibizumab were able to maintain a BCVA of 20/40 or better after 4 years.[26] "These outcomes are promising as they demonstrate that results from real-world studies can be very comparable to study results, with a clinically relevant improvement in visual acuity with treatment," said Prof. Prünte. "The good news is that the number of treatments required is similar to those that we find in Protocol I and the treat-and-extend studies such as RETAIN."

Evidence for ranibizumab versus corticosteroids in DME

In addition to anti-VEGF therapy, sustained-release intravitreal corticosteroid implants of dexamethasone and fluocinolone acetonide are approved treatment options for DME in the United States and Europe. However, there are limited head-to-head clinical trial data comparing corticosteroids with anti-VEGF therapy in DME. One of the few such studies available is the MAGGIORE study comparing ranibizumab with the dexamethasone intravitreal implant (Figure 9).[27] MAGGIORE was a multicenter, open-label, 12-month study in which 181 patients were randomized to the dexamethasone intravitreal implant every 5 months, and 182 patients were randomized to receive ranibizumab according to its European label. At 12 months, patients in the ranibizumab arm achieved a mean gain of 7.6 letters with 8.7 injections, compared with 4.3 letters in patients receiving an average 2.9 dexamethasone implants.[27]

As the lower limit of the between-group difference 95% CI was -4.74 letters, dexamethasone was judged to be noninferior to ranibizumab based on the prespecified noninferiority margin of 5 letters. Ocular adverse events were more frequent in the dexamethasone group, namely increase in IOP and cataract.[27] "When the dexamethasone implant was first introduced, we hoped that the frequency of treatment would be very low, while the visual outcomes would be the same as with ranibizumab treatment," said Prof. Eter. "However, evidence from studies such as MAGGIORE have shown that this is unfortunately not the case. Visual gains in the first year of treatment tend to be greater with ranibizumab than with the dexamethasone implant, and the implant requires more frequent replacement than initially expected. The side effects associated with the implant, such as elevated IOP, also require some consideration."

The safety profile of ranibizumab in DME

There has been a consistent and well-documented long-term

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> — Prof. Prünte

> "In my clinical routine, anti-VEGF therapy, in particular, ranibizumab, because of the wealth of supporting evidence available, is the standard treatment today for patients with DME."
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safety profile across all of ranibizumab's licensed indications (Figure 10, page 6).[8,30,31] Safety findings from clinical trials of ranibizumab in DME report a lower incidence of ocular safety events such as increased IOP and cataract than steroids, and similar rates of systemic adverse events compared with steroids or laser.[14,16] These findings are reflected by real-world evidence in patients with DME treated with ranibizumab in clinical practice. For example, in the real-world study performed by Epstein and Amrén, there were no events of endophthalmitis, retinal tear, or retinal detachment during the 4-year follow-up, and rates of systemic adverse events were low.[26] In an analysis of 1,828 patients with DME who were enrolled into the LUMINOUS observational study and who had 1 year of follow-up within the study, the rates of ocular and non-ocular serious adverse events reported were 0.38% and 4.86%, respectively.[28] Endophthalmitis occurred at a rate of 0.06% or one case in 7,550 injections.[28] "With the very low rates of ocular side effects with ranibizumab, there is little for us to discuss as a relevant problem. With respect to systemic side effects, there is always concern in this population as patients with diabetes have a range of systemic comorbidities, and some of these may be vulnerable to VEGF inhibition," said Prof. Prünte. "However, we now have evidence from multiple studies including many patients, and this does not show a relevant signal for systemic side effects. I think we can therefore be confident that the benefits of ranibizumab treatment definitely outweigh the risks, even in this vulnerable population."

SUMMARY

In conclusion, ranibizumab selectively targets VEGF-A in the eye, helping to control macular edema in patients with DME.[6,7] Ranibizumab has been proven to be efficacious across all DME patient populations (including those with severe vision loss at baseline), as demonstrated in the Protocol I and Protocol S studies, as well as a number of other clinical trials and real-world studies.[9,10,13-18,22-27] "In my clinical routine, anti-VEGF therapy, in particular, ranibizumab, because of the wealth of supporting evidence available, is the standard treatment today for patients with DME," said Prof. Prünte.

Comparative clinical trial data show that ranibizumab provides greater vision gains than steroids with a lower incidence of ocular safety events,[27] and maintenance of visual gains with long-term ranibizumab use has been demonstrated over 5 years, with a low treatment burden that decreases over time.[15] "Ranibizumab has been proven to be a successful treatment for DME, with a very good safety profile," said Prof. Eter. "In addition, with a treat-and-extend regimen, the number of clinic visits can be greatly reduced, helping to ease the burden of illness for diabetic patients." ■

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