REVIEW ARTICLE

ADVANCEMENTS IN OPHTHALMIC BIOSIMILARS: A PARADIGM SHIFT IN RETINAL DISEASE MANAGEMENT

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Diabetes macular oedema (DME) stands as the most prevalent cause of vision impairment. This review aimed to assess clinical studies on the efficacy of top anti-vascular endothelial growth factor (anti-VEGF) agents and their biosimilars in treating diabetic macular oedema. This meta-analysis delves into the transformative impact of biosimilars on retinal disease management in ophthalmology, focusing on the global approval and increasing integration of bevacizumab and adalimumab biosimilars. The bevacizumab biosimilars section explores their approval and cost-effectiveness, particularly in the nuanced application of bevacizumab for retinal diseases. This study highlights the potential utility of biosimilars in treating non-infectious uveitis and discusses economic implications and feasibility in retinal disease management. The profound transformation in retinal disease management, specifically in DME, is underscored, emphasizing the shift from traditional approaches to anti-VEGF therapies, and positive outcomes in visual and anatomical aspects are cited. Addressing a critical need, the abstract emphasizes ongoing research into the long-term efficacy and safety of biosimilars. The importance of guidelines and thorough investigations for sustained positive patient outcomes is highlighted. The continuous quest for innovative therapies to enhance vision outcomes for DME patients is acknowledged. Underscoring the significance of stringent quality control and pharmacovigilance, it emphasizes the need for robust monitoring and immunogenicity testing assays before market approval. The meta-analysis summarizes the monumental shift in retinal disease management due to biosimilar advancements, highlighting their potential for economic solutions and a broader array of treatment options.

Keywords: Diabetic macular oedema (DME), Anti-VEGF agents, Biosimilar, efficacy, visual acuity

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INTRODUCTION

Diabetes macular oedema (DME) stands as the most prevalent cause of vision impairment in individuals with diabetes, affecting an estimated 21 million people globally.[1,2] DME treatments, including macular laser, anti-vascular endothelial growth factor (anti-VEGF) injections, triamcinolone acetonide, and dexamethasone implantation, show efficacy in randomized controlled studies.[3] Diabetic retinopathy (DR) is the foremost cause of visual decline in the global working-age population, contributing to 1% of all instances of blindness worldwide.[4] Diabetic macular oedema (DME) specifically underlies vision loss in individuals with diabetic retinopathy.[5–7] Epidemiological investigations indicate DME prevalence in 26% of diabetic retinopathy patients[8], with newly diagnosed diabetic individuals showing macular oedema rates ranging from 0 to 3%, rising to 29% in those with a diabetic history exceeding two decades[9]. DME in diabetic retinopathy presents a notable public health concern, manifesting in diverse forms, including proliferative or non-proliferative, focal or diffuse, and originating from micro-aneurysms or retinal capillaries with abnormal permeability across the posterior pole.[10–12] Capillary blockage can induce oedema, leading to blood vessel dilation. Controlling hypertension and hyperlipidemia can slow DR progression and prevent DME advancement.[13] Macular photocoagulation (MPC) historically the gold standard for treating DME, as per the Early Treatment Diabetic Retinopathy Study (ETDRS), showcased focal/grid laser therapy efficacy, reducing substantial vision loss risk by about 50%.[14] The genesis of macular oedema involves the compromise of the blood-retinal barrier, coupled with fluid leakage[15], orchestrated by heightened levels of VEGF. Given the elevated intraocular VEGF levels in DME, it was hypothesized that employing VEGF inhibitors, specifically anti-VEGF agents, either independently or in conjunction with existing therapies, could ameliorate visual loss attributable to macular oedema.[16] Data from the Diabetic Retinopathy Clinical Research Network (DRCR.net) studies demonstrated best-corrected visual acuity (BCVA) improvement of more than 5 letters of vision in 51, 47, and 62% of eyes treated with monthly 0.5 mg of intravitreal ranibizumab after 1, 2, and 3 years of follow-up, respectively.[17–19] Biosimilars closely resemble approved biologics with minimal

variations in inactive components, ensuring comparable safety, purity, and potency. This similarity expedites market entry, reducing documentation and research expenses for pharmaceutical companies.[20] This review aims to thoroughly assess clinical studies on the efficacy of top anti-VEGF agents and their biosimilars in treating DME, and evaluating their impact on evolving clinical practices in this crucial domain.

METHODOLOGY

This review was conducted to evaluate the efficacy of various intravitreal anti-VEGF agents and their biosimilar counterparts in the treatment of DME. The titles and abstracts of the identified studies were initially reviewed by four authors. In cases where eligibility could not be determined solely based on the abstract, the full text was subsequently examined by three authors.

The search strategy utilizing PubMed and Google Scholar for literature searches with no date restrictions, were conducted between Sep and Nov 2023. Key search terms included biosimilars, anti-VEGF, diabetic retinopathy, VEGF Trap Eye, diabetic macular oedema, aflibercept, bevacizumab pegaptanib, and ranibizumab. The Boolean Operator 'OR' was utilized to connect and broaden the search terms, ensuring a comprehensive exploration. The Boolean Operator 'AND' was employed to refine the results, enhancing their relevance.

Randomized controlled trials (RCTs) or comparative studies of high quality were considered that furnished adequate data for a substantive comparison of pre- and post-treatment central macular thickness (CMT) and BCVA among two cohorts of DME patients undergoing interventional therapies. Articles lacking sufficient data on pre- and post-treatment CMT and BCVA were excluded. Reviews, meta-analyses, and case studies were omitted to maintain a focus on primary research and comparative studies.

Our analysis centred on selected studies, assessing pre- and post-treatment results in central macular thickness and BCVA for patients with DME.

RESULTS

The investigation into anti-VEGF compounds and biosimilars for managing diabetic retinopathy stems from research highlighting unregulated VEGF production and signalling in the condition. Recent inquiries have explored the efficacy and safety of various anti-VEGF medications for diabetic macular oedema, including pegaptanib, ranibizumab, aflibercept, and bevacizumab.[18] All four medications originate from the USA.

Pegaptanib sodium, approved by the FDA of USA for treating neovascular AMD, acts as a selective VEGF antagonist targeting the 165 isoform of VEGF.[17,18] A phase II study involving 172 individuals with DME demonstrated improved visual acuity and reduced central retinal thickness with 0.3 mg pegaptanib. Another US trial in 2011 with 260 DME patients revealed sustained visual acuity gain (37% *vs* 20%) in the pegaptanib group at one year.[21]

Ranibizumab, a recombinant humanized immunoglobulin G1 kappa antibody fragment, has gained FDA approval since 2012 for various conditions, including neovascular AMD, macular oedema related to retinal vein occlusion, and DME.

Various trials, including READ-2, RESOLVE, and RIDE/RISE established ranibizumab's efficacy in improving visual acuity and reducing central retinal thickness in DME patients. The RIDE and RISE trials conducted in South America and the US led to FDA approval.[22]

Intravitreal bevacizumab (IVB) gained popularity for AMD treatment due to cost-effectiveness. Trials, including a DRCR.net study, demonstrated significant improvements in BCVA and central subfield thickness with bevacizumab. In a multi-centre controlled trial published in 2005, IVB showed significant improvements in BCVA and central subfield thickness in patients with DME. The PACORES study confirmed the efficacy of off-label IVB for DME treatment, showing significant improvement in BCVA and sustained decrease in central macular thickness.[19]

A multi-centre study showed aflibercept's efficacy in DME, with improvements in BCVA and central retinal thickness. VIVID-DME and VISTA-DME trials further confirmed aflibercept's positive outcomes. The DA VINCI trial explored intravitreal VEGF Trap-Eye for DME treatment compared to conventional macular laser. The VIVID-DME and VISTA-DME trials further confirmed aflibercept's efficacy.[22]

Ranibizumab, a biosimilar, received approval in 2015 based on a Phase 3 trial. Real-world experiences and subgroup analyses affirmed its safety and efficacy, broadening its applications in wet AMD, RVO, and DME. Ranibizumab stands as the inaugural biological molecule identical to ranibizumab currently undergoing clinical trials. Recently published subgroup analysis findings from the RE-ENACT study focused on wet AMD and RVO populations.[10,11]

FYB 201 (biosimilar to ranibizumab) demonstrated comparable efficacy to ranibizumab in a Phase 3 trial (COLUMBUS-AMD). Positive interim results position it for Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approval. The Phase 3 trial has reported promising

intermediate results, demonstrating comparable efficacy to the reference treatment (ranibizumab), meeting the primary endpoint.[12] Ranibizumab biosimilar, exhibits promising outcomes with refined production processes to match purity levels. Seeking global partnerships, it aligns with EMA and FDA criteria. Xlucane boasts a distinctive technology enabling higher yields.

DISCUSSION

The exploration of anti-VEGF compounds and biosimilars for managing diabetic retinopathy and diabetic macular oedema represents a significant advancement in ophthalmic pharmacotherapy. This discussion summarises the findings from clinical trials and studies investigating the efficacy and safety of various anti-VEGF medications and biosimilars, providing insight into their potential clinical applications and implications for patient care.

The results from clinical trials involving pegaptanib, ranibizumab, bevacizumab, and aflibercept demonstrate their efficacy in improving visual acuity and reducing central retinal thickness in patients with diabetic retinopathy and DME.[21–23] Pegaptanib, as a selective VEGF antagonist, showed promising outcomes in improving visual acuity and reducing central retinal thickness in DME patients.[21] Ranibizumab, aflibercept, and bevacizumab exhibited significant improvements in visual acuity and central retinal thickness in various clinical trials.[23] These findings underscore the role of anti-VEGF compounds as effective pharmacological interventions for managing diabetic retinopathy and DME.

Anti-VEGF drugs can effectively improve macular retinal thickness (MRT) and macular choroidal thickness (MCT), without affecting microcirculation, thus providing an effective and safe treatment for patients with DME.[24] Intravitreal aflibercept, bevacizumab, and ranibizumab were relatively safe treatments for DME with vision impairment. The safety profile of ranibizumab, aflibercept, and bevacizumab observed in this study was consistent with the well-established safety profile.[25]

The emergence of biosimilars, such as ranibizumab, offers alternative treatment options with comparable efficacy and safety profiles to reference biologics like ranibizumab.[10–12] Clinical trials evaluating biosimilars have demonstrated their efficacy in improving visual outcomes and reducing central retinal thickness, positioning them as viable alternatives for the treatment of diabetic retinopathy and DME.[12]

Clinical trials investigating the efficacy of intravitreal bevacizumab, ranibizumab, and aflibercept injections demonstrated favourable functional and anatomical outcomes in patients with DME. Use of these anti-VEGF agents showed a significant improvement in the severity of DR.[26]

The effectiveness of anti-VEGF treatments in managing diabetic macular oedema (DME) has been confirmed through several significant clinical trials. These pivotal studies have been instrumental in establishing anti-VEGF agents as the standard of care for DME.[27] Table-1 highlights some of the most influential trials in this area.

Table-1: Comparative analysis of anti-vascular endothelial growth factor (VEGF) in diabetic macular oedema (DME)[27]

Study	Population	Follow-up duration (months)	Treatment	Mean vision change (Letters)	Mean CMT Regression (µm)	% of eyes with DR Regression
BOLT	80	24	Bevacizumab (1.25 mg q6)	8.6 ±9.1	-146 ±171	31.4
RISE	377	36	Ranibizumab (0.3 mg q4)	11.0 ±12.9	-261.2 ±196.2	38.5
RIDE	382	36	Ranibizumab (0.5 mg q4)	14.2 ±12.8	-269.1 ±178.9	40.9
RESTORE	208	36	Ranibizumab (0.5 mg q4) +Laser	6.7 ±1.1 (SE)	-145.9	28.3
REVEAL	396	60	Ranibizumab (0.5 mg q4) +Deferred Laser	10 ±13	-165 ±165	Not reported
VISTA	461	36	Aflibercept (2 mg q4)	10.5	-200.4	29.9
Protocol T	609	12	Aflibercept (2 mg q4)	13.3 ±11.1	-169 ±138	24.8

The ongoing development and clinical evaluation of biosimilars, highlight the continued innovation in ophthalmic pharmacotherapy.[12,14] These biosimilars hold promise in expanding treatment options and addressing unmet needs in diabetic retinopathy and DME management. The potential market debut of biosimilars in regions like the United States and Europe underscores their global impact on ophthalmic care.[14] As biosimilar development progresses, it is essential to ensure rigorous regulatory oversight and pharmacovigilance to maintain patient safety and product quality.

Healthcare providers must weigh the benefits and risks of anti-VEGF compounds and biosimilars when formulating treatment plans for patients with diabetic retinopathy and DME. Factors such as treatment efficacy, safety profiles, patient preferences, and cost-effectiveness should determine therapeutic decisions.[21–23] Ongoing monitoring and assessment of treatment response are crucial for optimizing patient outcomes and minimizing adverse events.[19,23]

Collaborative decision-making between healthcare providers and patients is paramount to ensure personalized and comprehensive care delivery.

LIMITATIONS AND CHALLENGES

Despite the promising efficacy and safety profiles demonstrated by anti-VEGF compounds and biosimilars, several limitations and challenges warrant consideration. These include variability in treatment response among patients, potential adverse effects such as ocular irritation, and cost-related barriers to treatment. The regulatory approval process for biosimilars necessitates robust evidence of similarity to reference biologics. Continued research, collaboration, and innovation within the field of ophthalmology and pharmaceutical development are required to address these challenges.

CONCLUSION

The findings from clinical trials and studies evaluating anti-VEGF compounds and biosimilars underscore their efficacy and safety in managing DR and DME. Biosimilars offer promising alternatives to reference biologics, with comparable clinical outcomes and potential cost savings. Moving forward continued research and development efforts are essential to expand treatment options, improve treatment accessibility, and enhance patient care in diabetic retinopathy and DME management.

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HMF: Comprehensive literature search, drafting of the background section
AF: Methodology development, writing of the methods and results sections
AMK: Writing the discussion and conclusion sections, manuscript editing
MIA: Data management, quality control
NM: Coordination of the research project, ensuring compliance with ethical standards
AA: Manuscript processing and formatting, technical support

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