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Progress in the Treatment of DME

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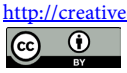

Abstract

Diabetic macular edema (DME) is a common ocular complication of diabetes mellitus (DM) and an important cause of vision loss. The pathogenesis of DME is complex and can occur at any time of diabetic retinopathy (DR). Effective methods of treating DME are essential to prevent irreversible damage to visual function. To date, laser photocoagulation, vascular endothelial growth factor (VEGF) inhibitors, and corticosteroids have demonstrated their therapeutic efficacy in large randomized controlled trials and real-life observational studies. Clinicians need to consider various factors, such as efficacy, safety, accessibility, and cost, in the selection of various options. This review summarizes the current therapeutic approaches for DME to provide new references for the treatment of DM.

Keywords

Diabetic Macular Edema, Anti-Vascular Endothelial Growth Factor, Corticosteroids, Laser Photocoagulation, Vitrectomy

1. Introduction

DM affects 463 million globally in 2019 and will reach 700 million by 2045 [1]. DR is one of the most common complications of DM. DR is a leading cause of blindness and visual impairment, especially in the adult population of working age [2]. Vision loss due to DR is primarily associated with two advanced diseases: DME and proliferative diabetic retinopathy (PDR). DME has surpassed PDR as the most common cause [3]. DME can present at any stage of DR, and the main clinical treatments for DME include retinal photocoagulation, vitrectomy, and anti-VEGF therapy. Due to the efficacy and safety of anti-vascular endothelial growth factor (anti-VEGF) injections, it has become the current first-line

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therapeutic option for improving vision in DME; however, 40% of patients with DME do not respond or respond poorly to anti-VEGF treatment [4]. Clearly, the pathogenesis of DME is complex, so patients with inadequate response to anti-VEGF agents may benefit from controlling the inflammatory response, and VEGF-non-dependent pathways and other modalities should also be of interest. In addition to this, frequent intravitreal injections can be extremely burdensome for the patient and, at the same time, increase the risk of endophthalmitis. Therefore, finding effective treatments for DME has become a worldwide challenge. Individualized treatment protocols for DME are also being improved to achieve therapeutic efficacy while reducing the therapeutic burden of monthly intravitreal injections. Therefore, this article provides an overview of the current major therapeutic advances for DME.

2. Anti-Vascular Endothelial Growth Factor

Currently, anti-VEGF therapy is the first-line treatment for DME, and a number of large-scale clinical trials have demonstrated its positive effects on DME. The VEGF family, which includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PIGF), has been shown to promote increased vascular permeability, extracellular matrix denaturation, vascular endothelial cell migration proliferation and angiogenesis, etc. [5]. High expression of VEGF is closely related to the development of DME, especially VEGF-A. Pharmacological treatment targeting VEGF can pathogenetically inhibit neovascularization and attenuate leakage-induced exudation, edema, and inflammation [6] [7]. There are three main classes of drugs targeting VEGF: anti-VEGF monoclonal antibodies, fusion proteins, and dual-targeted anti-VEGF drugs. The monoclonal antibodies include ranibizumab (Lucentis) and brolucizumab (Beovu); the fusion proteins include aflibercept (Elyea) and conbercept; and the dual-targeted anti-VEGF drugs include faricimab (Vabysmo).

2.1. Anti-VEGF Monoclonal Antibody

2.1.1. Ranibizumab.

It is the world's first anti-VEGF drug approved for ophthalmic use. It is a recombinant monoclonal antibody fragment with a molecular weight of 48 kDa, which mainly acts on VEGF-A. The small molecule Ranibizumab, which does not contain Fc fragment, is characterized by strong penetration, rapid penetration into the whole layer of the retina, fast onset of action, and strong effects [8] [9] [10].

Based on the results of two multicenter, randomized, double-blind, dose-parallel, sham-injection-controlled, Phase III clinical studies, The RISE and The RIDE studies, the FDA approved ranibizumab for the treatment of the DME indication in 2012. The RISE and The RIDE studies compared the efficacy of once-monthly, low-dose (0.3 mg and 0.5 mg) ranibizumab versus sham ranibizumab in patients with centrally involved DME. The primary endpoint was the proportion of sub-

jects with at least +15 letters of improvement at 24 months, and secondary endpoints included improvement in BCVA, improvement in macular thickness, and safety measures. The improvement in visual acuity (VA) from baseline levels was no less than 15 letters in 18.1%, 44.8%, and 39.2% of patients in the sham-injection group, and the ranibizumab 0.3 mg and 0.5 mg treatment groups, respectively, in The RISE study, and The RIDE study 12.3%, 33.6%, and 45.7%, respectively. The decrease in CRT from baseline was 133.4, 250.6, and 253.1 μm in the sham-injection group, and the ranibizumab 0.3 mg and 0.5 mg treatment groups in The RISE, and 125.8, 259.8, and 270.7 μm in The RIDE study, respectively. The two studies demonstrated that ranibizumab treatment of patients with DME significantly improved VA and retinal structure at 24 months [11]. The RESTORE and REVEAL studies were phase 3 laser therapy-controlled RCTs (randomized controlled trials), and the primary objective of the trial was to demonstrate better mean BCVA improvement at 12 months in patients receiving either ranibizumab monotherapy or ranibizumab in combination with laser therapy compared to laser monotherapy [12] [13]. However, in both studies, there was no significant difference in VA when combining laser with ranibizumab compared to ranibizumab monotherapy. The fixed dosing regimen, which involves monthly or bimonthly treatment, has been shown to be effective in various clinical trials, but may be impractical in the real world. Therefore, the pro re nata (PRN) approach has been proposed to reduce the number of injections while maintaining a fixed follow-up time to closely monitor treatment response. The RELIGHT study and The DRCR.net study evaluated the potential benefits of ranibizumab 3+ PRN for the treatment of DME [14] [15]. The RESTORE study was extended to 3 years and found that performing a PRN approach, ranibizumab was effective in improving BCVA and CST outcomes and reducing the number of injections [16]. Srinivas *et al.* [17] found that the injecting laser bead monocular antibody treatment in the monthly vitrus can significantly reduce the intravinum hard exudate (HES), and parallel parallel with the thickness and volume of the macular. Both Chatziralli *et al.* [18] and Mori *et al.* [19] found that DME patients exhibited significant photoreceptor recovery after intravitreal injection of ranibizumab.

In addition to improving VA and retinal structure, treatment with ranibizumab improves retinal function in patients with DME. Yigit *et al.* [20] found that multifocal electroretinography recordings (mf-ERG) began to improve after 6 months of treatment with ranibizumab in patients with DME. Significant improvement was obtained at months 9 and 12 post-injection. Significant improvement in full-field electroretinography recordings (ff-ERG) was observed at month 12. Consistent with the findings of the previous LUCIDATE study [21].

Zarbin *et al.* [22] An assessment of the cardiovascular safety of 1767 patients with DME from six phase 2 and phase 3 clinical trials revealed relatively low rates of cardiovascular events in all groups. The safety of treatment with ranibizumab was demonstrated, but further evaluation of treatment options and safety

in high-risk patients is needed.

2.1.2. Brolucizumab (Beovu)

Brolucizumab is a 26 kDa humanized single-chain variable antibody fragment (scFv) targeting VEGF-A. It retains only two variable regions, is smaller than ranibizumab, and has high affinity. Currently, Brolucizumab has three completed pivotal clinical studies in DME patients (The KITE, KESTREL and KINGFISHER studies) and is undergoing a registrational clinical KINGLET study in DME patients in China. The KITE and KESTREL studies are both RCTs, aflibercept -controlled, Phase III Brolucizumab 6 mg was administered as a loading dose in 5 doses every 6 weeks and then every 12 weeks, and the 52-week results of The KESTREL and KITE trials demonstrated improved best-corrected visual acuity (BCVA) and sustained reductions in central retinal thickness (even better than with aflibercept), with more than 40% of the patients being able to maintain the 12-week dosing interval [23]. Results at week 100 were also consistent with week 52, and the overall safety profile of brolucizumab remained unchanged at the second year [24]. Unlike KITE and KESTREL, brolucizumab was administered every 4 weeks in the KINGFISHER study, and the 52-week results showed no clinically meaningful differences in visual outcomes between the brolucizumab and aflibercept groups, but it was still superior to aflibercept in terms of improvement in central subfield thickness, and, in addition, eyes treated with brolucizumab showed no difference in visual outcomes at 52 weeks. In addition, fewer brolucizumab-treated eyes had subretinal fluid (SRF) or intraretinal fluid (IRF) at week 52 (58.2% and 78.2%, respectively) [25]. Brolucizumab is relatively safe for use in diabetic patients, with few adverse events observed, and a higher incidence of adverse events at the 3 mg dose compared with the 6mg dose [26]. Hirano *et al.* [27] found that the short-term response of DME patients treated with conventional anti-VEGF therapy after switching to brolucizumab was retrospectively evaluated, and the results showed significant improvements in BCVA as well as central macular thickness (CMT) and macular volume (MV) at 1 month with conventional anti-VEGF treatment and intravitreal injection of brolucizumab (IVBr), but significant improvements in CMT and MV at 1 month with IVBr treatment. BCVA, as well as CMT and MV, improved significantly at 1 month, but the decrease in MV was more pronounced at 1 month of IVBr treatment, which may be related to the more effective reduction of retinal effusion with brolucizumab, effective in reducing retinal fluid.

Brolucizumab may be a viable therapeutic option for patients with DME who are considering switching from a traditional anti-VEGF agent for various reasons, such as poor response or inability to extend dosing intervals.

2.2. Fusion Protein

2.2.1. Aflibercept

Aflibercept was first approved for marketing in 2011 for the treatment of neovascular age-related macular degeneration (nAMD). In 2014, based on two stu-

dies, VIVID and VISTA, Aflibercept was approved by the FDA for the treatment of DME. In 2018, Aflibercept was approved domestically for the treatment of nAMD and DME.

Aflibercept is a soluble receptor fusion protein consisting of a humanized IgG1 Fc fragment, and a combination of receptors that can bind to VEGF to form a receptor trap that can simultaneously block VEGF-A, VEGF-B, and PLGF, with a wider range of targets of action. VISTA and VIVID were two RCT, laser photocoagulation treatment-controlled Phase III clinical studies. After 52 and 100 weeks of treatment, BCVA was significantly higher in the 2q4 (Aflibercept 2mg every 4 weeks) and 2q8 (2mg every 4 weeks for 5 consecutive doses + 2mg every 8 weeks thereafter) than in the laser photocoagulation groups in the VIVID and VISTA studies ($p < 0.0001$), and overall efficacy was similar in the 2q4 and 2q8 groups [28]. Dhoot *et al.* [29] post hoc analysis of VISTA and VIVID showed that approximately 40% of patients achieved and maintained grade ≥2 Diabetic Retinopathy Severity Scale (DRSS) improvement within ≥1 year and were associated with greater VA improvement. Patients with DME treated with aflibercept improved earlier compared with laser therapy, suggesting that anti-VEGF reversed disease progression in these patients. The finding of sustained improvement in DRSS may help clinicians establish an optimal anti-VEGF treatment strategy. In addition, the VIVID-EAST study, which was conducted in an Asian population with the same design as VISTA and VIVID, enrolled 378 subjects and similarly demonstrated significant improvements in vision and anatomy in DME patients treated with aflibercept compared to laser photocoagulation [30]. Wang *et al.* [31] conducted a retrospective analysis of 8234 DME patients treated with anti-VEGF, showed that after one year of treatment, intravitreal ranibizumab (IVR) or intravitreal conbercept (IVC) had a greater beneficial effect on BCVA than intravitreal aflibercept (IVT-AFL). The beneficial effect of intravitreal aflibercept (IVT-AFL) on BCVA was greater, with a higher proportion of patients with ≥15 letters of improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) (especially in the DME patients with poor baseline VA and fewer ocular adverse events occurred in the IVT-AFL group. Xiao *et al.* [32] compared the long-term (12 or 24 months) efficacy and safety of IVT-AFL for the treatment of DME and PDR, with significant advantages over other treatments (ranibizumab, focused/grid laser photocoagulation, panretinal photocoagulation (PRP), etc.) for the treatment of DME and PDR with poor baseline VA. Bhandari *et al.* [33] noted that when the initial VA was 20/50 or worse, greater VA gains were observed with aflibercept treatment.

Sarda *et al.* [34] evaluated the change in choroidal thickness (CT) in patients with DME after treatment with ranibizumab and aflibercept, and showed that the CT of the macula decreased after 5 anti-VEGF treatments, especially after aflibercept. Moradian *et al.* [35] did not find a significant association between aflibercept treatment and changes in CT, and it was speculated that it might be related to different receptor densities and the sensitivity of the retinal and cho-

roidal vasculature systems to VEGF.

The Phase 3 trial of PHOTON is investigating high-dose (8 mg) aflibercept to find the efficacy and safety of using high-dose aflibercept at 12- or 16-week intervals compared to DME treatment with 2 mg aflibercept. Bayer recently announced that PHOTON for two years (96 weeks) showed long-term sustained vision benefits and longer treatment intervals with aflibercept 8 mg compared to aflibercept 2 mg at the current fixed intervals of 8 weeks, and that its safety profile was consistent with that in previous trials [36]. The safety and efficacy of aflibercept have been demonstrated in major trials and could provide additional options for patients with DME.

2.2.2. Conbercept

Conbercept is a fully humanized soluble VEGF receptor (VEGFR) fusion protein containing VEGFR-1 binding domain 2 and VEGFR-2 binding domains 3 and 4, with a molecular weight of approximately 143 kDa. Conbercept is structurally different from aflibercept, the first marketed anti-VEGF fusion protein, in that conbercept contains the VEGFR-2 binding domain 4, which binds more VEGF isoforms and prolongs their half-life in the vitreous [37].

The SAILING study was a 12-month RCT, laser photocoagulation treatment-controlled phase III clinical study that included 248 patients with DME. The aim was to compare the efficacy and safety of IVC and laser photocoagulation for the treatment of DME. The results of the SAILING study showed that after 12 months of treatment, the mean improvement in BCVA compared to baseline in the IVC and laser photocoagulation groups was 8.2 ± 9.5 letters ($p < 0.001$) and 0.3 ± 12.0 letters ($p = 0.810$), respectively, and the mean reduction in CRT was 200 ± 210 μm ($p < 0.001$) and 130 ± 190 μm ($p < 0.001$), respectively. The results demonstrated that IVC resulted in a greater reduction of edema compared to laser photocoagulation, resulting in a significant BCVA vision benefit. A subsequent 12-month open-label extension study of patients in both groups followed monthly and treated with IVC PRN showed that patients in the laser photocoagulation group showed significant improvement in BCVA after switching to IVC (8.0 ± 11.4, vs. baseline, $p < 0.001$), and that the IVC group was able to maintain the VA benefit (8.3 ± 12.4, vs. baseline, $p < 0.001$) and that at the There was no significant difference in BCVA between the two groups at the end of the extension study, and overall, the safety profile of conbercept was similar to that of other anti-VEGF agents [38]. Evidence from SAILING and its extension study confirms the favorable efficacy and safety of IVC for 2 years.

Sun *et al.* [39] evaluated the efficacy and safety of treatment with IVC versus IVR in 588 patients with DME showed improvement in BCVA and CMT superior to that of ranibizumab, with a lower number of adverse events observed in all studies. Cui *et al.* [40] evaluated the cost-effectiveness of IVC and IVR in the treatment of DME from a pharmacoeconomic point of view, with a view to obtaining greater benefits at minimal cost and optimizing the allocation and utilization of healthcare resources. The results showed that IVC was less costly and

more effective in treating DME than IVR.IVC can be a preferred choice for DME treatment.

2.3. Dual-Target Anti-VEGF

Faricimab

Faricimab is the first bispecific antibody approved for ophthalmic diseases that inhibits the VEGF pathway and the Ang-2/Tie pathway by targeting VEGF-A, a major promoter of neovascularization, and ang-2, a key regulator of vascular stability and maturation, by targeting VEGF-A and angiopoietin-2 (Ang-2) respectively. The dual inhibitory mechanism of faricimab achieves synergistic promotion of vascular stability [41].

The BOULEVARD study is a 36-week RCT, ranibizumab-controlled Phase II clinical trial to evaluate the safety and efficacy of of faricimab in the treatment of DME patients. A total of 229 DME patients were enrolled in the study. The results of the study demonstrated significant improvements in BCVA and central subfield thickness (CST) in both the faricimab and ranibizumab groups at week 24, in addition to a dose-dependent reduction in CST, improved DR severity, and longer duration of efficacy with faricimab compared to ranibizumab [42]. Validated the clinical significance of faricimab for simultaneous inhibition of Ang-2 and VEGF-A in patients with DME.

Based on the results of the Phase II studies, two identical aflibercept-controlled pivotal phase III clinics, The YOSEMITE and The RHINE further evaluated the efficacy and, safety of faricimab and the potential benefit of a personalized treatment interval (PTI) approach. The two studies enrolled 940 and 951 patients with DME, respectively, and the 1-year primary outcomes demonstrated that faricimab administered every 8 weeks (Q8W) or according to a PTI-based regimen provided non-inferior VA gains and anatomical improvements compared to abciximab Q8W. The PTI treatment group also demonstrated longer duration of efficacy with faricimab, and in both The YOSEMITE and The RHINE >50% of patients in the PIT group received every 16-week (Q16W) dosing and >70% received every 12-week (Q12W) dosing or longer during treatment year 1. The study also found that the safety profile of faricimab was comparable to that of aflibercept [43].

Takamura *et al.* [44] found that intravitreal faricimab (IVF) inhibited vascular permeability and improved vascular structure, with a decrease in the number of microaneurysms (MAs) after treatment.MA is a risk factor for refractory DME. The effectiveness of faricimab in reducing the number of MA may reduce the frequency of residual edema after injection [45]. Ohara *et al.* [46] found that faricimab also prolonged the treatment interval in patients with DME refractory to ranibizumab or aflibercept.

Research suggests that faricimab may improve VA and macular structure to a greater extent than current anti-VEGF injection therapy, extending treatment intervals and reducing the burden of treatment. It has been approved for DME

in 2022, and IVF may be considered when other anti-VEGF resistance is present in the patient population.

3. Corticosteroids

There is growing evidence that DME is mediated by a combination of inflammatory cytokines and VEGF and that inflammation plays an important role in DME [47] [48]. Increased pro-inflammatory mediators and activation of cellular inflammatory processes will disrupt the drainage function of Müller glial cells and the retinal pigment epithelium (RPE), resulting in the development of DME [49] [50] [51].

Corticosteroids reduce the synthesis of adhesion molecules, chemokines and inflammatory molecules, and indirectly reduce VEGF synthesis [52]. This reduces vascular permeability and restores the integrity of the blood-retinal barrier and Müller cell function in DR patients [53] [54]. The steroids currently available for the treatment of DME are triamcinolone acetonide (TA), dexamethasone intravitreal implant (DEX-I, OZURDEX®), and fluocinolone acetonide (FAc) intravitreal implant (ILUVIEN®).

3.1. Triamcinolone Acetonide

The mechanism of action of TA is unclear and may be related to the inhibition of inflammation induced by VEGF, TNF-α, and IL-1β and the reduction of retinal vascular permeability [55]. Zając-Pytrus *et al.* [56] evaluated the efficacy and safety of intravitreal injection TA for the treatment of DME and showed significant improvement in BCVA and retinal thickness in patients with DME compared to the previous period, but the improvement in BCVA was not significant after repeated injections. There was a short-term increase in IOP (<3 months) after the first injection, and no vision-threatening side effects were observed. A reduction in the number of microaneurysms in the superficial capillary plexuses (SCP) and deep capillary plexuses (DCP) after intravitreal injectionTA has been demonstrated. Therefore, intravitreal TA may be effective in patients with DME caused by microaneurysm leakage, but further studies are needed [57]. Intravitreal injection TA treatment helps improve delayed DME, however, its therapeutic effect may be limited and there is a risk of elevated intraocular pressure (IOP). Subtenon injection of TA has comparable efficacy and lower risk than intravitreal TA [58]. Some studies have shown that combination therapy with anti-VEGF may have better therapeutic outcomes [59] [60].

3.2. Dexamethasone

Dexamethasone intravitreal implant (DEX-I, Ozurdex®) has been used for the treatment of DME as a sterile, extended-release (up to 6 months) intraocular implant. European Society of Retina Specialists (EURETINA) Guidelines promote intravitreal steroid injection as second-line treatment [6], primarily due to the relatively high risk of ocular side effects, particularly IOP-related and cata-

ract-related adverse events (AEs) [61] [62] [63]. Two RCTs, phase III clinical trials (MEAD study) demonstrated the safety and efficacy of DEX-I in the treatment of DME, in which the incidence of adverse events such as IOP elevation and cataract onset or progression was low and mostly mild to moderate, and generally did not require interruption of therapy [64]. Ozurdex therapy was not inferior to anti-VEGF therapy in patients with non-resistant DME, according to a meta-analysis. In patients with resistant DME, Ozurdex was associated with more significant improvements in VA and reductions in CRT compared with anti-VEGF therapy [65]. AUSSIEDEX findings also support DEX for the treatment of anti-VEGF-refractory DME [66]. A retrospective analysis of 75 DME cases showed a mean improvement of 5 ETDRS letters in BCVA during the first 6 months of follow-up. However, this improvement was not maintained at subsequent visits, but a more durable benefit was obtained in the IOL (36 months) [67]. The European DME Registry study demonstrated optimal VA and anatomical improvement 3 months after injection, followed by a decline, and a greater benefit in patients with early DME compared to advanced DME [68]. In fact, anatomical recurrence of DME may occur approximately 4 - 5 months after DEX injection, followed by rapid onset of dysfunction. [69] suggests that early treatment with corticosteroids may be considered in first-treatment patients, but that clinically adjusted re-injection intervals based on patient need may be effective in ensuring maximal improvement in VA and anatomy.

Dexamethasone implants may be considered in patients with contraindications to anti-VEGF drug therapy (patients at high risk for cardiovascular events), patients with IOLs, patients who do not want frequent treatment or follow-up, and patients with refractory DME.

3.3. Fluocinolone Acetonide

Fluocinolone acetonide (FAc) is a selective glucocorticoid receptor agonist with similar anti-inflammatory potency to DEX [70], ILUVIEN® is a non-biodegradable implant containing 0.19 mg of FAc, releasing 0.20 μg of FAc per day, and is the only FDA-approved sustained-release up to 3-year corticosteroid intraocular implant for the treatment of DME in patients with no significant elevation of IOP on prior corticosteroid therapy [71] [72].

The 3-year Phase 4 clinical PALADIN study confirmed the long-term benefits of a significant reduction in DME and an improvement in mean VA after 36 months of 0.19 mg FAc intravitreal implant injection. Patient treatment burden was reduced by 70.5%, 25% of DME patients did not need to be re-treated, and IOP fluctuations were low, maintaining a favorable safety profile [73]. REACT study evaluated the efficacy and safety of FA treatment in patients with chronic DME who had an inadequate response to other treatments, with significant improvement in BCVA, CST and MV at month 24 after FAc injection and no additional adverse events [69]. In the ILUVI1MOIS study, switching to FAc injections 1 month after the last DEX-I in patients with chronic DME (recurrence

time ≤ 6 months) with frequent DEX-I-treated IOLs maintained stable BCVA and CMT while reducing the need for additional treatments without significantly increasing IOP [74]. Leite *et al.* [75] reported that 45 eyes with refractory DME treated with FAc for 6 months significantly improved the classification of diabetic maculopathy and reduced the proportion of eyes with combined intraretinal cysts, retinal thickness 30% above the upper normal value, and disrupted or absent ellipsoid zone (EZ) and/or external limiting membrane (ELM).

FAc implant maintains stable concentrations for a longer period (36 months) than DEX-I. However, optimal functional and anatomic status is reached more slowly, usually at 6 months after implantation [76]. The most common adverse events continue to be cataracts and elevated intraocular pressure. However, VA after cataract surgery is comparable to IOL patients [77]. Most patients do not need IOP-lowering therapy after FAc implant treatment [78]. In summary, it is a valuable treatment for patients with persistent or recurrent DME who have not responded well to other therapeutic options.

4. Laser Therapy

Laser photocoagulation used to be the primary treatment for DME. In the ETDRS, the use of focal laser photocoagulation (to treat focal areas of leakage) and grid-pattern laser photocoagulation (to treat diffuse retinal thickening secondary to diffuse leakage) for the treatment of DME prevented severe vision loss [79]. In the current era of anti-VEGF drugs, laser therapy is no longer considered the standard of care for DME, and may be used as a second-line treatment and combination therapy [6]. The PLACID study noted that at months 1 and 9, the proportion of patients who improved by at least 10 letters was significantly higher in the Ozurdex combined with laser treatment group than in the laser treatment group [80]. The READ-2 Study compared the efficacy of ranibizumab monotherapy to combined lasers, and found additional laser therapy helped reduce the number of injections [81]. The RESTORE study showed that laser photocoagulation in combination with ranibizumab was as effective as ranibizumab monotherapy, but there was no significant difference in the frequency of injections required [12]. On the other hand, the DRCR. Net Protocol I study showed no significant difference in 5-year visual prognosis between the 6-month delayed combined laser group and the early combined laser group, but delayed laser treatment reduced macular damage, eliminated the need for grid-pattern photocoagulation in about 56% of patients, and provided a better visual prognosis in patients with poor baseline VA (<20/50) with delayed laser treatment [15]. The LyoMAC2 study noted that focal photocoagulation of capillary macroaneurysm (CMA) was effective in reducing the number of injections in patients with chronic DME, at 12 months after laser treatment, the number of anti-VEGF treatments was reduced by nearly 50%, and the number of DEX-I treatments was reduced by 25% [82]. Laser therapy still has an irreplaceable role in the treatment of DME, and further studies are needed to explore the optimal timing of

laser photocoagulation to provide better anatomical and functional improvement and to reduce the number of injections.

5. Surgical Treatment

Surgical treatments mainly consist of pars plana vitrectomy (PPV) or combined peeling of the internal limiting membrane (ILM). After PPV, the vitreous oxygen content is elevated and the VEGF concentration is reduced, which prevents the formation of DME. [83]. ILM peeling not only eliminates physical traction on the retina, but also eliminates the natural reservoir of reactive oxygen species (ROS), advanced glycosylation end products (AGEs) inflammatory molecules [84]. Ivastinovic *et al.* [85] followed 99 patients who underwent PPV combined with peeling of the ILM glazing for at least 12 months and found that BCVA and CMT improved significantly at a mean of 2 years, and the final visual outcome was significantly better in eyes with an intact preoperative external limiting membrane (ELM). Rinaldi *et al.* analyzed 672 patients with non-traction DME in a in a retrospective analysis, combined with peeling of the ILM did not yield a significant difference in VA and anatomical improvement compared with PPV [86]. Similarly, Ranno *et al.* reached a similar conclusion [87]. Currently, there is an ongoing VVV-DME study aimed at exploring the effect of early PPV combined with ILM stripping in patients with primary DME [88], More clinical trials are needed to demonstrate the efficacy and safety of different surgical approaches and timing of surgery for DME.

6. Conclusion

The increasing incidence of DME every year prompts the importance of early and effective treatment. Anti-VEGF therapy is still the first-line treatment option for DME, but frequent drug injections bring great economic burden and safety risks to patients. The emergence of new dual-antagonist drugs is expected to prolong the duration of treatment and bring greater benefits to patients. More clinical studies are needed in the future to verify their long-term efficacy and safety. For refractory and recurrent DME, especially in IOL patients, cortisol may be a preferred option. In the meantime, laser therapy remains an important adjunctive treatment. What is more important is to provide personalized treatment to patients according to their specific conditions. Given the complexity of the etiology of DME, there is still a subset of patients with DME who do not achieve anatomical or functional improvement. Therefore, the search for more effective and long-lasting therapies to reduce the burden of treatment and improve VA in these patients is a direction for future research.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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