Expert Opinion

Upcoming therapeutic advances in diabetic macular edema: an intravitreal dexamethasone drug delivery system

Albert J Augustin
Staedtisches Klinikum Karlsruhe, Department of Ophthalmology, Moltkestraße 90, Karlsruhe, Germany

Introduction: Diabetes mellitus, through its ophthalmic complications diabetic retinopathy and diabetic macular edema (DME), is a leading cause of vision loss in industrialized countries.
Areas covered: This review covers laser treatment, which is a standard treatment strategy that has proven efficacy and safety through large clinical trials in DME. Several intravitreal drug applications currently being investigated are also discussed.
Expert opinion: First results suggest that the administration of anti-VEGF compounds is effective for DME. However, frequent injections may compromise safety. In order to enhance patient compliance, sustained delivery systems are being evaluated as potential treatment approaches. So far, only steroids have been included as active in such non-biodegradable or biodegradable delivery systems. Non-biodegradable systems are more complicated to administer as surgery is required and they need to be retrieved at the end of treatment. Also, in some cases safety issues have arisen, especially around intraocular pressure control. A new biodegradable dexamethasone delivery system seems to show promising efficacy results in addition to a more favorable safety profile, which will potentially improve patient compliance. All new therapeutic approaches, alone and in combination, will need to demonstrate their efficacy and safety in DME in future trials.

Keywords: anti-VEGF compounds, biodegradable, corticosteroids, dexamethasone, diabetic macular edema, diabetic retinopathy, intraocular drug delivery, intravitreal, macular edema, non-biodegradable, pathophysiology of DME, persistent macular edema, sustained drug-delivery systems, triamcinolone

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1. Introduction

Macular edema (ME) is defined as an abnormal thickening of the macula associated with the accumulation of excess fluid in the extracellular space of the neurosensory retina. Intracellular edema involving Mueller cells has also been observed histopathologically in some cases. In terms of manifestations, it can be differentiated between an ischemic and non-ischemic as well as focal and diffuse ME [1]. The term 'cystoid macular edema' applies when there is evidence by biomicroscopy, fluorescein angiography and/or optical coherence tomography of fluid accumulation into multiple, radially oriented, cyst-like spaces within the macula [2].

Several basic pathophysiologic processes may contribute to the development of ME, which occurs in association with a wide variety of pathologic conditions. ME presents the final common pathway in many prevalent retinal disorders and

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Article highlights.

- Diabetic macular edema (DME) is a complex multifactorial disease increasing with duration of diabetes and severity of diabetic retinopathy.
- DME is characterized by a breakdown of the blood–retinal barrier, leading to fluid accumulation in the extra- and intracellular space and causing a loss of visual acuity. Several inflammatory mediators such as Angiotensin II, VEGF and prostaglandins play a major role in the local inflammatory process.
- While in the past laser photocoagulation has been the only treatment approach backed by sufficient clinical data, research has recently been focused on intravitreal administration of drugs.
- Injections of corticosteroids and anti-VEGF compounds have shown initial positive results, but frequent injections create a burden on the patient.
- To reduce the number of injections, several sustained release delivery systems are being investigated.
- Non-biodegradable systems are accompanied by surgical interventions for insertion and removal. Also, adverse events such as raised intraocular pressure and cataract formation have been issues.
- One biodegradable option to date is dexamethasone drug delivery system, which has shown initial promising efficacy results and an acceptable safety profile.
- Final results for all treatment approaches, alone or in combination, are yet to be presented.

This box summarizes key points contained in the article.

can be considered the leading cause of central vision loss in the developed world. It is thus of markedly medical and socioeconomic importance.

As the pathogenesis of ME depends on the underlying etiology and because it may be multifactorial, an effective management is based on recognizing and addressing each factor that is expressed in a given clinical setting. The treatment of ME has evolved dramatically over the past 2 decades. Research has led to a better understanding of its causes, but also to the development of new therapeutic options [3].

Just recently, an intravitreal Dexamethasone Drug Delivery System (DDS) has obtained EU approval for treatment of vision loss due to ME associated with retinal vein occlusion (RVO) (Ozurdex®, Allergan) (**Box 1**) [4]. RVOs have been defined as retinal vascular disorders characterized by engorgement and dilation of the retinal veins with secondary intraretinal hemorrhages, intraretinal and subretinal edema, and retinal ischemia including cotton wool spots, exudates and ME [5]. As soon as the foveal region is impacted by ME, central visual acuity (VA) drops, leading to a progressive painless loss of vision [6].

Additionally, the dexamethasone DDS has also just received FDA approval for the treatment of non-infectious ocular inflammation, or uveitis, affecting the posterior segment of the eye [7].

To our knowledge, no product has received market approval for treatment of diabetic macular edema (DME) so far.

2. Pathologic conditions and pathophysiology in DME

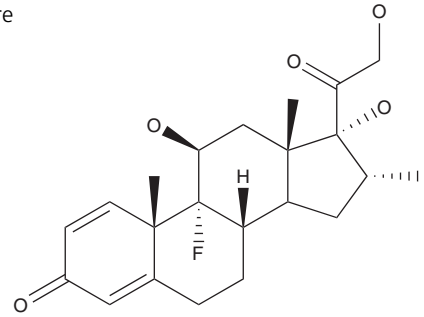
Diabetes mellitus, through its ophthalmologic complications, principally diabetic retinopathy (DR), is a leading cause of vision loss and blindness in industrialized nations. Despite the fact that significant advances are being made in early diagnosis and treatment of patients, numbers of patients likely to develop vision loss or blindness due to DR are expected to rise parallel to the incidence of diabetes. Underlying causes are the changing dietary habits leading to obesity as well as an overall increasing in ageing population. Estimates have projected that by 2050, there will be in excess of 50 million diabetics in the US, 50% of whom are projected to develop DR [8,9].

In contrast to other underlying causes resulting in formation of ME, such as RVO, the pathogenesis of DME is much more complex and multifactorial. DME can develop at any stage of DR, but it occurs more frequently as the duration of diabetes and the severity of DR increase [10].

DME can be divided into a focal and diffuse form. Focal ME refers to localized areas of retinal thickening triggered by vascular abnormalities accompanied by fluid leakage and hard exudates. Diffuse ME is caused by a general diffuse leakage from dilated retinal capillaries throughout the posterior pole of the retina; it is commonly observed in both eyes. While there is also a classification of ischemic and exudative ME, hybrid types can be observed in most cases. Hyperglycemia – the distinguishing feature of diabetes mellitus – leads to serious cellular damage. Endothelial cells are extremely vulnerable to high glucose levels, which can seriously damage such cells and lead to DR. DR is characterized by abnormal vascular flow, hyperpermeability and leakage as well as non-perfusion of capillaries resulting in damage to retinal vasculature. Early stages of vasculature dysfunction are characterized by a breakdown of the blood–retinal barrier (BRB), leading to accumulation of fluid and serum macromolecules in the intercellular space and in turn to loss of VA [11].

Inflammatory components within the vascular tissue also play a central role in the development of ME. Several inflammatory mediators such as Angiotensin II, VEGF, prostaglandins, cytokines, ILs, VCAM-1 and ICAM-1 as well as macrophages and neutrophils are part of the local inflammatory process. To date, the complex chain of interaction of all these substances is not fully clarified [12,13]. Spontaneous resolution of DME is rare and usually secondary to improvement in systemic risk factors such as glycemic control, hypertension or hypercholesterolemia. If left untreated, 29% of eyes with DME and foveal involvement experience moderate visual loss (doubling of visual angle) after 3 years. Spontaneous visual recovery is also unusual, with only 5% of cases experiencing an improvement of 3 EDTRS (Early Diabetic Retinopathy Study) lines. The diagnosis of DME is clinical. The term 'clinically significant macular edema' characterizes the severity of the disease and provides a threshold to apply laser photocoagulation according to EDTRS [14].

Box 1. Drug summary.

Drug name	Dexamethasone
Phase	III
Indication	Diabetic macular edema
Pharmacology description	Glucocorticoid agonist Corticosteroid agonist
Route of administration	intravitreal
Chemical structure	
Pivotal trial(s)	Phase 3 RCTs currently ongoing

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3. Current treatments for DME

3.1 Traditional treatment approaches

Based on the observations made in a number of large clinical trials, such as EDTRS, laser photocoagulation has been considered a standard treatment method for patients with DME in the last decades [15]. EDTRS treatment including both focal and grid methods was judged to be somewhat superior to modified grid photocoagulation alone in improving vision and reducing macular thickness [16]. Eyes with diffuse or refractory DME are, however, much less responsive to laser treatment [14].

When attempting to treat DME by conventional topical administration of drugs, effective concentrations near the macula could not be achieved, as uptake and penetration were limited. Systemic administration has also shown to provide a limited ocular penetration accompanied by systemic toxicity. This is why intravitreal applications have been chosen to achieve targeted delivery, with the down side of being invasive, inconvenient and short lasting [17].

3.2 Intravitreal administration of anti-VEGF compounds

VEGF inhibitors include compounds such as ranibizumab (Lucentis®, Novartis), pegaptanib sodium (Macugen®, OSI Eyetech) and VEGF trap (VEGF Trap-Eye®, Regeneron). They are meant to target the leakage and perhaps neovascularization associated with DME [18].

Ranibizumab has so far been investigated in DME patients in a Phase I–II open-label evaluation (READ study) as well as a Phase II trial (RESOLVE): at the end of the 12 month study period, the pooled ranibizumab group gained 10.2 letters compared to the sham group that lost a mean of 1 letter ($p < 0.001$) [19]. Several Phase III studies in DME are currently ongoing such as RESTORE [20], RISE [21], RIDE [22] as well as the DRCR net Phase III trial (intravitreal ranibizumab or triamcinolone in combination with laser photocoagulation) [23].

Multiple trials are also ongoing looking at efficacy and safety of bevacizumab compared to steroids or laser or respective combinations with bevacizumab in DME [24].

A recent study has shown that intravitreal injection with bevacizumab significantly decreased intraocular VEGF expression, but in order to prolong this reduction, monthly re-treatments had to be performed [25-27].

Pegaptanib sodium is also being investigated for the indication of DME in a Phase III study in 260 patients. After 54 weeks, 37% of patients in the active group gained at least 2 lines in best corrected visual acuity (BCVA) compared to 20% in the sham group [28].

Large multi-center Phase II studies have evaluated the efficacy and safety of VEGF trap (a soluble VEGF receptor fusion protein that bind to all isoforms of VEGF-A) in naive DME patients. The 24 week results showed a BCVA increase of 8 letters in patients having received the 0.5 mg dose and an increase of 11 letters after administration of the 2 mg dose [29].

3.3 Intravitreal steroid administration

For a number of years, the use of intravitreally applied corticosteroids has been investigated, initially in uncontrolled pilot trials and case studies. Recently, a variety of prospective randomized clinical trials as well as data analyses have shown a useful role of such compounds in the treatment of DME [30-33]. Use in patients refractory to laser treatment [10] as well as in aphakic patients [34] has shown favorable results. The mechanism of action is thought to be complex: there are a variety of effects such as lyosomal stabilization, inhibition of ICAM and TNF pathways and anti-VEGF effects [35-37]. Corticosteroids have been shown to stabilize the BRB. The main hypotheses include the following effects: anti-inflammatory and immunosuppressive activities [38], protection against apoptotic signals evoked by, for example, cytokines and cAMP [39], antiedematous [40] and antiangiogenic properties [41-43].

A number of biodegradable and non-biodegradable delivery systems (DDSs) have been developed to achieve sustained levels of steroids in the vitreous. These new developments target a variety of retinal diseases, amongst them DME. Such DDSs are meant to maximize efficacy in chronic diseases requiring frequent and repeated administration to the back of the eye over longer time periods [44]. Additionally, they are striving to improve safety by reducing the risk of complications due to the actual injection, such as injury to the lens, retinal detachment and – most significantly – endophthalmitis [45].

3.3.1 Non-biodegradable DDSs

Retisert® (Bausch & Lomb) and Iluvien® (Alimera Sciences) contain fluocinolone acetonide and I-vation™ (SurModics) contains triamcinolone acetonide in non-biodegradable reservoirs. Such implants, however, may need to be surgically removed once the drug release is complete because non-biodegradable devices are not metabolized *in vivo*. In addition, there is an increased risk for such adverse events as retinal detachment, vitreous hemorrhage and endophthalmitis while anchoring, retrieving and re-implanting non-biodegradable devices [46-48]. Some designs also require large incision for implantation which can only be closed through suturing [23].

For Alimera's fluocinolone acetonide delivery system [49], two multi-center studies known as the FAME study included about 1000 patients receiving 0.23 or 0.45 µg dose a day or sham over periods of 24 and 36 months, respectively. Preliminary results of the low dose application (similar to the high dose) were positive, with 26% of patients experiencing a VA improvement of 15 letters or more at 24 months ($p = 0.002$, VA mean change values not available) [50]. However, intraocular pressure (IOP) elevation seemed to be a major concern: over the 24 months period, 2.1% of patients receiving the low dose and 5.1% of patients receiving the high dose had undergone a filtration procedure to reduce their eye pressure [51]. The product has been submitted to the FDA for the indication of DME and is awaiting approval.

Bausch & Lomb's fluocinolone acetonide delivery system has also recently undergone Phase III trials for DME [52]. After 3 years, the implant demonstrated a 3 line gain in 27.6% of eyes, compared to only 14.5% of eyes receiving standard care ($p < 0.05$, VA mean change values not available). Concerns about steroid side effects have led to only a limited approval in the indication of uveitis [53].

Sur Modics' triamcinolone micro-implant has only just completed Phase I trials in long-term treatment of DME [18]. A Phase II study was terminated and so the current development status of this DDS is unclear [54].

3.3.2 Biodegradable DDSs: dexamethasone DDS

Dexamethasone DDS is a biodegradable sustained release system approved for an ME indication. Dexamethasone DDS is indicated for the treatment of ME following RVO and is inserted into the vitreous cavity by an applicator (**Figure 1A, B**) [34,55].

In sharp contrast to the short half-life of directly injected dexamethasone, dexamethasone DDS has been observed to release drug in bio-relevant amounts for 6 months after implantation [56]. Inside the eye, the polylactic-co-glycolic acid copolymer is slowly hydrolyzed to lactic and glycolic acids. A single use applicator is used to insert the drug pellet (6.5 mm × 0.45 m) into the vitreous through a 22-gauge pars plana injection. The procedure does not require sutures for wound closure. Sequential implants can be placed without the need for surgical removal [23,57,58].

Two concentrations of dexamethasone were evaluated in a 6-month, Phase II, multi-center, randomized clinical trial. Rather than using the delivery system and the long extruded form described above, a tableted version was placed into the vitreous via surgery. Of the 315 patients treated (baseline VA 20/40 to 20/200), 171 suffered from DME. Eyes were randomized to either observation, a 350 or 700 µg dose [59].

In the analysis of the DME subset, the percentage of patients gaining 2 lines or more of VA 90 days after implantation were 33.3% in the group having received the 700 µg dose ($p = 0.007$ vs observation), 21.1% in the group having received 350 µg and 12.3% in the observation group ($p = 0.4$, mean change values not available). While the percentage of patients gaining 3 lines or more after 60 days was statistically significant in the 700 µg ($p = 0.01$ vs observation) and the 350 µg ($p = 0.04$ vs observation) group, a trend toward statistical significance was only found in the higher dose at day 90 ($p = 0.05$). Central retinal thickness (CRT) and fluorescein leakage also improved significantly in eyes receiving the 700 µg dose compared to observation ($p = 0.03$; day 90). Most ocular adverse events were mild to moderate. There was no significant difference in the number of reports of cataract (as an adverse event) among the study groups.

During 6 months of observation, 15% percent of patients who had received the actives had an IOP increase of 10 mmHg or more from baseline, compared with 2% among patients from the observation group. Most patients had only a single occurrence of IOP increase of this magnitude or greater. All cases were successfully managed by just observing or with topical IOP lowering medications. The authors concluded that in eyes with persistent ME due to DR, treatment with the 700 µg concentration of the intravitreal dexamethasone DDS is well tolerated and significantly (statistical significance $p < 0.05$ at day 90) improves BCVA, central retinal thickness and fluorescein leakage compared to observation [60].

Further analysis demonstrated that a similar degree of efficacy was maintained across patients with DME regardless of the pattern of ME, such as focal, cystoids, diffuse or cystoids/diffuse [61].

The safety of the dexamethasone DDS was also compared to the incisional placement used in Phase II studies. The authors concluded the dexamethasone DDS had performed well, allowing safe, effective and sutureless intravitreal placement of 700 µg dexamethasone DDS [62].

The CHAMPLAIN study, a prospective, multi-center, Phase II trial, looked at efficacy and safety of 700 µg dexamethasone DDS in DME patients with vitrectomized eyes over 26 weeks (NCT 00799227) [63]. Preliminary results were presented at the Annual Macula Society Meeting on 24 February 2010. The study was based on the concept of altered

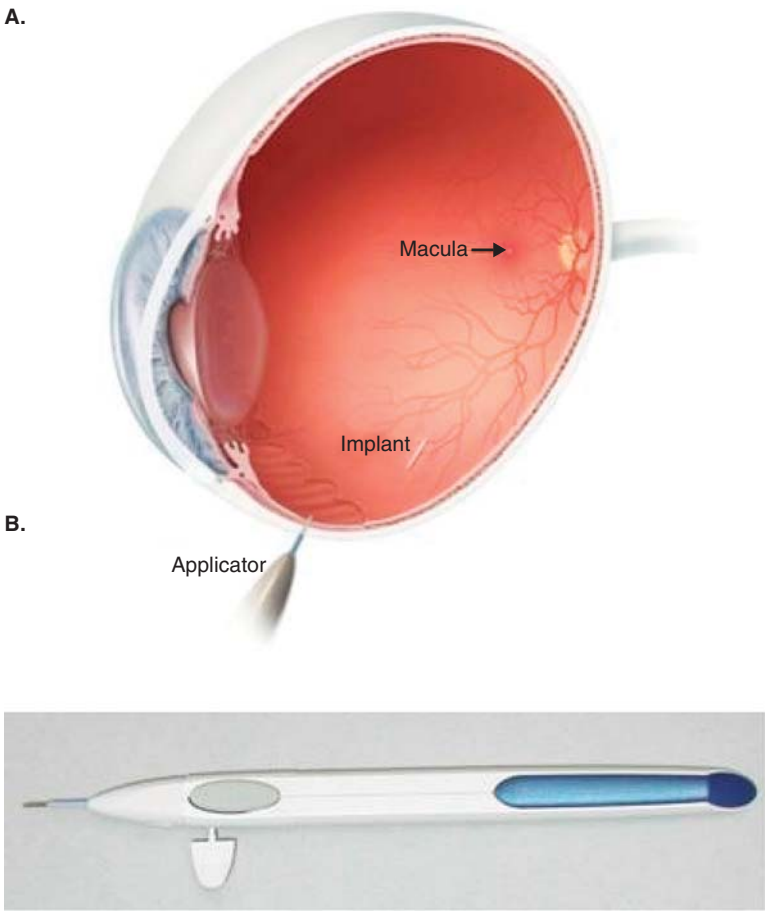

Figure 1. A) Dexamethasone implant with approximate ocular location after implantation. **B)** Dexamethasone posterior segment drug delivery system applicator.

pharmacokinetics in the vitrectomized eye, including more rapid clearance from the vitreous cavity [64-66]. Furthermore, a reduced half-life limits the potential clinical benefits of drug delivery to the retina [67]. By 8 weeks following injection of the dexamethasone DDS implant, 30.4% of patients gained at least 2 lines of VA. By 26 weeks, 21.4% had gained at least 10 letters and 42.9% of patients had gained at least 5 letters. CRT was decreased by 27% at week 13 and 9.6% at week 26 (mean change values not available). Increased IOP was not a significant problem. These findings demonstrate that sustained-release delivery of dexamethasone may be particularly beneficial in vitrectomized eyes [53].

Currently, further large international, randomized clinical studies are ongoing to determine safety and efficacy of the dexamethasone intravitreous DDS in patients with DME. A controlled, double-masked study is determining efficacy and safety of 350 and 700 µg dexamethasone DDS against sham control in about 860 patients over 3 years. Injections are taking place every 6 months. The trial is due to be completed in 2014 (NCT00168389) [68]. A second trial of the exact same set up is performed in a different set of countries worldwide (NCT00168337). Again data are scheduled to become available in 2014 [69].

Furthermore, an additional study is evaluating the efficacy of the intravitreal implant in combination with laser treatment versus laser treatment alone [70].

4. Conclusion

Management of DME is complex and often multiple treatment approaches are needed. In many instances, large programs to better control diabetes mellitus have been put in place.

Additionally, major progress is currently being made in the use of sustained release steroid implant devices for DME. Preference should be given to such devices that are biodegradable.

Novel delivery approaches using sustained release approaches are likely to provide much needed benefit for patients afflicted with conditions resistant to more conservative therapy, though long-term data on ocular tissue response to continuous drug exposure is so far not known. When considering a new therapeutic approach in the treatment of

Table 1. Relative potency of corticosteroids.

Corticosteroid	Relative potency*
Cortisol	1
Cortisone	0.8
Triamcinolone	5
Betamethasone	25 – 40
Dexamethasone	30

*Potency relative to cortisol [81].

complicated vitreoretinal disorders such as DME, innovators should consider a biodegradable delivery system as part of their treatment strategy, as it will provide constant drug delivery and does not need to be retrieved.

Compared to non-sustained intravitreal injections, there could also be an economic benefit by reduction of repeated injections; compared to non-biodegradable sustained delivery systems, there will be less follow-up clinical interventions (e.g., to remove the empty device).

Their efficacy over a long-term period as well as their potential role in combination with other treatments needs to be shown in future trials.

Future generation devices should allow even longer release durations and increased target specificity to prolong their action, minimize side effects and achieve patient compliance. Among those are biodegradable formulations, liposomes or micro- and nano-particles not yet available for treatment [71].

5. Expert opinion

Control of systemic risk factors influences the course of ME secondary to DR. Several studies have clearly demonstrated that persistent hyperglycemia is strongly associated with the incidence and progression of ME [72,73]. Especially, lower levels of glycosylated hemoglobin have turned out to be associated with a lower incidence of ME, independent of the duration of diabetes mellitus [74]. Furthermore, systolic blood pressure [75], prevalence of diabetic nephropathy [76], smoking [77] as well as hyperlipidemia [78] were found to be associated with ME.

While focal or grid laser photocoagulation has consistently shown efficacy in clinical trials, treatment is not without potential complications and new treatments are necessary for those who are either unresponsive to it or show less than ideal response. To fulfill this unmet need, several pharmaceutical therapies are currently under development for DME. The majority are intravitreally injected anti-inflammatory or anti-angiogenic agents [50].

The overall results of anti-VEGF drugs currently under review for efficacy and safety in DME seem to promising. An obvious drawback is the frequency of having to inject which puts a great burden on patients suffering from this chronic disease.

Intravitreally applied corticosteroids at low dose have been observed to exert no relevant retinal toxicity [79].

For quite a number of years, triamcinolone acetonide has been used in ophthalmic practice as off-label injectable suspensions of between 4 and 20 mg. However, it does not achieve significant systemic serum levels when injected intravitreally [80]. Differences in particle size may contribute to variability in clearance times and durations of action following intravitreal injections [81]. Results of such preparations for the treatment of ME are far from ideal.

As described above non-biodegradable delivery systems releasing corticosteroids are also under clinical investigation for DME. However, the need to perform initial surgery rather than to do a simple injection as well as the need to remove the empty device could be considered a hurdle to usage. Also, concerns about side effects remain.

Although the biodegradable dexamethasone DDS is so far not yet approved for treatment of DME, it has shown most positive characteristics. Compared to other steroid systems, it is easier to apply and does not need to be removed. Compared to anti-VEGF injections it needs to be administered less often, which should lead to a better patient compliance and less injection-related risks and adverse events.

The relative potencies of corticosteroids are listed in **Table 1** [82].

Dexamethasone has the highest relative strength of any other corticosteroid used in ophthalmic practice [83,84]. A single dose of 0.18 mg/ml dexamethasone is equivalent to 1 mg/ml triamcinolone in terms of corticosteroid efficacy; however, it is short acting, with faster clearance from the vitreous [85,86].

Furthermore, the use of intravitreal drug delivery in combination with mechanical approaches such as laser therapy show promise for improving visual outcomes and decreasing the need for re-treatment [87].

Use of triple therapy has also been investigated, so far mostly for the treatment of AMD. Findings again suggest that using complimentary mechanisms of action allow a reduced number of intravitreal injections whilst maintaining or improving VA [88,89]. Similar findings for the treatment of DME are yet to be demonstrated.

Declaration of interest

AJ Augustin has received clinical trials support/speakers honoria from Allergan.

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Affiliation

Albert J Augustin MD
Staedtisches Klinikum Karlsruhe,
Department of Ophthalmology,
Moltkestraße 90,
76133 Karlsruhe, Germany
Tel: +0721 9742001; Fax: +0721 9742009;
E-mail: albertjaugustin@googlemail.com