CLINICAL INVESTIGATION

Ranibizumab for the treatment of visual impairment due to diabetic macular edema: evidence from recent clinical trials

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Diabetic macular edema is the most common cause of visual impairment among diabetic patients. VEGF plays a major role in the pathogenesis of retinal edema in this context, as it induces angiogenesis and increases the permeability of retinal vessels. Inhibiting therapies are being studied, and ranibizumab – a recombinant humanized antibody fragment – has been approved for intravitreal use. Ranibizumab has been shown to improve functional and anatomical outcomes at 24 months, according to recent studies that compared it with standard focal/grid photocoagulation treatment, however, longer follow-up is needed to assess how this improvement is maintained over time. Guidelines for scheduled visits and retreatment have to be established to guarantee maximum effectiveness.

Keywords: clinical trials • diabetes mellitus • focal/grid photocoagulation • macular edema • ranibizumab

Visual impairment in diabetic patients is most commonly due to macular edema. Macular edema is defined as a thickened macula due to fluid accumulation within the retina layers. Clinically significant macular edema as defined by ETDRS criteria is a macular edema that affects or threatens the center of the fovea [1].

Classically, focal/grid photocoagulation has been the treatment of choice as it can reduce moderate visual loss due to macular edema by about 50%, but still 24% of patients will lose three or more lines of vision at 3 years. However, there is a high percentage of patients that do not respond to this focal/grid photocoagulation treatment and continue to lose vision [1]. Other treatment modalities include intravitreal steroids and pars plana vitrectomy, but partial efficacy or potential adverse effects limit their use [2,3].

From research on the pathogenesis of macular edema, various cytokines have been implicated, especially VEGF; and inhibiting therapies have been developed. Ranibizumab is a fully humanized monoclonal antibody fragment, which binds to all known isoforms of VEGF-A. Recently, several clinical, randomized, multicenter trials have demonstrated better visual acuity outcomes in diabetic patients with macular edema treated with ranibizumab, either as a monotherapy or in combination with focal/grid photocoagulation treatment, when compared with focal/grid photocoagulation treatment alone.

Pathophysiology of diabetic macular edema

In diabetic retinopathy, fluid accumulation within the retina is secondary mainly to the breakdown of the internal blood–retinal barrier, formed by the vascular endothelium. The weakness of this wall, as a consequence of cellular death of pericytes and endothelial cells, results in the formation of microaneurysms and

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leakage of fluid through the vessel wall, as well as the development of localized areas of ischemia [4,5]. The relative condition of hypoxia is responsible for the increase of proangiogenic factors and vascular permeability inductors, such as VEGF [6]. VEGFs are a family of proteins (VEGF-A [7], VEGF-B [8], VEGF-C [9], VEGF-D [10] and PlGF [11]) that are expressed particularly in growing or remodeling tissues, but can be generated by almost any cell under hypoxic or stress conditions. They contribute to physiological processes such as reproduction, wound healing and glomerular function, among others, through binding to VEGF receptors, which induces angiogenesis or increased permeability [12].

When VEGF binds to endothelial receptors and initiates an intracellular cascade that ends with the activation of a PKC [13], a series of ultrastructural changes occur within the cell: formation of vesicular vacuolar organelles that may form pathways for movement of plasma and solutes through the vessel wall [14]; loss of junctional integrity [15]; and formation of fenestrations [16]. Fluorescein angiography plays an important role in identifying these sites with increased permeability, showing contrast leakage and macular edema. Also, the increased number of leukocytes in the retinal vasculature indicates the major role that inflammation plays in the damage of endothelial cells [17], supported by the improvement of the edema with the use of intravitreal steroids.

Treatment of diabetic macular edema

Focal/grid photocoagulation

Focal/grid photocoagulation has been the standard treatment for diabetic macular edema since the ETDRS criteria proved that visual acuity outcomes were better than without treatment [1]. The technique consists of treating areas of thickened retina with grid pattern retinal burns, and direct photocoagulation of leaking microaneurysms.

Despite the extensive use of this modality and its proven effectiveness, the mechanism of action is still not accurately understood. Hypotheses have been made that focal/grid photocoagulation results in closure of leaking microaneurysms, and that decreased fluid flow, due to reduced retinal tissue [18], improves oxygenation. Biochemical changes in retinal pigment epithelial cells may also play a role as indirect mechanisms of action in focal/grid photocoagulation [19]. However, focal/grid photocoagulation treatment has potential side effects. These include retinal pigment epithelial atrophy, which can triple the size of the initial scar [20], paracentral scotoma, elevation of thresholds in central visual field, decrease in color vision, secondary choroidal neovascularization and subretinal fibrosis [21,22]. Even with the new pattern scan laser photocoagulator system (Pascal®, OptiMedica, CA, USA), immediate morphologic alterations in the outer retinal layers can be seen with optical coherence tomography [23]. In order to reduce the incidence of these adverse effects, retinal specialists now perform lighter, smaller and less intense burns than originally described in the ETDRS criteria (termed the modified ETDRS technique) [24].

Recent trials have confirmed focal/grid photocoagulation efficacy, and have even demonstrated a long-term superiority in relation to improved visual acuity and central retinal thickness (CRT) outcomes, when compared with the use of intravitreal steroids [2]. However, only 23% of patients show improvement in the CRT within the first 16 weeks post-focal/grid photocoagulation and just 10% thereafter [25]. Complete resolution is infrequent with one focal/grid photocoagulation session, so multiple sessions may be necessary.

Steroids

Widespread use of intravitreal triamcinolone in the treatment of diabetic macular edema began in 2001 as the first reports were published suggesting its effectiveness [26,27]. The rationale for its use was its demonstrated inhibition of VEGF [28,29] and anti-inflammatory properties, two mechanisms implicated in the pathogenesis of macular edema.

As mentioned above, in 2008 a multicenter, Phase III, randomized trial compared focal/grid photocoagulation with 1 and 4 mg intravitreal triamcinolone. Despite an initial benefit of 4 mg triamcinolone on retinal thickness and visual acuity when compared with focal/grid photocoagulation, the authors concluded that over a 3-year period visual acuity, retinal thickness and safety (in terms of cataract formation and intraocular pressure elevation) were significantly better in the focal/grid photocoagulation group than in either triamcinolone arms [2]. When triamcinolone associated with consecutive focal/grid photocoagulation was compared against focal/grid photocoagulation alone, the same results were seen, except in the subgroup of 273 pseudophakic patients, in which the 2-year mean change in visual acuity was significantly greater when treated with the combination of triamcinolone and focal/grid photocoagulation than with focal/grid photocoagulation alone [30]. This demonstrates that the combination of these two monotherapies – focal/grid photocoagulation and intravitreal triamcinolone injection – is superior to focal/grid photocoagulation alone for pseudophakic patients. However, intraocular pressure elevation, due mostly to an increase in aqueous outflow resistance,

is still an issue to be considered when intravitreal corticosteroids are used [31].

Dexamethasone implants have also been used, especially in patients that do not respond to other treatments. Their safety profile seems to be better than triamcinolone's, with a lower reported incidence of cataract and glaucoma [32].

Recently published Phase III trials have shown fluocinolone acetonide injectable implants to increase at least 15 visual acuity letters in 29% of patients, compared with 16% in the placebo group at 24 months follow-up. However, cataract formation and intraocular pressure elevation were significantly more frequent than in the no treatment arm [33].

Antiangiogenic therapy

Antiangiogenic agents have demonstrated to be comparable with steroids in terms of efficacy, but with lesser potential adverse effects. Their mechanism of action consists of inhibiting the effects of VEGF, and the resultant leakage and inflammation.

Bevacizumab (Avastin®, Genetech Inc., CA, USA) is a monoclonal antibody that targets human VEGF. It is approved for metastatic colorectal cancer and used off-label in the treatment of age-related macular degeneration and macular edema. Currently, to our knowledge, there are no published comparative Phase III trials supporting its ocular use in diabetic macular edema. Several pilot and Phase II trials demonstrate its short-term effectiveness, although it seems that this improvement may not be sustained over time [34]. Besides, the incidence of long-term complications has to be assessed in order to define its safety profile.

Ranibizumab (Lucentis®, Genentech Inc., CA, USA) is a recombinant, humanized monoclonal IgG1 κ-isotype antibody fragment that inhibits VEGF [35]. It was developed for intravitreal use and binds to all isoforms of VEGF-A, preventing its binding with VEGF receptors (VEGFR-1 and VEGFR2).

Ranibizumab was first approved by the European Medicines Agency for the treatment of neovascular (wet) age-related macular degeneration. Later on, in 2011, its use was also approved for visual impairment due to diabetic macular edema, and macular edema secondary to retinal vein occlusion [101]. The US FDA approval was obtained in 2006 for wet age-related macular degeneration, and in 2010 for macular edema following retinal vein occlusion [102]. At the time of writing this paper, FDA approval for its use in diabetic macular edema was still pending.

Vitrectomy

Surgical management has its role when significant vitreomacular traction exists. Studies have shown that two thirds of patients show a 50% reduction in retinal thickness. However, visual acuity can either improve, as observed in 38% of patients, or decrease, as seen in 22% of patients [3].

Ranibizumab

Evidence from recent clinical trials

In 2006, a dose-escalating pilot study demonstrated that ranibizumab 0.3 and 0.5 mg intravitreal injections were well tolerated in patients with diabetic macular edema. At the 3-month follow-up, half of the ten patients treated gained ten or more letters from baseline, and showed 45 and 198 µm mean decrease in CRT subfield for the ranibizumab 0.3 and 0.5 mg arms, respectively [36].

Ranibizumab compared with sham injections

Later on, 151 patients were included in a Phase II 12-month study (the RESOLVE study) to evaluate the efficacy and safety of ranibizumab [37]. Type 1 or 2 diabetic patients over 18 years of age were included, and were eligible if visual acuity was between 20/40 and 20/160, CRT by time domain optical coherence tomography of 300 µm or more, HbA1c of 12% or less, and decreased vision attributed to diabetic macular edema was not explained by any other cause. Subjects were randomized into group 1 (ranibizumab 0.3 mg), group 2 (ranibizumab 0.5 mg) or group 3 (sham injections), and initially received three consecutive monthly injections. Patients received further treatment every month unless a successful outcome was achieved (best corrected visual acuity [BCVA] of ≥79 letters and CRT of ≤225 µm), or treatment failed (<50 µm decrease in CRT or <five letters gain in BCVA).

One special feature of the study was the possibility of doubling the dose depending on whether CRT remained >300 µm, or >225 µm if the previous reduction in CRT from the previous optical coherence tomography was only <50 µm.

The investigators found a mean change in BCVA from baseline at 12 months to be statistically superior in the ranibizumab groups (improved by 10.3 letters) when compared with the sham injections (declined 1.4 letters). A similar difference was seen with the mean change in CRT from baseline at 12 months, with an improvement of 194.2 versus 48.4 µm in ranibizumab and sham injection arms, respectively. At month 12, 60.8% of patients in ranibizumab groups gained ten letters or more of BCVA from baseline when compared with 18.4% in the sham group.

One limitation of this study was the lack of a focal/grid photocoagulation arm to compare the results. However, rescue focal/grid photocoagulation was permitted from month 3, after the three consecutive

monthly injections, if BCVA in the study eye had decreased by more than ten letters from baseline at two consecutive visits, or if CRT was 225 µm or more. In the sham and ranibizumab injection arms, 35 and 5% of patients, respectively, received focal/grid photocoagulation treatment, the majority receiving between one or two focal/grid photocoagulation sessions. The impact of this intervention on final BCVA was not assessed.

With regard to adverse events suspected to be related to ranibizumab, one patient suffered a myocardial infarction in the ranibizumab group, however, the incidence of hypertension and arterial thromboembolic events were comparable in both arms. Ocular adverse events included two cases of endophthalmitis, one retinal artery occlusion and one episode of vitreous hemorrhage in the ranibizumab arm, with one case of retinal detachment in the sham injection group. Nevertheless, the proportion between both groups remained comparable (4 and 2% in ranibizumab and sham arms, respectively).

Ranibizumab plus focal/grid photocoagulation compared with focal/grid photocoagulation alone

Focal/grid photocoagulation, as the most effective known treatment for diabetic macular edema, is the standard against which newer treatment modalities have to be compared, so several studies were designed to accomplish this goal.

A Phase III multicenter trial designed by the Diabetic Retinopathy Clinical Research group randomized 854 diabetic study eyes with macular edema into four arms: ranibizumab 0.5 mg plus prompt (187 patients) or deferred focal/grid photocoagulation treatment (188 patients), triamcinolone plus prompt focal/grid photocoagulation (186) or sham injection plus focal/grid photocoagulation treatment (293) [38]. Main inclusion criteria were a BCVA between 78 and 24 ETDRS letters (~20/32 to 20/320), and a CRT of 250 µm or more. Patients received a ranibizumab, triamcinolone or sham injection at baseline, followed by focal/grid photocoagulation treatment after 1 week or deferred focal/grid photocoagulation up to 6 months later, depending on the assigned arm. Three consecutive monthly injections were then given, regardless of visual acuity or retinal thickness. From month 3 onwards, a web-based retreatment protocol was followed according to success or failure criteria.

After 2 years of follow-up, the mean change in BCVA was significantly better in both ranibizumab plus focal/grid photocoagulation groups when compared with triamcinolone plus focal/grid photocoagulation treatment or with focal/grid photocoagulation alone. Approximately, half of patients treated with ranibizumab had an improvement of ≥ ten letters from baseline, and only 1–2% had lost ≥ ten letters from baseline at 2-years follow-up. No differences were found between both ranibizumab plus focal/grid photocoagulation groups in terms of visual acuity or change in retinal thickness.

With regards to mean CRT, reduction from baseline was similar in the ranibizumab plus focal/grid photocoagulation and triamcinolone plus focal/grid photocoagulation groups when compared with focal/grid photocoagulation alone.

Continuous follow-up of patients is mandatory, with most patients requiring additional treatment for at least 2 years. Even good initial outcomes require observation, as two-thirds of patients that initially met success criteria (visual acuity 20/20 and CRT <250 µm) at the 16-week visit, needed further injections. During the first year of follow-up, patients in the ranibizumab plus prompt focal/grid photocoagulation and ranibizumab plus deferred focal/grid photocoagulation arms received a mean of eight and nine injections, respectively, with a maximum of 13 injections, compared with a mean of 11 sham injections received in the focal/grid photocoagulation-alone group. Between the first and second year of follow-up, the number of injections required declined significantly, with a mean of two in the arm associated with prompt focal/grid photocoagulation, and three in the deferred focal/grid photocoagulation group, which underlines the suggestion that as time progresses the number of injections needed could decrease. In the same period of time, 57% of patients in the ranibizumab plus prompt focal/grid photocoagulation and 72% in the ranibizumab plus deferred focal/grid photocoagulation arms received no additional focal/grid photocoagulation treatment.

Important data can be obtained from this trial, but the lack of a treatment arm with ranibizumab alone is a limitation that has to be pointed out.

Ranibizumab as monotherapy compared with focal/grid photocoagulation alone

A total of 126 diabetic patients with BCVA between 20/40 and 20/320 due to macular edema, and a CRT <250 µm were included and randomized in a Phase II multicenter trial (READ-2 study) [39]. Patients were assigned into three treatment arms: ranibizumab 0.5 mg at baseline and months 1, 3 and 5 (ranibizumab arm), focal/grid photocoagulation treatment alone at baseline and month 3 if needed (focal/grid photocoagulation arm), and a combination of ranibizumab 0.5 mg followed by focal/grid photocoagulation treatment at baseline and month 3 (ranibizumab plus focal/grid photocoagulation arm). After month 6, subjects

could be treated with ranibizumab if necessary.

At the 6-month primary end point, mean improvement in BCVA from baseline was 7.4, 0.5 and 3.8 letters for the ranibizumab, focal/grid photocoagulation and ranibizumab plus focal/grid photocoagulation groups, respectively; at month 24, patients gained a mean of 7.7, 5.1 and 6.8 letters, respectively. At final follow-up, 45% of subjects in group 1, 18% in group 2 and 26% in group 3, had gained ≥ three lines, compared with 21, 0 and 6% at the 6-month visit, respectively [40].

At the end of the follow-up period, mean CRT was 340, 286 and 258 µm in the ranibizumab, focal/grid photocoagulation and ranibizumab plus focal/grid photocoagulation arms, respectively. The percentage of patients with a CRT <250 µm was 36% in group 1, 47% in group 2 and 68% in group 3.

Mean number of injections received during the study was 5.3 out of 13 possible in the ranibizumab arm, 4.4 out of nine in the focal/grid photocoagulation arm, and 2.9 out of six in the ranibizumab plus focal/grid photocoagulation arm.

More recently, results from the Phase III RESTORE study have been published [41]. The aim of this study was to compare ranibizumab injections as monotherapy (116 eyes) or combined with focal/grid photocoagulation treatment (111 eyes), with focal/grid photocoagulation treatment alone (118 eyes). Patients were included if baseline BCVA was between 78 (20/32) and 39 (20/160), medication for diabetes was stable during the last 3 months, they exhibited visual impairment due to focal or diffuse diabetic macular edema without a CRT criteria and glycosylated hemoglobin was below or equal to 10%. Injections were given monthly during the first 3 months, and then as required every 4 weeks, except when no visual acuity improvement attributable to treatment or BCVA of 84 letters (20/20) or more was reached in the last two visits (stable visual acuity achieved).

The mean number of injections was similar in all groups, with an average of 7.0, 6.8 and 7.3 injections given in the 12-month follow-up period for ranibizumab alone, ranibizumab plus focal/grid photocoagulation and focal/grid photocoagulation only arms, respectively. This approach proved to maintain visual acuity gained after the initiation phase in ranibizumab arms, but the question remains whether visual acuity would have improved further if monthly injections were given without taking into account visual acuity or retinal thickness values.

After 1 year of follow-up, ranibizumab groups showed a superior improvement in mean change from baseline in BCVA when compared with the focal/grid photocoagulation group: 6.1 letters with ranibizumab, 5.9 with ranibizumab plus focal/grid photocoagulation, and 0.8 with focal/grid photocoagulation treatment alone.

At month 12, a significantly greater proportion of patients had a BCVA score level >73 (20/40 Snellen equivalent) in the ranibizumab (53%) and ranibizumab plus focal/grid photocoagulation group (44.9%) compared with focal/grid photocoagulation alone (23.6%). The proportion of patients that did not respond to treatment was lower in the ranibizumab groups: at month 12, 3.5 and 4.2% of participants had lost ten letters or more from baseline, compared with 12.7% in the focal/grid photocoagulation only arm. Anatomic end points accompanied functional improvement. Mean CRT change from baseline was significantly higher in the ranibizumab (reduction of 118.7 µm) and ranibizumab plus focal/grid photocoagulation groups (128.3 µm), compared with focal/grid photocoagulation alone (61.3 µm).

In terms of safety profile, there were no serious ocular adverse events suspected to be related to the study drug, and no cases of endophthalmitis were reported during the whole follow-up period. Systemic severe adverse event suspected to be related to ranibizumab were intestinal obstruction (0.9%), hypoglucemia (0.9%), pulmonary embolism (1.7%), dyspnea (0.9%), peripheral arterial thrombosis (0.9%) and coronary artery occlusion (0.8%).

These results seem to demonstrate that ranibizumab could be superior to focal/grid photocoagulation in terms of visual acuity improvement and, possibly, that final outcomes may show no difference when administering ranibizumab as a monotherapy or in combination with focal/grid photocoagulation treatment. Remarkably, these differences in final outcomes were maintained when dividing patients into subgroups. Patients with focal or diffuse edema, those with or without macular ischemia, or those previously or not previously treated with focal/grid photocoagulation, showed a better mean improvement in BCVA in the ranibizumab groups when compared with focal/grid photocoagulation alone. However, there is still a need for further clinical trials to evaluate the differences in ranibizumab's efficacy in treating focal or diffuse macular edema.

Large prospective studies designed to determine comparative effectiveness of ranibizumab have been published recently. The RESOLVE study shows that treatment with ranibizumab is more effective than placebo. Diabetic Retinopathy Clinical Research Network group has reported that final visual acuity is better with the combination therapy of ranibizumab plus focal/grid photocoagulation, rather than focal/grid photocoagulation treatment alone or combined

with triamcinolone. However, in the pseudophakic group the final visual acuity change in the triamcinolone arm is comparable to ranibizumab-treated groups, showing the importance of the adverse effects of intravitreal steroid use such as cataract and intraocular pressure elevation. During the second year of follow-up, the number of injections of ranibizumab needed was considerably lower than during the first year, showing a possible stabilization effect of the drug.

Phase II READ-2 and Phase III RESTORE trials showed that ranibizumab is effective in the treatment of diabetic macular edema even in monotherapy, as visual results seem to be better than those obtained with focal/grid photocoagulation therapy alone.

Clinical studies have also demonstrated the safety profile of ranibizumab in the short to medium term, although we must be alert to possible long-term adverse effects.

Future perspective

Current Phase II and III studies are being conducted in order to determine the ideal treatment regimen. Non-published results of RIDE and RISE studies have recently been presented, where 759 patients were randomized to receive either monthly injections of ranibizumab 0.3, 0.5 mg or sham injections during 24-month follow-up [103,104]. Focal/grid photocoagulation therapy was allowed in all groups after month 3 based on predefined criteria [42]. At the final follow-up visit, patients in the ranibizumab 0.3, 0.5 mg and sham injections groups had gained a mean of 12.5, 11.9 and 2.6 ETDRS letters from baseline (RISE) and 10.9, 12 and 2.3 letters (RIDE), respectively. Center subfield thickness showed a significant improvement from day 7 in ranibizumab arms compared with sham injections. A more individualized protocol of retreatment is being considered in other clinical trials (OPTIMAL study) [105], as well as the safety and response to higher doses (READ-3 study) [106]. These results, along with the expanded 2- and 4-year follow-up of RESTORE and Diabetic Retinopathy Clinical Research Network group trials will help determine the response and outcomes of ranibizumab in the treatment of diabetic macular edema.

Combination therapy with steroids may also play a role, as well as the newer molecule, VEGF-Trap©, a fusion protein built assembling Fc fragments of IgG to parts of VEGF receptors. Primary results of the DA VINCI study indicate improvement in visual acuity compared with focal/grid photocoagulation treatment at 6 months of follow-up. In this study, 221 diabetic patients with clinically significant macular edema were assigned to one of these groups of treatment: VEGF Trap-Eye 0.5 mg every 4 weeks; VEGF Trap-Eye 2 mg every 4 weeks; VEGF Trap-Eye 2 mg for 3 initial monthly doses and then every 8 weeks; VEGF Trap-Eye 2 mg for 3 initial monthly doses and then on

Executive summary

Pathophysiology of diabetic macular edema

- Macular edema is a retinal thickening that affects the macula, with fluid accumulation secondary to breakdown of the blood–retinal barrier. Significant macular edema is the most common cause of visual impairment in diabetic patients, as it affects or threatens the center of the fovea.
- Recently, research into macular edema pathogenesis has demonstrated the major role of VEGFs, a family of proteins that physiologically induce angiogenesis and increase permeability. It has been shown that with endothelial damage and the subsequent development of ischemic areas within the retina, VEGF production increases, which induces leakage and proliferation of perfused vessels. Inhibiting therapies have been developed successfully, including ranibizumab, a recombinant humanized antibody fragment that inhibits VEGF. It has been approved for intravitreal use.

Treatment of diabetic macular edema

- Focal/grid photocoagulation has been the treatment of choice for diabetic macular edema for over 25 years, but more recently, newer therapeutic modalities have been studied. Steroids seem to be effective in terms of functional and anatomical recovery, but cataract formation and intraocular pressure elevation limit their use. Surgical management can be an option when significant vitreomacular traction exists.

Ranibizumab: evidence from recent clinical trials

- From the data of recent reports, there is strong evidence of the efficacy and tolerability of ranibizumab in the treatment of diabetic macular edema, at least during the first 2 years of follow-up. Ranibizumab has proven to be more effective than focal/grid photocoagulation treatment alone in increasing visual acuity and decreasing macular thickness, either when used in combination therapy with focal/grid photocoagulation sessions or as a monotherapy. Longer follow-up is needed to assess whether the improvement described is maintained over time. In addition, as in wet age-related macular degeneration, best retreatment schemes and follow-up visit guidelines have to be established, as monthly visits and retreatments are often not possible in clinical practice. Benefits of ranibizumab seem to outweigh safety risk, considering the low incidence of severe adverse events observed in clinical studies.

an as-needed basis; or macular focal/grid photocoagulation. All VEGF-Trap arms showed mean visual acuity improvements of 8 to 11 ETDRS letters from baseline, compared with 2.5 in the focal/grid photocoagulation group, and a mean reduction of CRT from -127 to -194 µm, compared with 68 µm in the focal/grid photocoagulation group [43]. Larger trials are needed in order to determine their importance in the treatment of diabetic macular edema.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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