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Advancements in the Treatment of Diabetic Macular Edema: Current Strategies and Future Directions

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Abstract

This narrative review examines current and emerging treatment strategies for diabetic macular edema (DME), a complication of diabetic retinopathy characterised by fluid accumulation in

the macula, which can lead to vision impairment. The incidence of DME is particularly high in patients with long-standing diabetes and advanced retinopathy. The current treatment options for DME include anti-vascular endothelial growth factor (anti-VEGF) agents, corticosteroids, and laser therapies. Anti-VEGF agents, including bevacizumab, ranibizumab, aflibercept, and the more recently developed brolucizumab and faricimab, have been demonstrated to reduce macular thickness and improve visual acuity. Brolucizumab offers the advantage of fewer injections due to its longer duration of action, although it carries a higher risk of ocular inflammation compared to other anti-VEGF agents. The dual inhibition of the VEGF and angiopoietin-2 (Ang-2) pathways by faricimab may enhance vascular stability and reduce inflammation, potentially improving patient outcomes. Steroid therapies, including dexamethasone, fluocinolone acetonide, and triamcinolone acetonide, represent an alternative for patients who do not respond adequately to anti-VEGF treatment. Laser therapies, including focal, navigated, and subthreshold laser treatments, remain a crucial component in the management of DME, with the ability to seal leaking vessels and reduce fluid accumulation. In order to achieve the best outcomes for patients, it is essential to continue to advance these treatment modalities and adopt a personalised, multifaceted approach.
Keywords: Diabetic Macular Edema; Macular Edema; Anti-Vascular Endothelial Growth Factor; Laser Photocoagulation

Introduction

The IDF Diabetes Atlas (2021) indicates that approximately 10.5% of the global adult population aged 20-79 years has diabetes. Of this figure, almost half are unaware of their condition. Projections suggest that by 2045, approximately 783 million adults, or 1 in 8 people worldwide, will be living with diabetes, representing an increase of 46% [1]. DME is the leading cause of blindness in people with diabetes [2].

Diabetic macular edema (DME) can develop in any form of diabetic retinopathy. Its incidence is higher in patients with long-standing diabetes and a more advanced form of retinopathy [3].

DME is easily diagnosed by biomicroscopic examination of the retina and confirmed by optical coherence tomography (OCT). Hyperglycaemia-induced vasogenic changes lead to a breakdown of the blood-retinal barrier (BRB), initiating the development of macular edema. At the same time, activation of low-grade inflammation exacerbates retinal damage, resulting in chronic macular changes [2].

DME is a multifactorial condiction characterised by thickening of the macula due to fluid leakage from retinal capillaries. This leakage is caused by loss of pericytes, thickening of the basement membrane and disruption of tight junctions in the retinal endothelium due to chronic hyperglycaemia. Several biochemical pathways contribute significantly to the pathophysiology of DME, including upregulation of vascular endothelial growth factor (VEGF), placental growth factor (PGF), angiopoietin-2 (Ang-2), intercellular adhesion molecule-1 (ICAM-1), interleukins, pigment epithelium-derived factor, matrix metalloproteinases, prostaglandins and other cytokines [4,5].

Aim

This narrative review aims to provide a comprehensive examination of the current treatment strategies for DME, with a particular focus on the efficacy, safety, and mechanisms of various therapeutic modalities. The objective of this review is to provide a comprehensive analysis of anti-VEGF agents, corticosteroids, and laser therapies, including their roles in reducing macular thickness, improving visual acuity, and managing inflammation. The review will synthesise recent clinical trial data and studies in order to highlight the benefits and limitations of each treatment option, explore the potential of novel therapies such as brolucizumab and faricimab, and discuss future directions for optimising DME management.

Material and methods

Databases such as Pubmed, Medline, Google Scholar, and Europe PMC were used for the literature review with the following keywords: Diabetic Macular Edema; Macular Edema; Anti-Vascular Endothelial Growth Factor; Diabetic Retinopathy; Intravitreal Corticosteroids; Systematic Review.

Thirty-nine articles published between 1986 and 2024 were reviewed for inclusion to ensure they reflected current understanding and practices. Articles with poor research quality, outdated information, or lacking direct relevance to the topic were excluded.

Classification

The Early Treatment Diabetic Retinopathy Study (ETDRS) introduced the term clinically significant macular edema (CSME). CSME is characterised by slit-lamp biomicroscopy by

the following criteria: “(1) thickening of the retina at or within 500 μm of the center of the macula; (2) hard exudate at or within 500 μm of the center of the macula associated with thickening of adjacent retina; or (3) a zone of retinal thickening 1 disc area or larger, any part of which is within 1 discdiameter of the center of the macula” [6].

DME has also been divided into focal and diffuse subtypes. Focal DME is primarily caused by localised leakage from microaneurysms, often surrounded by a ring of hard exudate. In contrast, diffuse DME results from a widespread breakdown of the inner blood-retinal barrier, with leakage from microaneurysms, retinal capillaries and arterioles. Hard exudates are typically absent in diffuse DME [7].

Treatment

The current treatment strategies for diabetic macular edema encompass the use of anti-VEGF agents, which diminish vascular dysfunction, restrict angiogenesis, and enhance tissue integrity within the macular region. Laser photocoagulation therapy is employed to halt the progression of vascular lesions and to preserve or improve visual acuity. Corticosteroids are administered to attenuate the inflammatory response by inhibiting the activity of inflammatory mediators (TNF-, IL-6, MCP-1, VEGF) [8]. Combination therapy is also utilised to address the multifactorial nature of the disease. Monotherapy is often inadequate, likely due to the complex pathophysiology of DME.

Anti-VEGF Therapy

Anti-VEGF agents represent the first-line therapy for centre-involving DME and have been demonstrated to be effective in improving and maintaining visual acuity, as evidenced by large-scale randomised controlled trials [9–13].

Bevacizumab, Ranibizumab, and Aflibercept

Three anti-VEGF agents—bevacizumab, ranibizumab, and aflibercept—are commonly utilised in the treatment of DME, with their efficacy having been well-established in clinical trials [8,14].

Bevacizumab has been officially approved for oncological applications. However, it is also used off-label globally for retinal angiogenic diseases due to its significantly lower cost compared to other anti-VEGF agents [8,14].

Although anti-VEGF therapy has been demonstrated to be more efficacious than laser therapy for DME, approximately 50% of patients do not experience an improvement in visual acuity in response to these treatments [14,15]. In the RISE and RIDE trials, approximately 20%–25% of patients exhibited persistent macular thickening [16]. A secondary analysis of protocol T, which compared the efficacy of intravitreal aflibercept, bevacizumab, and ranibizumab for centre-involved diabetic macular oedema (CI-DME), revealed that persistent DME at 24 weeks was observed in 31.6%, 65.6%, and 41.5% of eyes treated with aflibercept, bevacizumab, and ranibizumab, respectively [17]. Despite exhibiting incomplete responses, the visual acuity outcomes of eyes with chronic persistent DME were comparable to those of eyes with complete resolution of edema [17].

Intravitreal administration of anti-VEGF therapy is typically considered safe. However, due to the necessity of repeated treatments for DME, there is a potential for an increased incidence of local and systemic complications throughout the treatment regimen. Infrequent ocular complications include infective endophthalmitis, intraocular inflammation, retinal detachment, and elevated intraocular pressure or glaucoma.[14,18]

A number of studies have indicated that reducing the overall exposure to anti-VEGF agents is crucial in order to prevent prolonged suppression of plasma VEGF levels, which may potentially lead to thromboembolic events in patients with DME [19,20].

Brolucizumab

Brolucizumab, a relatively novel anti-VEGF agent for the treatment of DME, has demonstrated efficacy in reducing macular thickness and has shown significant potential in improving best-corrected visual acuity (BCVA) and central subfield macular thickness (CSMT) in patients with DME [21]. Furthermore, it is possible that fewer injections may be required compared to other anti-VEGF agents [21,22]. The efficacy of brolucizumab has been demonstrated to persist for up to 16 weeks, thereby reducing the treatment burden [22]. The safety profile of brolucizumab has been evaluated, revealing a relatively low incidence of adverse effects, with retinal vasculitis and retinal vascular occlusion being the most concerning [21].

Ocular inflammation, a potential complication associated with all intravitreal anti-VEGF agents utilised prior to brolucizumab, exhibits varying incidence rates. These range from 0.05% to 2.1% for aflibercept, 0.05% to 1.1% for bevacizumab, and 0.005% to 1.9% for ranibizumab. In contrast, it reaches 4.4% for brolucizumab [22].

Faricimab

Faricimab represents a novel approach to the treatment of vascular disorders, employing a dual-pathway inhibition strategy that targets both VEGF-A and Ang-2 in order to enhance vascular stability and mitigate inflammation. This offers a potential avenue for the management of a range of vascular conditions.The dual inhibition of Ang-2 and VEGF by Faricimab suggests that it may be an effective treatment for retinal vascular disease, with the potential to improve outcomes and prevent vision deterioration, thereby positively influencing patients' quality of life [23].

The treatment can be implemented within a treat-and-extend (T&E) protocol with minimal treatment requirements, thereby providing individuals affected by DME with increased autonomy. This addresses current capacity limitations in numerous healthcare systems and anticipated rises in ophthalmology service demand [23,24].

The safety profile of faricimab has been demonstrated to be favourable, with rates of inflammation and endophthalmitis comparable to those observed in other widely used treatments [25].

Steroid Therapy

Steroid therapy has the capacity to mitigate inflammation in cases of DME [14,26,27].

A number of long-acting, sustained-release steroid implants have been developed with the objective of reducing side effects and prolonging the therapeutic duration of intravitreal steroid medications [14].

Dexamethasone (DEX), fluocinolone acetonide (FA), and triamcinolone acetonide (TA) have been employed as topical steroid therapies for DME, with documented efficacy [28] . DEX is administered as a sustained-release implant or via intravitreal injections, FA is utilized in the form of a sustained-release implant, and TA is administered through intravitreal or subtenon injections. A number of studies have indicated the effectiveness of all three agents [28–31].

A favourable long-term balance between efficacy and safety was established [32,33] . The principal adverse effects linked with the administration of DEX implants were elevated intraocular pressure and cataract formation [33].

Although anti-VEGF therapy appears to demonstrate superior efficacy, steroid treatment modalities may be considered in instances where patients exhibit inadequate responses to anti-VEGF therapy, or for the purpose of reducing treatment frequency in cases of chronic persistent or recurrent diabetic macular edema, particularly in patients who have undergone cataract surgery [14,34].

Furthermore, a single sub-Tenon's capsule injection of TA has been demonstrated to have beneficial effects in preventing PRP-induced foveal thickening and visual impairment in patients with severe diabetic retinopathy who have good visual acuity. This is achieved by acting as a pretreatment for panretinal photocoagulation (PRP) [35].

Laser Therapy

Focal, direct laser therapy has been demonstrated to seal leaking microaneurysms and promote endothelial repair, thereby reducing leakage through the compromised blood-retinal barrier [14].

However, it is important to note that this laser treatment protocol carries a risk of inducing scotomas, in addition to the complications associated with other laser-induced lesions. Therefore, it is essential to ensure that the procedure is performed at a safe distance from the fovea [28].

A navigated laser system, designated Navilas, has been developed, featuring an eye-tracking laser delivery system. This technology enables the delivery of precise laser irradiation, even to small microaneurysms [36].

A non-damaging laser technique, known as subthreshold laser treatment, is currently utilized as an alternative to grid laser therapy for the improvement of DME. Subthreshold laser treatments have been observed to limit the spread of heat to the adjacent retinal and choroidal layers, whereas conventional lasers have been found to cause more extensive thermal damage and scarring. Both treatment modalities have been noted to effectively resolve DME without inducing visible retinal changes [28]. It has been postulated that these treatments exert their effects by directly stimulating the retinal pigment epithelium (RPE) [28,37,38].

The ongoing advances in laser technology, coupled with a deeper understanding of laser-retinal interactions and the underlying pathophysiology, suggest that laser therapy will remain a critical component in the management of diabetic macular edema for the foreseeable future [39].

Conclusions

The management of DME has undergone a significant evolution, providing a diverse range of therapeutic options. Each of these options has its own benefits and limitations.

A multifaceted approach, tailored to the individual patient's needs, combining anti-VEGF agents, steroid therapies, and advanced laser techniques, appears to be the most effective strategy for managing diabetic macular edema.

However, ongoing research and clinical trials are essential for the refinement of these treatments, the enhancement of patient outcomes, and the addressing of unmet needs in the management of DME. By elucidating the pathophysiology and treatment mechanisms of DME, we can develop more effective and personalised therapeutic strategies.

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References

1. Magliano DJ, Boyko EJ, IDF Diabetes Atlas 10th edition scientific committee. IDF DIABETES ATLAS. Published online 2021. http://europepmc.org/books/NBK581934
2. Romero-Aroca P, Baget-Bernaldiz M, Pareja-Rios A, Lopez-Galvez M, Navarro-Gil R, Verges R. Diabetic Macular Edema Pathophysiology: Vasogenic versus Inflammatory. *J Diabetes Res*. 2016;2016:1-17. doi:10.1155/2016/2156273
3. Scanlon PH, Aldington SJ, Stratton IM. Epidemiological issues in diabetic retinopathy. *Middle East Afr J Ophthalmol*. 2013;20(4):293-300. doi:10.4103/0974-9233.120007
4. Kuroiwa DAK, Malerbi FK, Regatieri CVS. New Insights in Resistant Diabetic Macular Edema. *Ophthalmologica*. 2021;244(6):485-494. doi:10.1159/000516614
5. Shah SU, Maturi RK. Therapeutic Options in Refractory Diabetic Macular Oedema. *Drugs*. 2017;77(5):481-492. doi:10.1007/s40265-017-0704-6
6. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991;98(5 Suppl):786-806.
7. Bresnick GH. Diabetic Macular Edema. *Ophthalmology*. 1986;93(7):989-997. doi:10.1016/S0161-6420(86)33650-9

8. *Wytyczne Postępowania w Terapii Cukrzycowego Obrzęku Plamki*.; 2017.
9. Iglicki M, González DP, Loewenstein A, Zur D. Next-generation anti-VEGF agents for diabetic macular oedema. *Eye*. 2022;36(2):273-277. doi:10.1038/s41433-021-01722-8
10. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for Diabetic Macular Edema. *Ophthalmology*. 2012;119(4):789-801. doi:10.1016/j.ophtha.2011.12.039
11. Mitchell P, Bandello F, Schmidt-Erfurth U, et al. The RESTORE Study. *Ophthalmology*. 2011;118(4):615-625. doi:10.1016/j.ophtha.2011.01.031
12. Massin P, Bandello F, Garweg JG, et al. Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study). *Diabetes Care*. 2010;33(11):2399-2405. doi:10.2337/dc10-0493
13. Clark WL, Boyer DS, Heier JS, et al. Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion. *Ophthalmology*. 2016;123(2):330-336. doi:10.1016/j.ophtha.2015.09.035
14. Tan GS, Cheung N, Simó R, Cheung GCM, Wong TY. Diabetic macular oedema. *Lancet Diabetes Endocrinol*. 2017;5(2):143-155. doi:10.1016/S2213-8587(16)30052-3
15. Sim DA, Keane PA, Tufail A, Egan CA, Aiello LP, Silva PS. Automated Retinal Image Analysis for Diabetic Retinopathy in Telemedicine. *Curr Diab Rep*. 2015;15(3):14. doi:10.1007/s11892-015-0577-6
16. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for Diabetic Macular Edema. *Ophthalmology*. 2012;119(4):789-801. doi:10.1016/j.ophtha.2011.12.039
17. Bressler NM, Beaulieu WT, Glassman AR, et al. Persistent Macular Thickening Following Intravitreous Aflibercept, Bevacizumab, or Ranibizumab for Central-Involved Diabetic Macular Edema With Vision Impairment: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Ophthalmol*. 2018;136(3):257-269. doi:10.1001/jamaophthalmol.2017.6565
18. Ghasemi Falavarjani K, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye*. 2013;27(7):787-794. doi:10.1038/eye.2013.107
19. Avery RL, Gordon GM. Systemic Safety of Prolonged Monthly Anti–Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema. *JAMA Ophthalmol*. 2016;134(1):21. doi:10.1001/jamaophthalmol.2015.4070
20. Hirano T, Toriyama Y, Iesato Y, Imai A, Murata T. CHANGES IN PLASMA VASCULAR ENDOTHELIAL GROWTH FACTOR LEVEL AFTER INTRAVITREAL INJECTION OF BEVACIZUMAB, AFLIBERCEPT, OR RANIBIZUMAB FOR DIABETIC MACULAR EDEMA. *Retina*. 2018;38(9):1801-1808. doi:10.1097/IAE.0000000000002004
21. Abu Serhan H, Taha MJJ, Abuawwad MT, et al. Safety and Efficacy of Brolucizumab in the Treatment of Diabetic Macular Edema and Diabetic Retinopathy: A Systematic Review and Meta-Analysis. *Semin Ophthalmol*. 2024;39(4):251-260. doi:10.1080/08820538.2023.2271095
22. Kuo BL, Singh RP. Brolucizumab for the treatment of diabetic macular edema. *Curr Opin Ophthalmol*. 2022;33(3):167-173. doi:10.1097/ICU.0000000000000849
23. Watkins C, Paulo T, Bührer C, Holekamp NM, Bagijn M. Comparative Efficacy, Durability and Safety of Faricimab in the Treatment of Diabetic Macular Edema: A Systematic Literature Review and Network Meta-Analysis. *Adv Ther*. 2023;40(12):5204-5221. doi:10.1007/s12325-023-02675-y
24. Gale R, Cox O, Keenan C, Chakravarthy U. Health technology assessment of new retinal treatments; the need to capture healthcare capacity issues. *Eye*. 2022;36(12):2236-2238. doi:10.1038/s41433-022-02149-5

25. Penha FM, Masud M, Khanani ZA, et al. Review of real-world evidence of dual inhibition of VEGF-A and ANG-2 with faricimab in NAMD and DME. *Int J Retina Vitreous*. 2024;10(1):5. doi:10.1186/s40942-024-00525-9
26. Funatsu H, Noma H, Mimura T, Eguchi S, Hori S. Association of Vitreous Inflammatory Factors with Diabetic Macular Edema. *Ophthalmology*. 2009;116(1):73-79. doi:10.1016/j.ophtha.2008.09.037
27. Jonas JB, Jonas RA, Neumaier M, Findeisen P. CYTOKINE CONCENTRATION IN AQUEOUS HUMOR OF EYES WITH DIABETIC MACULAR EDEMA. *Retina*. 2012;32(10):2150-2157. doi:10.1097/IAE.0b013e3182576d07
28. Tatsumi T. Current Treatments for Diabetic Macular Edema. *Int J Mol Sci*. 2023;24(11):9591. doi:10.3390/ijms24119591
29. Campochiaro PA, Brown DM, Pearson A, et al. Long-term Benefit of Sustained-Delivery Fluocinolone Acetonide Vitreous Inserts for Diabetic Macular Edema. *Ophthalmology*. 2011;118(4):626-635.e2. doi:10.1016/j.ophtha.2010.12.028
30. Boyer DS, Yoon YH, Belfort R, et al. Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema. *Ophthalmology*. 2014;121(10):1904-1914. doi:10.1016/j.ophtha.2014.04.024
31. SUTTER F, SIMPSON J, GILLIES M. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatmentThree-monthefficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology*. 2004;111(11):2044-2049. doi:10.1016/j.ophtha.2004.05.025
32. Bucolo C, Gozzo L, Longo L, Mansueto S, Vitale DC, Drago F. Long-term efficacy and safety profile of multiple injections of intravitreal dexamethasone implant to manage diabetic macular edema: A systematic review of real-world studies. *J Pharmacol Sci*. 2018;138(4):219-232. doi:10.1016/j.jphs.2018.11.001
33. HALLER JA, DUGEL P, WEINBERG D V., CHOU C, WHITCUP SM. EVALUATION OF THE SAFETY AND PERFORMANCE OF AN APPLICATOR FOR A NOVEL INTRAVITREAL DEXAMETHASONE DRUG DELIVERY SYSTEM FOR THE TREATMENT OF MACULAR EDEMA. *Retina*. 2009;29(1):46-51. doi:10.1097/IAE.0b013e318188c814
34. Dugel PU, Bandello F, Loewenstein A. Dexamethasone intravitreal implant in the treatment of diabetic macular edema. *Clinical Ophthalmology*. Published online July 2015:1321. doi:10.2147/OPTH.S79948
35. Shimura M, Yasuda K, Shiono T. Posterior Sub–Tenon's Capsule Injection of Triamcinolone Acetonide Prevents Panretinal Photocoagulation-Induced Visual Dysfunction in Patients with Severe Diabetic Retinopathy and Good Vision. *Ophthalmology*. 2006;113(3):381-387. doi:10.1016/j.ophtha.2005.10.035
36. Kozak I, Oster SF, Cortes MA, et al. Clinical Evaluation and Treatment Accuracy in Diabetic Macular Edema Using Navigated Laser Photocoagulator NAVILAS. *Ophthalmology*. 2011;118(6):1119-1124. doi:10.1016/j.ophtha.2010.10.007
37. Sivaprasad S, Dorin G. Subthreshold diode laser micropulse photocoagulation for the treatment of diabetic macular edema. *Expert Rev Med Devices*. 2012;9(2):189-197. doi:10.1586/erd.12.1
38. Lavinsky D, Sramek C, Wang J, et al. SUBVISIBLE RETINAL LASER THERAPY. *Retina*. 2014;34(1):87-97. doi:10.1097/IAE.0b013e3182993edc
39. Everett LA, Paulus YM. Laser Therapy in the Treatment of Diabetic Retinopathy and Diabetic Macular Edema. *Curr Diab Rep*. 2021;21(9):35. doi:10.1007/s11892-021-01403-6