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Review Article

Clinical Outcomes of anti-VEGF intravitreal injection in Patients with diabetic retinopathy

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Abstract

Background: Intravitreal anti-VEGF therapy is now the dominant treatment for diabetic macular edema and an alternative to panretinal photocoagulation for proliferative retinopathy, following evidence that intraocular VEGF drives both processes [4].

Objective: This review synthesizes clinical outcomes of ranibizumab, aflibercept, and bevacizumab intravitreal injection in diabetic retinopathy, including comparative efficacy, treat-and-extend durability, and regression of retinopathy severity.

Methods: We synthesized randomized trials, extension studies, and large registries addressing anti-VEGF therapy for diabetic macular edema and retinopathy, including DRCR.net Protocol T, S, and V, and the RISE/RIDE, VISTA/VIVID, BOLT, TREX-DME, and PANORAMA programs [6,27].

Findings: Aflibercept, ranibizumab, and bevacizumab produce similar 1-year gains of roughly 8-12 letters, aflibercept modestly favored in worse-acuity eyes [6]; treat-and-extend preserves efficacy while lowering injection burden [23]; and anti-VEGF monotherapy induces regression of retinopathy severity and can substitute for panretinal photocoagulation [27,31].

Conclusions: Anti-VEGF injection delivers durable benefit across retinopathy severity, though real-world outcomes stay limited by undertreatment relative to trial dosing [25].

Keywords: anti-VEGF; diabetic retinopathy; diabetic macular edema; intravitreal injection; aflibercept

1. Introduction

Diabetic retinopathy remains the leading microvascular complication of diabetes mellitus and, together with diabetic macular edema, the most common cause of vision loss in working-age adults worldwide, with global prevalence estimates placing roughly one in three people with diabetes at some stage of retinopathy [1]. The disease progresses along a well-characterized continuum from mild non-proliferative changes to proliferative disease with neovascularization, and center-involved macular edema can complicate any stage of that continuum, driven fundamentally by chronic hyperglycemia-induced breakdown of the inner blood-retinal barrier and upregulation of vascular endothelial growth factor (VEGF) in the vitreous and retina [2,3]. The demonstration that intraocular VEGF concentrations track with active neovascularization and macular edema, first established convincingly in the early 1990s, reoriented the entire therapeutic landscape away from destructive laser-only strategies and toward pharmacologic suppression of the angiogenic and permeability signal itself [4].

Three anti-VEGF agents, ranibizumab, aflibercept, and off-label bevacizumab, now anchor first-line management of diabetic macular edema and, increasingly, of proliferative diabetic retinopathy, having displaced panretinal photocoagulation as monotherapy in many practice settings [5]. Two decades of randomized trials, from the earliest ranibizumab feasibility work through large multicenter comparative-effectiveness studies, have produced an unusually rich evidence base by ophthalmic standards, permitting fairly granular claims about relative efficacy, durability, and safety across agents and dosing strategies. This review synthesizes that evidence, focusing on visual and anatomic outcomes of intravitreal anti-VEGF therapy in diabetic retinopathy and diabetic macular edema, the comparative performance of individual agents, the durability of treat-and-extend regimens relative to fixed dosing, and the capacity of anti-VEGF therapy to induce regression of retinopathy

severity independent of macular edema status.

2. Methods

We synthesized findings from randomized controlled trials, their pre-specified extension studies, and large real-world registries addressing intravitreal anti-VEGF therapy for diabetic macular edema and diabetic retinopathy, drawing on the pivotal Diabetic Retinopathy Clinical Research Network (DRCR.net) protocols, the ranibizumab RISE, RIDE, RESTORE, RESOLVE, and READ-2 trial programs, the aflibercept VISTA, VIVID, and PANORAMA trials, the bevacizumab-focused BOLT study, and comparative or network meta-analyses that pooled across these agents [6,7,8,9,10]. Studies were selected for their direct relevance to visual acuity, central subfield thickness, diabetic retinopathy severity scale (DRSS) change, or treatment durability endpoints, and mechanistic and epidemiologic sources were included where needed to frame the pathophysiologic rationale and disease burden. Outcomes were extracted narratively rather than through formal statistical pooling, given the heterogeneity of dosing regimens, follow-up duration, and comparator arms across the source literature; where trials reported outcomes at multiple time points, both early (52-week) and later (2- to 5-year) results are discussed to capture durability.

3. Results

Comparative efficacy of individual anti-VEGF agents

The DRCR.net Protocol T trial provided the most direct head-to-head comparison of the three agents in clinical use, randomizing eyes with center-involved diabetic macular edema to aflibercept, bevacizumab, or ranibizumab and finding that aflibercept produced superior 1-year visual acuity gains in eyes presenting with worse baseline vision (20/50 or worse), while the three agents performed comparably in eyes with better baseline acuity [6]. By two years the between-group differences in the worse-vision subgroup had narrowed substantially, though aflibercept retained a modest anatomic advantage

in central subfield thickness reduction, and adverse event rates were similar across arms [11]. These findings were broadly consistent with the earlier phase III registration trials for each agent individually: ranibizumab produced mean gains of roughly 11-12 letters at one year in RISE and RIDE that were sustained through 36 months of as-needed extension dosing [7,12], while aflibercept produced comparable or slightly larger gains of 10-12 letters at one year in VISTA and VIVID that persisted through 148 weeks of follow-up [8,13]. Table 1 summarizes visual and anatomic outcomes across these landmark comparative trials, and Figure 1 depicts mean letter gains at one year across the principal agents and regimens.

Table 1: Visual and anatomic outcomes at one and two years across comparative and pivotal anti-VEGF trials for diabetic macular edema [6,11,7,8,9].			
Trial	Agent(s)	1-year BCVA gain	2-year outcome
Protocol T [6]	Aflibercept vs bevacizumab vs ranibizumab	Aflibercept superior in worse-VA subgroup	Between-group gap narrowed by 2 years [11]
RISE/RIDE [7]	Ranibizumab vs sham	~11-12 letters	Sustained through 36 months [12]
VISTA/VIVID [8]	Aflibercept vs laser	~10-12 letters	Persisted through 148 weeks [13]
BOLT [9]	Bevacizumab vs laser	+8 letters vs -0.5 with laser	Largely sustained at 24 months [18]

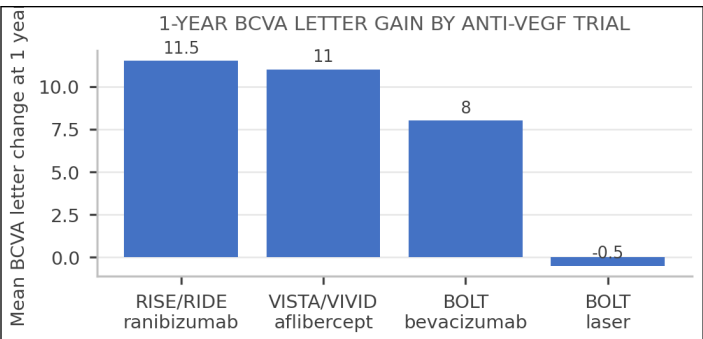


Figure 1: Mean best-corrected visual acuity gain at one year with anti-VEGF therapy for diabetic macular edema across landmark trials: RISE/RIDE ranibizumab, VISTA/VIVID aflibercept, and BOLT bevacizumab versus laser [7,8,9].

The DRCR.net Protocol I trial had earlier established that adding ranibizumab to laser was itself a substantial advance: ranibizumab with prompt or deferred laser

produced significantly greater one-year visual gains than laser alone, an advantage persisting through three and five years with continued as-needed retreatment [14,15,16]. At the other end of the severity spectrum, Protocol V asked whether eyes with good baseline acuity and center-involved edema benefit from immediate pharmacotherapy at all, finding that aflibercept, laser, and observation with as-needed treatment produced statistically equivalent two-year outcomes provided eyes were monitored closely, suggesting immediate anti-VEGF therapy is not mandatory in every eye meeting anatomic treatment criteria [17].

Bevacizumab, despite lacking a diabetic macular edema licensing indication in most jurisdictions, performed comparably to laser and to on-label agents in independently sponsored trials. The BOLT study found intravitreal bevacizumab superior to modified grid laser photocoagulation for persistent macular edema, with a mean gain of approximately 8 letters versus a loss of roughly 0.5 letters with laser at one year, an advantage largely sustained at 24 months with continued as-needed injections [9,18]. Earlier ranibizumab feasibility data from the READ-2 program had already established the biological plausibility of this class effect at six months, largely maintained through two years despite reduced injection frequency in the extension phase [19,20], and the RESOLVE and RESTORE trials extended these findings to European populations and to a laser-combination comparator, respectively, both confirming clinically meaningful acuity gains relative to sham or laser monotherapy [21,22].

Treat-and-extend regimens and treatment durability

A persistent practical question is whether fixed monthly or bimonthly dosing schedules used in registration trials can be relaxed without sacrificing efficacy, since injection burden drives much real-world nonadherence. The TREX-DME trial randomized eyes to treat-and-extend ranibizumab or aflibercept and found that extension

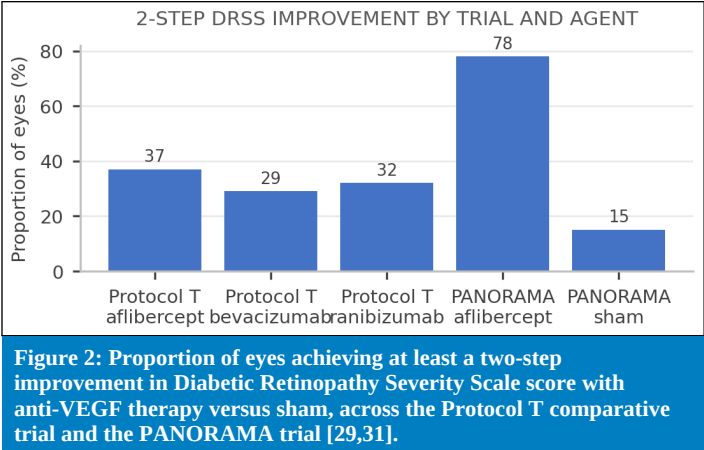
intervals of up to twelve weeks could be achieved in a substantial proportion of eyes while preserving visual gains comparable to fixed-dosing registration trials, with a meaningfully lower mean injection count over the first year [23], and two-year follow-up confirmed that these gains were durable with continued extension in eyes showing an early anatomic response [24]. Real-world registries corroborate the gap this durability question implies: the IRIS Registry found visual gains in routine United States practice considerably smaller than in RISE, RIDE, or Protocol T, attributable largely to lower injection frequency than the trial protocols specified [25], and four-year LUMINOUS registry data from European practice similarly attributed the shortfall between real-world and trial-reported outcomes chiefly to undertreatment relative to trial dosing schedules [26].

Regression of retinopathy severity and proliferative disease

Beyond macular edema, anti-VEGF therapy induces regression of diabetic retinopathy severity itself, independent of edema status, with direct implications for whether pharmacotherapy can substitute for panretinal photocoagulation in proliferative disease. The DRCR.net Protocol S trial randomized eyes with proliferative diabetic retinopathy to panretinal photocoagulation or intravitreal ranibizumab and found ranibizumab noninferior for visual acuity at two years, with better preservation of peripheral visual field and fewer vitrectomies [27]; five-year follow-up confirmed durability, though a substantial minority of ranibizumab-treated eyes eventually required supplemental laser for recurrent neovascularization [28]. Bressler and colleagues' secondary analysis of Protocol T participants found that a substantial proportion of study eyes achieved at least a two-step improvement in DRSS score with anti-VEGF monotherapy over two years, with aflibercept producing the largest proportion of two-step improvers among the three agents [29]. CLARITY extended the proliferative-disease comparison to

aflibercept, finding it noninferior to panretinal photocoagulation at 52 weeks with fewer treatment-related adverse events [30]. PANORAMA randomized eyes with moderately severe to severe non-proliferative retinopathy but no center-involved edema to aflibercept or sham, and found aflibercept reduced progression to proliferative disease or center-involved edema by roughly two-thirds relative to sham, a benefit substantially preserved through three years [31]. Table 2 and Figure 2 summarize these findings.

Table 2: Anti-VEGF outcomes for proliferative and non-proliferative diabetic retinopathy severity endpoints [27,28,30,31].			
Trial	Comparison	Key endpoint	Result
Protocol S [27]	Ranibizumab vs panretinal photocoagulation	2-year visual acuity	Ranibizumab noninferior; better visual field preserved
Protocol S 5-year [28]	Ranibizumab vs panretinal photocoagulation	Durability	Noninferiority sustained; minority needed rescue laser
CLARITY [30]	Aflibercept vs panretinal photocoagulation	52-week visual acuity	Aflibercept noninferior; fewer adverse events
PANORAMA [31]	Aflibercept vs sham	Progression to PDR/CI-DME	~2/3 risk reduction, preserved through 3 years



4. Discussion

Taken together, this evidence supports several converging conclusions. First, the three agents produce broadly

similar visual and anatomic benefit for diabetic macular edema, with aflibercept showing a modest advantage specifically in eyes with the worst baseline vision, a distinction shaping many algorithms toward agent selection by presenting acuity [6,11]. The Cochrane network meta-analysis reached a compatible conclusion, ranking aflibercept marginally ahead of ranibizumab and both ahead of bevacizumab, while noting the clinical magnitude of these differences is modest for most patients [10]. A pragmatic reading, reinforced by bevacizumab's comparable performance in BOLT despite its off-label status, is that all three are reasonable first-line choices [9,32].

Second, the gap between trial-reported and real-world outcomes in the IRIS Registry and LUMINOUS cohorts is a genuine clinical problem, arguing for treat-and-extend regimens as a structural solution rather than merely a convenience [25,26]. The TREX-DME data suggest extension can be achieved without an efficacy penalty when guided by objective anatomic response criteria, but registry data imply that even flexible regimens fail when injection frequency falls well below what any trial protocol actually delivered [23,24], so closing this gap likely requires attention to visit burden and adherence at least as much as to drug or dosing algorithm choice.

Third, the demonstration across Protocol S, Protocol T's secondary DRSS analysis, CLARITY, and PANORAMA that anti-VEGF therapy can substitute for panretinal photocoagulation in proliferative disease without compromising visual outcomes represents a genuine expansion of the therapeutic rationale beyond macular edema alone [27,29,30,31]. This shift has caveats: a meaningful minority of eyes treated with ranibizumab monotherapy for proliferative disease in Protocol S eventually required rescue laser, cautioning against complete panretinal photocoagulation avoidance in patients unlikely to sustain the required visit frequency [28]. Limitations of the underlying evidence include

heterogeneity in follow-up and injection frequency across studies, and continued off-label reliance on bevacizumab for cost reasons, supported by BOLT and comparative-effectiveness data but without an on-label framework [32,2].

5. Conclusion

Intravitreal anti-VEGF therapy has reshaped management of diabetic retinopathy and diabetic macular edema, with ranibizumab, aflibercept, and bevacizumab each delivering clinically meaningful, durable gains across an extensive randomized and real-world evidence base [6,7,9]. Aflibercept holds a modest advantage in eyes with the poorest baseline vision, treat-and-extend regimens preserve efficacy while lowering injection burden, and anti-VEGF monotherapy can substitute for panretinal photocoagulation in selected proliferative disease, albeit with a meaningful rescue-laser rate over long-term follow-up [24,28,31]. The remaining challenge is translating trial-level efficacy into real-world outcomes, where undertreatment continues to erode the visual benefit these agents can deliver [25,26].

6. Conflicts of Interest

The authors declare no conflicts of interest relevant to this review.

7. Funding

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