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REVIEW ARTICLE

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Next-generation anti-VEGF agents for diabetic macular oedema

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The treatment and outcomes of diabetic macular oedema (DMO) have improved with the introduction of intravitreal injections. However, real-world data reveal that the burden of DMO treatment causes large gaps in outcomes between randomized clinical trials and daily clinical practice. Long-lasting intravitreal drugs and devices for DMO might reduce this disparity by achieving optimal treatment due to more feasible injection regimens. In this manuscript, we cover pharmacodynamics, preliminary results from clinical trials, and safety behavior about brolucizumab, faricimab, conbercept, KSI-301, and port-delivery system WR42221. These treatments might present the first step to control the global epidemic of diabetic eye disease in real life.

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INTRODUCTION

Diabetes mellitus is a major healthcare concern in people of working age. Worldwide, about 93 million are estimated to have diabetic retinopathy (DR) [1]. Diabetic macular oedema (DMO) affects 7% of diabetic patients and it is the main cause for vision loss associated with DR [2, 3]. Anti-vascular endothelial growth factor (VEGF) agents are the first-line therapy for center-involving DMO and are effective in improving and maintaining visual acuity, as shown in large-scale randomized controlled trials [4–7].

In addition to the debilitating effect on vision, patients with DMO also suffer significant impairment of quality of life due to high treatment burden associated with intensive anti-VEGF injection regimens. Over a 12-month period, these patients require an average of at least 8.8 visits for their ocular condition, which is in addition to about 10 visits to other healthcare professionals for their diabetes care [8]. Current DMO treatment regimens are also associated with substantial direct medical costs for the patients, absenteeism for working patients, and need for carer's assistance for injection appointments [8, 9]. Moreover, patients report anxiety and high expectations that lead to negative impact on long-term anti-VEGF therapy and cause some delay in scheduling a new appointment for intravitreal injection. Results from real-life studies are not comparable with the data known from randomized control trials, revealing that the actual number of anti-VEGF injections administered and the proportion of patients achieving significant best-corrected visual acuity (BCVA) gain are lower [10, 11]. Second-line therapies using corticosteroids, such as dexamethasone implant 700 mcg (Ozurdex, Allergan, USA), and fluocinolone implant 0.19 mg (Illuvien, Allimera Sciences, USA), offer sustained release solution in suitable patients but are restricted to be used as second-line agents in several countries [12, 13].

Patients in real-life settings do not comply with mandatory follow-up visits and might miss appointments and injections. Loss to follow-up in the first year of treatment was reported in up to 25% [14], and therapy break-offs (lateness >100 days) in 46% of patients in real-world studies [15]. Therefore, in summary, there are a myriad of limitations in the current treatment options for DMO. The first is related to the drugs themselves, i.e., high costs to health systems and patient affordability, lack of accessibility, insufficient response, high treatment burden due to short duration of action of existing drugs, and need for monthly injections during the loading phase. The second is related to the current treatment regimens (fixed, treat and extend, and pro re nata). The last limitation is related to the patient: low adherence to frequent injections and missed injections due to comorbidities, patient perception, anxiety and discomfort, financial burden, lack of transportation, etc. There are new agents being investigated for DMO that might offer the potential to improve treatment outcomes and reduce treatment burden associated with the current algorithm of treatment.

The objective of this review is to analyze novel drugs and devices for treatment of DMO, explain their mechanism of action, summarize pivotal trials results, and discuss potential limitations and safety profile for brolucizumab, faricimab, conbercept, KSI-301, and port-delivery system (PDS) WR42221.

BROLUCIZUMAB

The drug

Brolucizumab (Beovu®; Novartis) is a humanized single-chain antibody fragment considered the smallest subunit of an antibody for treatment in medicine tested for human use with a molecular weight of ~26 kD. This drug demonstrated non-inferiority to aflibercept in pivotal trials, HAWK and HARRIER [16], and has been approved in October 2019 by the US Food and Drug Administration to treat neovascular age macular degeneration (nAMD). This agent inhibits VEGF-A binding to VEGF receptors VEGFR1 and VEGFR2 [17]. Its small molecular size and the absence of the crystallizable fragment provide augmented bioavailability with better tissue penetration and more sustained effect than full-size antibodies [18]. Due to its

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small molecular size, the drug can be concentrated in a smaller amount of net liquid volume, allowing it to supply 6 mg of brolucizumab in as little as 50 µl for intravitreal injection; meaning 11 times higher than aflibercept [19].

Pivotal trials: KITE and KESTREL

The KITE and KESTREL are ongoing 2-year, randomized, double-masked, multicenter, active-controlled studies [20, 21]. The main objective is to prove the efficacy and safety of brolucizumab 6 and 3 mg versus aflibercept 2 mg in treating previously untreated patients with visual impairment due to DMO. More than 300 patients have been recruited in both studies. The primary outcome is to evaluate the BCVA at the end of the first year to show non-inferiority of brolucizumab to aflibercept. Among the secondary outcomes highlight the safety and identifying the proportion of patients treated at an interval of 12 weeks with brolucizumab, interpreting the anatomical and functional state compared to the standard dosing in the aflibercept group.

The patients were randomized 1:1 in the KITE study, receiving 6 mg of brolucizumab five times at an interval of 6 weeks initially, followed by an extension to 12 weeks; in case of not showing stability, the extension is only to 8 weeks with the possibility of extending again to 12 weeks during the second year of the study. The control group will receive aflibercept initially five times at an interval of 4 weeks, with a subsequent extension to 8 weeks until the end of the study, as per its summary of product characteristics. In the KESTREL study, a third arm was included (1:1:1), administering brolucizumab at a dose of 3 mg, but under the same characteristics as the KITE study.

Preliminary 52-week results were recently presented. Both studies demonstrated that brolucizumab 6 mg was noninferior to aflibercept, with a comparable gain of 9–10 letters in BCVA, with fewer injections needed. More than half of the patients were maintained on 12 weekly intervals with brolucizumab 6 mg. Patients in the aflibercept arm received nine, compared to seven injections in each brolucizumab arm. In terms of anatomical response, brolucizumab was superior in drying both intraretinal and subretinal fluid. More patients in the brolucizumab groups achieved the prespecified endpoint of central subfield thickness of ≤280 µm at 52 weeks (54–57% vs. 40–41%). Regarding safety profile, no difference in serious adverse events between the two groups was found in the KITE study. However, in KESTREL, 16 eyes treated with brolucizumab developed intraocular inflammation, vs. one case in the aflibercept arm. These included four cases of retinal vasculitis and three cases of retinal vascular occlusion compared to none with aflibercept. Further information is needed in order to determine whether the underlying vascular disease has an impact on the brolucizumab-related incidence of intraocular inflammation [22].

The KESTREL and KITE studies have an estimated completion date in October 12 and July 6, 2021, respectively [20, 21].

FARICIMAB

The drug

Faricimab is a bi-specific antibody, i.e., a single molecule with a dual mechanism, blocking angiopoietin-2 (Ang-2) and VEGF-A simultaneously. In the general context, DMO is a multifactorial disease where inflammatory, vascular, and structural factors are involved. Blocking Ang-2 could stabilize the vascular structure, inhibiting the continuous loss of pericytes with less inflammation and, consequently, favoring the drug's efficacy and durability [23, 24].

Pivotal trials

BOULEVARD trial. The Boulevard trial is a prospective, randomized, double-mask, multicenter, and phase 2 study. The main objective was to compare the safety and efficacy of faricimab (Roche) vs. ranibizumab (Lucentis®; Novartis) in the treatment for patients with DMO [25].

Patients with naive DMO were included, as well as patients previously treated with anti-VEGF. The group of patients with naive DMO was randomized 1:1:1, as follows: faricimab 6.0 mg/faricimab 1.5 mg/ranibizumab 0.3 mg.

Patients previously treated with anti-VEGF were randomized 1:1, receiving 6.0 mg of faricimab and 0.3 mg of ranibizumab.

Both groups of patients were treated with monthly injections until week 20, with subsequent observation until week 36, thus comparing both drugs' durability.

The study met its primary efficacy endpoint in the group of patients with naive DMO, showing superior improvement in BCVA compared to ranibizumab at week 24, with a gain of 10.3 ETDRS letters. In the group of patients previously treated with anti-VEGF, the visual acuity endpoints between both drugs did not show a significant difference in BCVA gain at 24 weeks. During the observation period, the patients who received 6.0 mg of faricimab showed a greater probability of resilience for re-treatment than the group of patients who received ranibizumab. At the end of the trial, faricimab did not show unexpected safety signals.

These studies' favorable results led to better understanding of how faricimab as a combination therapy provided benefits and opened the path for succeeding clinical trials.

YOSEMITE and RHINE trials. YOSEMITE and RHINE [26–28] are two ongoing phase 3, multicenter, randomized, and double-mask studies, both with identical randomization for evaluation. The main objective is to evaluate the efficacy and safety of faricimab vs. aflibercept in the treatment of DMO. Over 1000 patients have been recruited. In both studies, three arms for evaluation were created (1:1:1):

1. Faricimab 6 mg administered at 16-week intervals.
2. Faricimab 6 mg at 8-week intervals.
3. Aflibercept 2 mg at 8-week intervals.

The primary endpoint was to analyze the average change in BCVA from baseline to the end of the first year. On December 21, 2020, positive results were announced. In both studies, the primary endpoint was reached, showing that faricimab administered at 8- and at 16-week intervals was not inferior and showed good visual improvement compared to aflibercept administered every 8 weeks. Faricimab also showed good tolerance with no safety signals.

As a second endpoint, it is worth mentioning that more than half of the participants managed to extend the interval to 16 weeks during the first year, hence corroborating an excellent durability level, seen for the first time in phase 3 studies in patients with DMO. A completion date is expected for the YOSEMITE trial on September 30, 2021, while RHINE is expected to be extended until July 2023.

THE PORT-DELIVERY SYSTEM (PDS)

The concept

The PDS consists of a permanent, refillable implant, approximately the size of a grain of rice, which is surgically inserted through a small incision in the sclera, accessing the vitreous cavity at the level of the pars plana. This system gives the potential to reduce the treatment burden while achieving optimal management, allowing a continuous release of a customized formulation of ranibizumab into the vitreous cavity [29].

There is a self-sealing septum at the outer surface of the implant that allows access to a cavity-reservoir, where a replenishment with the drug can be done without the need to remove it.

Once stored in the implant's cavity-reservoir, the drug moves by passive diffusion through a metallic porous element designed explicitly for the ranibizumab's molecular structure, hence

reaching the vitreous cavity. In this way, an active release of the drug is achieved over a longer time frame [30].

Given these promising results, Genentech/Roche have initiated studies implementing this device for treating DMO.

Pivotal trial: the PAGODA trial

The PAGODA trial [31] is a multicenter, randomized, active-comparator, non-inferiority study with the main objective to evaluate PDS's efficacy, safety, and pharmacokinetics in patients with DMO.

Currently, more than 500 patients have been recruited and will be randomized 1:1, receiving either treatment with PDS (ranibizumab 100 mg/ml) refilled at 6-month intervals or ranibizumab 0.5 mg monthly injections.

The primary outcome is the change in BCVA from baseline over week 60. The estimated completion date for this study is September 2024.

CONBERCEPT

KH902 is a recombinant fusion protein, and similar to aflibercept, it binds to all isoforms of VEGF-A, VEGF-B, and PlGF. In 2013, conbercept was approved for treating nAMD in China. In 2018, the results of the randomized phase 3 PHOENIX study revealed the effectiveness and good safety profile of the drug compared to sham injections in the treatment for nAMD [32]. Currently, the results of phase 3 of the PANDA-1 and PANDA-2 trials are awaited [33, 34]. Since then, the expectations have increased, and clinical trials treating other retinal vascular diseases including DMO have emerged.

Pivotal trial

The FRONTIER trial [35]. This study was designed to evaluate the safety and efficacy of conbercept in patients with DMO. Two study groups were established, in the first group (group A) patients receive 0.5 mg of conbercept during the first month, followed by a PRN dosing schedule based upon the monthly physician assessment of the need for re-treatment in accordance with prespecified criteria. In the second group (group B), patients will receive continuous monthly intravitreal injections of 0.5 mg KH902 for initial 3-month fixed-dosing phase, followed by a PRN dosing schedule. The primary and secondary outcomes consist of evaluating the safety of multiple injections in the first 12 months, as well as the change in BCVA at 3 and 12 months, respectively.

The SAILING trial [36]. This study was also designed to evaluate the safety and efficacy of conbercept in patients with DMO. Two study groups were established; in the first (experimental), treatment with conbercept and sham laser treatment was performed at day 0, and the researchers then decided if the subjects required repeated treatment according to monthly assessment.

In the second group (comparator), the subjects received a sham injection or laser treatment at day 0, the investigators then evaluated whether the repeated laser treatment is needed according to monthly assessments after the first three visits.

The primary outcome of this study was to evaluate the main change in BCVA from baseline to month 12. The safety and changes in central macular thickness (CMT) were evaluated as secondary outcomes. Results showed improvements in visual acuity and corresponding anatomical improvement with decreased CMT in the conbercept group [37].

KODIAK

KSI-301 is an intravitreal agent that constitutes part of a new therapeutic platform, called Antibody Biopolymer Conjugate or ABC Platform. This modality establishes the use of a much larger molecular structure that joins and inhibits VEGF. The antibody biopolymer on a conjugated ABC platform has the main concept to maximize intraocular durability. Molecularly, it has a specific anti-VEGF IgG1 antibody with an inert immune effector function that is covalently and stably linked to an intentionally high molecular weight biopolymer. In this sense, the molecular weight is around 950 kDa, much bigger in proportion, compared to ranibizumab with 48 and 115 kDa of aflibercept equal to 1000-fold greater than aflibercept shown in pre-clinical studies [38].

The phase 2b/3 DAZZLE pivotal study in patients with treatment-naive nAMD completed enrollment in November 2020 including a total of 550 patients worldwide, with an expected data readout in early 2022 [39].

Pivotal trials: the GLEAM and GLIMMER trials [40, 41]

Currently recruiting, these are global, multicentric, randomized studies, designed to evaluate the effectiveness, safety, and durability of KSI-301 in the treatment of patients with naive DMO.

In both studies, patients are randomized into two groups, the first one receiving 5 mg of KSI-301, every 4 weeks for 3 months followed by an individualized regime with an injection every 8–24 weeks. In the second group (comparator), patients receive 2 mg aflibercept every 4 weeks for 5 months, followed by an injection every 8 weeks. Each study intends to recruit approximately 450 patients worldwide.

In February 2021, Kodiak Sciences announced 1-year durability, efficacy, and safety data from the ongoing trials at the Angiogenesis, Exudation, and Degeneration 2021 Annual Meeting. A total of 84% of the patients in the respective trials are on a 4-month or longer treatment interval at 1 year. KSI-301 has been shown to have a strong anti-VEGF efficacy and safety profile [42].

DISCUSSION AND CONCLUSION

It is challenging to treat DMO despite the introduction of anti-VEGF drugs mainly due to the required treatment algorithms. Despite the fact that these agents have changed the visual prognosis of our patients with DMO, there are unmet needs in the management of DMO.

The burden of injections in working patients with multiple diabetes-related comorbidities is a challenge. Loss of vision due to undertreatment in real-life settings and the consequent inability to work increase costs not only for health services, but also for social security services. This situation might be avoided with the introduction of these novel agents for DMO.

More durable intravitreal effects characterize new DMO therapies. Although these new drugs and devices are still under investigation, they do have the potential to improve real-world results by receiving less procedures per year and achieving disease control.

As we have learned from long-lasting effect drugs in nAMD, these agents might cause severe intraocular inflammation, leading to possible blindness [43–45]. Even though these agents may show promising results on effectiveness, physicians should keep in mind the potential for ocular side effects.

However, these new generation of therapies have made it to phase 3 trials and appear to be the strongest pipeline for DMO. We await these agents to display the potential effectiveness and durability needed for approval.

In conclusion, we strongly believe that the potential durability of these novel therapies presents the first steps to control the global epidemic of diabetic eye disease in real life.

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AUTHOR CONTRIBUTIONS

MI, DPG, AL, and DZ were responsible for screening potentially eligible studies, designing the review manuscript, and updating reference lists.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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