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Pharmacological Approach to Diabetic Macular Edema

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Abstract
Diabetic macular edema (DME) is a highly prevalent cause of vision loss and has a remarkable impact on public health, and on the quality of life of diabetic patients. Even though laser photocoagulation has been the standard of care for decades, a substantial group of patients are unresponsive and fail to improve after laser treatment. Recently, new pharmacological approaches based on the use of intravitreal drugs, such as corticosteroids and anti-vascular endothelial growth factor, have revolutionized the treatment of DME. The use of intravitreal drugs is supported by the improvement in visual acuity reported by several clinical trials and can limit the potentially destructive effects of the laser treatment. Encouraging results also emerged from studies evaluating the use of a combination therapy, or the association of intravitreal drugs and laser treatment. This review aims at providing a brief synopsis of the main investigations regarding the current pharmacological approach to DME.

Introduction

Diabetic macular edema (DME) is a highly prevalent cause of vision loss and has a remarkable impact on public health, and on the quality of life of diabetic patients. Even though systemic risk factors and glycemic control optimization remain the first-line treatment [1, 2], they are often insufficient in controlling the DME evolution. The Early Treatment of Diabetic Retinopathy Study (ETDRS) showed that focal/grid laser retinal photocoagulation reduced the risk of moderate visual loss by approximately 50% at 3 years [3]; thus, laser treatment has been considered the standard of care for the management of DME. However, a substantial group of patients are unresponsive and fail to improve after laser photocoagulation [4].

Recently, the improved knowledge of the molecular mechanisms of DME has led to new pharmacological approaches based on the use of intravitreal drugs, such as corticosteroids and anti-vascular endothelial growth factor (anti-VEGF). Encouraging results emerged also from studies evaluating the use of a combination therapy, or the association of intravitreal drugs and laser treatment. However, DME-specific characteristics appear paramount in the choice of the best therapeutic approach [5].

This review aims at providing a brief synopsis of the main investigations regarding the current pharmacological approach to DME.

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Corticosteroids

Due to the anti-inflammatory, angiostatic and antipermeability properties, corticosteroids have gained great interest in the treatment of DME. Although the exact mechanism of action is not fully understood, corticosteroids have been shown to interfere with the modulation of cytokines and growth factor production, leading to the stabilization of the blood-retina barrier with consequent reduction of the vascular permeability [6, 7]. Several studies showed favorable responses to the treatment in terms of visual acuity recovery and DME resolution. However, relevant side effects are intraocular pressure increase and progression of cataract [8–11].

Currently, several formulations of steroids exist, with different durations of action, which may vary from nearly a month to 3 years [12].

Triamcinolone Acetonide

Intravitreal triamcinolone acetonide (IVTA) has been used for the treatment of DME in several clinical trials, showing improvement in morphological and functional outcomes [13–15], with a dose-dependent duration of its effect (about 6–9 months for a dose of about 20 mg, and about 2–4 months for a dose of 4 mg) [16].

The results of a 5-year randomized clinical trial (RCT) demonstrated that a visual improvement (defined as 5 or more letters gained) could be achieved in 42% of eyes treated with IVTA, compared to 32% of the placebo group [17].

The Diabetic Retinopathy Clinical Research Network (DRCR.net) in an RCT investigated the efficacy and safety of 1- and 4-mg doses of IVTA in comparison with focal or grid laser photocoagulation [18]. Analyses at 3 years showed that photocoagulation was more effective over time and had fewer side effects. Moreover a greater incidence of cataract progression and intraocular pressure increase was observed in the 4-mg triamcinolone group compared to the other groups [8].

In 2010, the DRCR.net published the results of a comparative RCT (DRCR.net protocol I) evaluating the efficacy of 3 different treatments for center-involved DME, including intravitreal ranibizumab (IVR) injection (0.5 mg) combined with prompt or deferred (≥24 weeks) laser, IVTA (0.4 mg) combined with prompt laser, compared to sham injection combined with prompt laser alone [9]. Even though IVR with prompt or deferred laser was shown to be more effective than the other treatment modalities, in a subset of pseudophakic eyes IVTA combined with prompt laser achieved results similar to IVR and was more effective than laser alone, but the risk of intraocular pressure elevation was increased [9, 10]. For these reasons, currently IVTA may be considered in pseudophakic eyes and in carefully selected patients of advanced DME who are refractory to laser or other interventions.

Sustained Drug Delivery Systems

The rationale in the use of slow-release intravitreal devices is in decreasing the number of intravitreal injections required coupled with a sustained concentration of the drug in the vitreous cavity. These two features of the sustained drug delivery systems lead to a decrease in the number of injection-associated adverse events.

Dexamethasone

Dexamethasone (DEX) is a powerful corticosteroid and plays an active role in the reduction of inflammatory mediators implicated in DME [19]. DEX can be delivered to the back of the eye via a sustained-release intravitreal implant (DEX implant 0.7 mg; Ozurdex; Allergan Inc., Irvine, Calif., USA) that is placed through a small pars plana incision using a customized applicator system and slowly releases the drug for up to 6 months [20, 21].

In 171 eyes with persistent macular edema (≥3 months of duration) Haller et al. [22] compared 2 doses of DEX (350 and 700 μm) to observation.

At 90 days, the 700-μm group showed a statistically significantly higher proportion of patients with a gain of 10 or more letters compared with the observation group (33 vs. 12%). Nonstatistically significant improvement was observed for the 350-μm group compared with the observation group (21 vs. 12%). At 180 days, there was no statistically significant difference between either the DEX group or no-treatment group. The treatment effect appeared to peak at 3 months. In a recent retrospective study evaluating the effects of intravitreal DEX implantation in 9 patients with persistent DME, an improvement in best-corrected visual acuity (BCVA) was seen as soon as the first days after the injection and was maintained until the fourth month [23]. Moreover results of a study conducted by Boyer et al. [24] showed that DEX implantation was effective also in vitrectomized eyes affected by DME.

Fluocinolone Acetonide

Recently, 2 nonbiodegradable fluocinolone acetonide (FA) sustained-delivery devices have been developed

(Iluvien®, Alimera Sciences, Alpharetta, Ga., and Retisert®, Bausch & Lomb, Rochester, N.Y., USA) to provide substantial benefit in patients with DME for up to 3 years. These implants can be inserted in the vitreous cavity through a 25-gauge needle.

The FAME Study Group assessed the long-term efficacy and safety of intravitreal inserts releasing 0.2 μg/day (low dose) or 0.5 μg/day (high dose) FA versus a sham injection [11].

Rescue laser was given after the first 6 weeks for persistent DME and was allowed every 3 months; 35–37% of patients in the FA group and 59% in the sham injection group required rescue laser. At 24 months, both doses of FA showed a statistically significant improvement in mean BCVA compared to sham treatment. There was a modest difference between FA groups. An extended follow-up at 36 months [25] showed that both FA arms continued to result in a statistically significant benefit compared to the sham group. However, high rates of intraocular pressure rise and cataract surgery were frequently registered in all groups receiving corticosteroids.

Almost all phakic patients in the FA insert groups developed cataract (88.7 and 81.7% for the low- and high-dose insert groups, respectively, compared to the 50.7% of untreated groups) even if, after cataract surgery, the visual benefit was similar to that in pseudophakic eyes. The incidence of glaucoma requiring incisional surgery was 8.1 and 4.8% in the low- and high-dose groups, respectively.

Pearson et al. [26] compared fluocinolone (0.59 mg) with standard of care, either laser or no treatment, in 196 patients with refractory DME. At 3 years, there was no statistically significant difference in the proportion of patients with a 15-letter gain or more (31% fluocinolone compared with 20% standard of care) between groups as well as the proportion of patients losing 15 letters or more (17% fluocinolone compared with 14% standard of care). An increased incidence of cataracts in the fluocinolone group may have contributed to this difference.

Anti-VEGF Therapy

Anti-VEGF therapy has revolutionized the treatment of DME. VEGF plays a critical role in promoting angiogenesis and vascular leakage [27], and several different anti-VEGF drugs have been studied in the management of DME, including ranibizumab, bevacizumab, pegaptanib and, more recently, aflibercept [28, 29]. They exhibit important differences in their sites of activity, formulation methods, binding affinities and biological activities.

Ranibizumab

Ranibizumab (Lucentis; Genentech USA Inc., San Francisco, Calif., USA/Novartis Ophthalmics, Basel, Switzerland) is an engineered, humanized, recombinant antibody fragment (Fab, or antigen-binding fragment) active against all VEGF-A isoforms [30]. A beneficial effect of IVR in DME has been shown by several RCTs. Two phase II studies (RESOLVE and READ-2) and two phase III studies (RESTORE and DRCR.net protocol I) compared the effect of ranibizumab with sham (RESOLVE and RESTORE) or with laser photocoagulation and triamcinolone (READ-2 and DRCR.net protocol I).

The RESOLVE (n = 151) study investigated IVR as monotherapy for DME, comparing patients receiving either 0.3 or 0.5 mg IVR with those receiving sham treatment only [31]. At month 12, data showed a mean BCVA gain of 10.3 letters in the IVR group compared with a loss of 1.4 letters in the sham treatment group. Only 4.9% of the patients receiving IVR required rescue laser compared with 34.7% of those receiving sham treatment. No differences were found in the rates of ocular and nonocular adverse events or serious adverse events between the two treatment groups.

The READ-2 study showed better visual acuity in eyes treated with IVR versus eyes treated with photocoagulation [32]. In this study 126 patients were randomized into 3 arms: in the first group, IVR (0.5 mg) was administered at baseline and months 1, 3 and 5; in the second group, laser was performed at baseline and month 3 if needed, and the third group was treated with a combination of IVR (0.5 mg) and macular laser at baseline and month 3. At month 6, the mean improvement in BCVA was significantly greater in the IVR group compared with the laser group with no statistical difference between the monotherapy IVR 0.5 mg and the combination group. The 2-year follow-up results further demonstrated that ranibizumab pro re nata was effective in maintaining the gained BCVA, showing mean BCVA improvements of 7.7 letters (IVR-only group), 5.1 letters (laser group) and 6.8 letters (combination therapy group) in the 101 patients who remained in the study [33]. Afterwards, only the patients who agreed to continue the study (in the ranibizumab group, 28 patients; in laser, 22; in ranibizumab + laser, 24) returned monthly and received ranibizumab pro re nata. At month 36 BCVA improvement in the ranibizumab group was 10.3 letters compared with 7.2 letters at month 24 whereas no statistically significant improvement was found for the laser and laser + ranibizumab groups.

However, edema resolution occurred more in the laser and ranibizumab + laser groups [34].

The RESTORE study included 345 patients with focal or diffuse DME receiving IVR monotherapy, laser monotherapy or IVR combined with laser. At 1 year, the study showed a larger mean BCVA improvement in patients treated with IVR monotherapy or IVR combined with laser than in patients treated with laser alone. No differences were detected between the IVR monotherapy and IVR + laser arms [35]. In the 2-year extension of the study ranibizumab was given pro re nata, and visual gain was maintained with fewer ranibizumab injections in the IVR group [36].

The DRCR.net protocol I (n = 691) assessed whether IVR, combined with either prompt (within 10 days) or deferred (no sooner than 6 months) laser, or IVTA combined with prompt laser, might result in improved visual acuity outcomes in comparison with the gold standard of focal/grid photocoagulation for DME involving the central macula [9]. The results at 1 and 2 years led to similar conclusions showing that IVR 0.5 mg in combination with prompt or deferred laser improved visual acuity more than laser photocoagulation alone (and than IVTA combined with laser) [9, 10].

Recently, in 2 parallel, phase III RCTs, RISE (n = 377) and RIDE (n = 382) [37], IVR has been evaluated in the treatment of DME compared with placebo again. These trials followed identical protocols, through 2 parallel, phase III, multicenter studies, comparing monthly injections of 0.3 mg IVR or 0.5 mg IVR with sham injection for 24 months. At 24 months, in the RISE group, 44.8% of 0.3-mg patients and 39.2% of 0.5-mg IVR patients gained ≥15 letters, compared to 18.1% of sham patients, while in the RIDE group, 33.6% of 0.3-mg patients and 45.7% of 0.5-mg IVR patients gained ≥15 letters, compared to 12.3% of sham patients. In the third year, the study design allowed for patients in the sham group to cross over and receive monthly ranibizumab injections. The 36-month outcomes were recently published and confirmed the long-term efficacy and safety of ranibizumab in DME. However, delayed treatment in patients receiving sham treatment initially did not seem to result in the same functional gain observed in patients originally randomized to ranibizumab [38].

Data from an exploratory analysis of the DRCR.net trial evaluating the effect on worsening of diabetic retinopathy of IVR and IVTA in comparison with sham + prompt laser have recently been published [39]. The results showed that IVR is associated with a reduced risk of diabetic retinopathy worsening in eyes with or without proliferative diabetic retinopathy. More specifically, for eyes without proliferative diabetic retinopathy at baseline, the 3-year cumulative probabilities for retinopathy worsening were 23% using sham with prompt laser, 18% with IVR with prompt laser, 7% with IVR with deferred laser and 37% with IVT with prompt laser. For eyes with proliferative diabetic retinopathy at baseline, the 3-year cumulative probabilities for retinopathy worsening were 40, 21, 18 and 12%, respectively.

Recently, a review of an expert panel [40] established new approaches and recommendations for the treatment of DME with ranibizumab. DME with or without visual impairment should be considered for treatment when the ETDRS criteria for clinically significant macular edema [3, 41] are respected. For DME with center involvement and vision loss due to DME, monthly ranibizumab monotherapy is recommended with treatment interruption and re-initiation based on visual acuity stability. For other types of clinically significant DME with no vision loss or without center involvement, laser treatment based on ETDRS guidelines is recommended.

Bevacizumab

Bevacizumab (Avastin; Genentech Inc., San Francisco, Calif., USA) is a full-length recombinant humanized antibody active against all isoforms of VEGF-A.

The use of intravitreal bevacizumab (IVB) to treat DME was first considered by the DRCR.net in a large phase II RCT [42]. A higher improvement in BCVA which was sustained up to 12 weeks was found in the IVB monotherapy group compared to the group who was treated with focal laser photocoagulation at baseline. A longer-term follow-up was reported by Arevalo et al. and the PACORES group [43], showing the visual acuity gain was preserved for up to 24 months. Later, Lam et al. [44] evaluated the efficacy of 2 doses of IVB (1.25 and 2.5 mg) in a small trial with a 6-month follow-up. The results showed that the 2 doses of IVB were similarly effective in improving BCVA. In the same year in a retrospective case series, Kook et al. [45] reported that a successful treatment with repeated IVB injections could be achieved over a 24-month follow-up period even in cases of chronic ischemic DME.

In an RCT, Soheilian et al. [46, 47] compared combined IVB (1.25 mg) + IVTA (2 mg) with IVB alone and laser alone in 97 patients who were laser naïve. At 36 weeks, IVB alone improved BCVA more than either combination therapy or laser, although the difference was not

statistically significant. An extended follow-up at 24 months showed that there was no statistically significant difference between groups for BCVA. However, there was a trend in favor of the bevacizumab and combination arms more than in the laser one [48]. Moreover IVB alone turned out to be superior to IVB + IVTA and macular laser photocoagulation only in eyes with an initial central macular thickness of ≥350 μm, indicating that in the primary treatment of DME the initial central macular thickness may be an important factor in decision making.

Recently, the results of a prospective RCT (BOLT study), comparing IVB versus laser in persistent DME in 80 patients, were published [49]. The 2-year results showed that the mean gain in ETDRS letters was 9 and 2.5 letters in the IVB and laser groups, respectively; an improvement of 10 or more letters was seen in the 45 and 7% of the two arms, respectively [50]. A post hoc analysis of the BOLT study aimed to explore the parameters that influence the injection frequency in the patients randomized in the IVB arm [51]. Results showed that the only determinant of fewer injections in the second year was a better baseline visual acuity. Moreover eyes with subretinal detachment required more injections than diffuse and cystoid edema.

However, there is a diffuse concern among clinicians about an increase in major cardiovascular events using bevacizumab. As underlined by a recent meta-analysis by Goyal et al. [52], few data are available to rule out this possibility. Therefore we suggest to avoid bevacizumab in high-risk patients.

Pegaptanib

Pegaptanib sodium (Macugen, Eyetech Inc., Cedar Knolls, N.J., USA) is a ribonucleic acid aptamer that binds specifically to the VEGF-A165 isomer, the major pathological VEGF protein in the eye.

The Macugen Diabetic Retinopathy Study was a phase II RCT studying 3 doses of intravitreal pegaptanib versus sham injection [53]. At the final visit at week 36, the group of patients receiving pegaptanib 0.3 mg had significantly superior results compared to the sham injection group, as measured by BCVA and central retinal thickness. Furthermore, fewer patients receiving pegaptanib required retinal photocoagulation. Higher doses of pegaptanib (1 or 3 mg) did not show a significant improvement.

The Macugen Study [54] was a phase II/III RCT that compared pegaptanib with sham in 260 patients for 1 year and 207 patients for 2 years of follow-up. The authors stated an improvement of visual acuity ≥10 ETDRS letters in week 54 in 36.8% of subjects in the pegaptanib sodium group and in 19.7% of the sham group compared with baseline values. A better visual acuity in the pegaptanib group was also reported at the end of the 2-year follow-up period. Moreover, fewer pegaptanib-treated subjects received laser treatment compared to sham-treated subjects.

Aflibercept

Aflibercept (VEGF Trap-Eye, Eylea, Regeneron/Bayer) is a soluble decoy receptor produced by fusing protein of portions of VEGF receptor 1 and 2 and the Fc region of human IgG. It binds all VEGF-A isoforms with higher affinity in comparison to all the other anti-VEGF substances. Moreover it has a longer half-life in the eye after intraocular injection and binds other members of the VEGF family as well, including placental growth factors 1 and 2 that have been shown to determine excessive vascular permeability. Thanks to these features, aflibercept achieved the same results as ranibizumab in neovascular age-related macular degeneration treatment, having also a longer duration of action [55]. The Da Vinci Study (n = 221) is a randomized, double-masked, phase II clinical trial designed to compare the different doses and dosing regimens of the drug in DME [56, 57]. Subjects were randomized to 1 of 5 arms: VEGF Trap-Eye 0.5 mg every 4 weeks; 2 mg every 4 weeks; 2 mg every 8 weeks after 3 initial monthly doses, or 2-mg dosing as needed after 3 initial monthly doses, or macular laser photocoagulation. A significant improvement in BCVA was achieved at week 24 and was maintained or enhanced at week 52 in all aflibercept arms. Recently aflibercept was approved by the European Union for neovascular age-related macular degeneration and central retinal vein occlusion treatment and by the Food and Drug Administration for extension to DME patients.

Combined Therapy

The combination of pharmacological therapy with focal laser photocoagulation has the potential to improve the efficacy of treatment for DME, reducing the burden of frequent intravitreal injections.

The RESTORE study showed a larger mean BCVA improvement in patients treated with a combination of IVR and laser than in patients treated with laser alone [35].

Conversely, in the READ 2 study there was no statistical difference for the combination group. However, the combination treatment with IVR + laser provided an improvement in BCVA and a greater decrease in macular edema, with a reduced number of intravitreal injections [33].

DRCR.net protocol I extended the follow-up only for eyes originally assigned to ranibizumab + prompt or deferred laser treatment [58]. Three-year follow-up results suggested that adding prompt laser treatment to IVR is no better and possibly worse for visual outcome than deferring laser for at least 24 weeks. The authors stated that some of the observed differences in visual acuity may be related to the lower number of injections during the follow-up in the prompt laser treatment group.

Also intravitreal steroids can play an important role as a part of combination treatment [59]. In a 2-year study recently reported by Gillies et al. [60], eyes with DME treated with IVTA + laser were twice as likely as eyes treated with laser alone to achieve at least a 10-letter improvement in BCVA from baseline at year 2. A recent study conducted by Lim et al. [61] compared bevacizumab alone, bevacizumab combined with triamcinolone and triamcinolone alone. After 12 months of follow-up, BCVA was comparable between the 3 study groups. Recently, the Ozurdex PLACID Study Group [62] evaluated a DEX intravitreal implant 0.7 mg combined with laser photocoagulation compared with laser alone for the treatment of diffuse DME. Up to month 9 significantly greater improvement in BCVA occurred in patients treated with the DEX implant + laser than in patients treated with laser alone. However, at month 12 there was no significant difference between groups.

Other Drugs

PF-04523655 is a short interfering RNA targeting the expression of a gene involved in increasing vascular permeability. RTP-801 gene showed a dose-related tendency for improvement in BCVA in DME patients [63].

Bevasiranib is a small interfering RNA molecule able to inactivate messenger RNA and to suppress RNA translation. It is designed to reduce the levels and activity of VEGF messenger RNA. In a phase II RCT, 48 eyes were treated with 3 monthly injections and followed for 1 additional month. There was no statistically significant change in macular thickness (the primary end point) or mean visual acuity at the 4-month time point [64].

Sirolimus, or rapamycin, is a macrocyclic antibiotic (produced by *Streptomyces hygroscopicus*) that binds specifically FKBP12; the active complex inhibits the mammalian target of rapamycin, a kinase which integrates growth factor-activated signals including signals that promote angiogenesis mediated by VEGF. Besides, mammalian target of rapamycin is an activator of VEGF gene transcription via the hypoxia-inducible factor 1a. Phase I/II study data showed the safety of subconjunctival and intravitreal injections of sirolimus in patients with DME [65, 66].

Conclusions

With the advent of intravitreal drugs, a new era was opened for the pharmacological approach to DME. Even though laser treatment is still applied, the use of intravitreal drugs is supported by encouraging results regarding improvement in visual acuity, and it can limit the potentially destructive effects of the laser treatment. However, the best frequency and dosing regimen of intravitreal drugs are not yet clearly defined. Moreover a longer follow-up is required to investigate the long-term results and the safety profile. To date, downsides of intravitreal injections appear to be: the relatively short half-life, and the need for repeated injections to obtain and maintain the desired therapeutic effects, producing an increased risk of injection-related complications, even though those risks are small. In light of this the combination therapy is a promising option to be better investigated. However, the best therapeutic approach to DME should be specifically defined on the basis of disease characteristics in the individual patient. Lastly, an important goal will be an improvement in the understanding of DME pathogenesis in order to study new selective molecules.

Disclosure Statement

The authors have no proprietary interest in the materials used in this study.

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