

Treatment of diabetic macular edema

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Diabetic macular edema (DME) is the leading cause of visual impairment in diabetic patients (1). The only treatment of DME, besides controlling systemic factors, has long been laser photocoagulation. In 2012, ranibizumab (Lucentis®, Novartis, Basel, Switzerland) has been approved for the treatment of DME associated with a significant visual loss, and has, since then, become the first-line treatment in this indication. In 2013 and 2015, three other treatments have been approved for the treatment of DME: fluocinolone acetonide intravitreal implant (Iluvien®, Alimera Sciences Inc, Alpharetta, GA, USA), aflibercept (Eylea®, Bayer, Leverkusen, Germany), and dexamethasone intravitreal implant (Ozurdex®, Allergan Inc, Irvine, California). The purpose of these recommendations is to propose a treatment scheme for DME, applicable when these medicinal products will be reimbursed.

THERAPEUTIC ARSENAL

The therapeutic arsenal of DME includes, in 2015, the control of systemic factors, laser photocoagulation, intravitreal (IVT) injections of anti-Vascular Endothelial Growth Factors (VEGFs) and corticosteroids, and vitrectomy.

1/ Control of systemic factors

The major risk factors for DME are the diabetes duration, quality of the blood glucose control and high blood pressure (2). The central role of blood glucose and blood pressure control has been confirmed in the 1990s by large interventional studies such as the *Diabetes Control and Complications Trial* (DCCT) in the United States and the *United Kingdom Prospective Diabetes Study* (UKPDS) that have shown that controlling these factors could reduce the incidence of DME (3-5). Other factors likely play a more modest role, including dyslipidemia (in particular increased plasma cholesterol levels), kidney disease, anemia, sleep apnea, glitazones and pregnancy (2). Assessing and controlling these factors is essential in the treatment of DME.

2/ Laser photocoagulation

For many years, laser therapy has been the only treatment available for DME, and has long been the reference treatment of DME. The study of the ETDRS has shown that laser therapy reduced by 50% the decrease in visual acuity at 3 years in eyes with "clinically significant" DME, i.e. threatening or reaching the center of the macula. A visual acuity improvement was rarely observed and at 3 years, about 15% of eyes continued to lose vision despite laser

therapy (5). Recently, the DRCR.Net has shown more favorable outcomes of laser therapy than those of the ETDRS study, since about 25% of eyes treated with laser showed a gain of 2 lines or more after a 2-year follow-up, but the beneficial effect of laser therapy is delayed and only appears several months after treatment (6-8). However, first focal laser and grid macular laser have not been distinguished in these studies and second, there is no standardization for performing grid laser between studies, making it difficult to draw formal conclusions. The superiority of laser photocoagulation combined with anti-VEGF treatment has not been shown compared to anti-VEGF treatment alone (10). In the DRCR.Net, the eyes treated with ranibizumab have achieved a lower visual acuity gain than those treated with ranibizumab combined with laser therapy delayed by at least 6 months (*most patients in this group did not receive laser therapy*) (8,9). The only benefit found in this study of combining immediate laser treatment is the decrease in the number of IVT injections with a difference in the median number of IVT injections of -4 IVT injections with immediate laser treatment at 5 years (11). Unlike conventional lasers emitting a continuous laser beam, micropulse lasers (usually infrared diode laser at 810 nm) deliver short pulse durations (about one millisecond or microsecond) grouped in a shooting envelope. Several studies, including a meta-analysis of 4 studies, have suggested that this type of laser was as effective as conventional laser with a better local tolerance profile (12). Finally, laser therapy complications have been described: paracentral scotoma, accidental laser burn of the fovea, choroidal neovascularization developed from a photocoagulation scar, progressive extent of photocoagulation scars at the posterior pole and thus at the foveola, leading to a severe decrease in visual acuity.

3/ Vitrectomy

Several studies have shown anatomical and functional benefits of vitrectomy on DME associated with proven vitreomacular traction or thick and retractable epimacular membrane (13). In the absence of vitreomacular traction, the results of vitrectomy are not convincing. Several randomized studies using various treatment protocols have been conducted. But the results are divergent. The conclusions of a recent meta-analysis on the effect of vitrectomy on DME are the following (13): "*There is little evidence to support vitrectomy as an intervention for diabetic macular edema in the absence of epiretinal membrane or vitreomacular traction. Although vitrectomy appears to be superior to laser in its effects on retinal structure at 6 months, no such benefit has been proved at 12 months. Furthermore, there is no evidence to suggest a superiority of vitrectomy over laser in terms of functional outcomes.*"

4/ Anti-VEGF agents

Two anti-VEGF agents are approved for the treatment of DME reaching the central area, associated with a decrease in visual acuity: ranibizumab and aflibercept.

- The efficacy of ranibizumab has been demonstrated in several randomized studies, including the studies RESTORE, DRCR.Net, RISE and RIDE (8-10, 14). In the RESTORE and DRCR.Net studies, ranibizumab (0.5 mg) as a monotherapy (RESTORE) or in combination with laser therapy delayed by at least 6 months (DRCR.Net) has been compared to the combination of ranibizumab (0.5 mg) and immediate laser versus laser therapy alone (8-10). These studies have shown a superiority of the ranibizumab arms over laser treatment, with a mean gain of + 7.9 and 7.1 letters at one year in the RESTORE study, + 9 letters at one year in the DRCR.Net study, versus a gain of 2.3 letters (RESTORE) and 4 letters (DRCR.Net) in patients treated with laser alone, and this result was statistically significant. This result has been achieved with an mean number of 7.4 injections in the RESTORE study

and 8-9 injections in the DRCR.Net study during the first year; it has been maintained during the second and third year in both studies with a decreasing need for injections. At 5 years, in the DRCR.Net study, more than 50% of patients treated with ranibizumab no longer needed injections (11).

The studies RISE and RIDE have compared two doses of ranibizumab as a monotherapy (0.3 and 0.5 mg) as monthly injections to laser therapy (14). The two groups of patients treated with ranibizumab achieved a mean gain of 11 letters at 24 months, without difference between the 2 doses, which was significantly higher than the gain achieved with laser therapy. In all studies, ranibizumab was well tolerated, especially without excessive cardiovascular events.

These studies have also shown that a delay before initiating ranibizumab treatment was accompanied by a lower improvement in visual acuity: in the studies RESTORE, RISE and RIDE, initiating a treatment with ranibizumab in patients initially treated with laser, respectively one and two years after the start of the studies, has led to an improvement in visual acuity in these patients, but the latter was lower than in patients treated with ranibizumab from the start of the study (15,16).

Finally, the RETAIN study has assessed a "Treat and Extend" dosing regimen, after achieving the visual acuity stabilization phase: patients were treated with intravitreal injections with gradually increasing intervals (17). This dosing regimen was compared to a PRN regimen, with comparable functional outcomes.

Finally, a slowdown of DR progression has been shown in patients treated with ranibizumab for their DME (18).

- Following the RESTORE study, ranibizumab (Lucentis®) has obtained an European marketing label (AMM in France) in 2012, that has been revised in 2014. Based on this label, Lucentis® is indicated for the treatment of DME reaching the central area, associated with a significant decrease in visual acuity. The treatment will be initiated with one monthly injection until the maximum visual acuity is reached and/or until the absence of signs of disease activity, i.e. no change in visual acuity or other signs and symptoms of the disease under continuous treatment.
- Then, the monitoring and treatment intervals should be determined by the physician and based on the disease activity, assessed by measuring visual acuity and/or anatomical criteria.
- If, in the opinion of the physician, the visual and anatomical criteria indicate that the continuous treatment is not beneficial for the patient, Lucentis® should be discontinued.

- Aflibercept.

The efficacy of aflibercept on DME has been demonstrated in the studies VIVID and VISTA (19). In these studies, two dosing regimens (monthly intravitreal injections of 2 mg of aflibercept or series of 5 monthly injections followed by one injection of 2 mg every two months) have been compared to laser therapy: the two groups of patients treated with aflibercept had a rapid improvement in visual acuity with a mean gain of 10-11 letters at one year which was significantly higher than the gain achieved with laser therapy. This result was maintained during the second year. No difference was observed between both dosing regimens. A lower DR progression was observed in patients treated with aflibercept. Aflibercept (Eylea®) has been approved in 2015 for the treatment of DME:

- Indicated for a decrease in visual acuity due to DME.
- The recommended dose of Eylea® is 2 mg of aflibercept, corresponding to 50 microliters.

- At the time of treatment initiation, Eylea® is injected once a month for 5 consecutive months followed by one injection every 2 months. Monitoring visits are not required between the injections.
- After the first 12 months of treatment with Eylea®, the time between two injections may be extended depending on visual and anatomical outcomes.

The DRCR.Net has compared the efficacy of 3 anti-VEGF agents: ranibizumab 0.3 mg, aflibercept 2 mg, and bevacizumab 1.25 mg, administered according to the same therapeutic regimen in a study referred to as protocol T (20). Overall, an equivalent clinical efficacy was obtained for all 3 treatments. But differences in efficacy were observed depending on the visual acuity: when the baseline visual acuity was equal to or greater than 20/40, the efficacy of all three treatments was identical. In contrast, when the visual acuity was less than 0.5, aflibercept was more effective than ranibizumab at a dose of 0.3 mg or bevacizumab (+19, +14, +12 letters, respectively, at one year).

4/ Corticosteroids

Two corticosteroids are approved for the treatment of DME: Ozurdex® (biodegradable dexamethasone intravitreal implant) and Iluvien® (fluocinolone acetonide intravitreal implant).

Iluvien® is a non-biodegradable implant containing 190 µg of fluocinolone acetonide, injected into the vitreous with a 25G needle. It allows the progressive delivery of fluocinolone over 36 months. The randomized studies FAME A and B have demonstrated the efficacy of this treatment compared to a placebo on the improvement in visual acuity in patients with laser-refractory DME (21). A subanalysis has shown a greater visual benefit in patients reporting a DME duration longer than 3 years.

Adverse reactions were reported. Almost all phakic patients developed cataract at 3 years. The incidence of a raised IOP (37.1% and 45.5%, for low and high doses, respectively), the need for hypotonic treatment (38.4% and 47.3%, respectively), the need for filtration surgery (4.8% and 8.1%, respectively), and trabeculectomy (1.3% and 2.5%, respectively) were higher in the 2 groups treated with fluocinolone compared to the placebo group.

Iluvien® is approved for the treatment of the visual loss associated with chronic DME when the response to the available treatments is deemed insufficient.

Ozurdex® is a biodegradable implant, containing 700 µg of slow-release dexamethasone. Its duration of action is of 4-6 months.

The MEAD study, comprising two multicentric, randomized, phase III trials with a similar design has assessed the efficacy and safety of an intravitreal implant containing two doses of dexamethasone for the treatment of DME: 0.7 mg of dexamethasone (DEX 0.7) or 0.35 mg of dexamethasone (DEX 0.35), compared to a placebo group (22). The percentage of patients showing an increase in visual acuity by 3 lines or more at 3 years was significantly higher with DEX 0.7 (22%) and DEX 0.35 (18.4%) than in the control group (12%, $p \leq 0.018$). The rate of cataract was of 67.9% and 64.1% in the DEX 0.7 mg and DEX 0.35 mg groups, respectively. A raise in IOP ≥ 10 mmHg was observed in 27.7% and 24.8% of eyes treated with DEX 0.7 mg and DEX 0.35 mg, respectively, and one patient in each group who received dexamethasone needed filtration surgery for glaucoma.

Ozurdex® has been approved for the treatment of DME. It is indicated in adult patients with a decrease in visual acuity due to DME in whom a non-corticosteroid treatment is not suitable, in pseudophakic patients and in patients who poorly respond to a non-corticosteroid treatment.

TREATMENT RECOMMENDATIONS

1. When should DME be treated?

- ***In patients without decrease in visual acuity:*** primary prevention with systemic factor control is always needed (including blood glucose and blood pressure control). Besides controlling systemic factors, the only recommended treatment when the visual acuity is normal, is laser therapy which is indicated in patients with moderate DME.
- ***In patients with significant decrease in visual acuity:***
 - If there is a large imbalance in inaugural systemic factors, without previous management, it is possible to wait 2-3 months before initiating a treatment with intravitreal injections, since systemic factor control may help to improve DME.
 - Otherwise, although there is no emergency to treat, it is recommended not to wait too long, since a too long time before initiating treatment with injections is detrimental.

2. How to treat?

In patients without significant decrease in visual acuity:

Besides systemic factor control, the only treatment to be considered is **laser therapy**.

- ME without central involvement: laser therapy is indicated in patients with moderate ME. A moderate treatment will be administered with a safe distance from the center of the macula. Only lesions (including microaneurysms) located more than 750-1000 microns from the center of the macula will be treated. Applying laser impacts closer to the center of the macula is not recommended.
- Severe ME (with central involvement): if the DME is essentially secondary to leakages from microaneurysms, laser therapy may be administered in compliance with the above-mentioned precautions. Otherwise, a monitoring is recommended (no preventive indication for IVT injections in the absence of additional data because of the risk of endophthalmitis and the possible spontaneous improvement in DME).

In patients with significant decrease in visual acuity due to severe DME (i.e. with central involvement):

- **Vitrectomy** may be proposed in patients with tractional DME, i.e. if an obvious vitreomacular traction or thick epimacular membrane is visible on OCT.
- If there is a doubt about the existence of a vitreomacular traction, vitrectomy may be proposed after failure of the treatment with intravitreal injections.
- In the absence of vitreomacular traction, a **first-line treatment with intravitreal injections will be proposed**. Only this treatment will rapidly allow achieving a gain in visual acuity. Eventually, it will subsequently be followed by laser therapy.

Three first-line treatments may be proposed in patients with severe DME associated with a decrease in visual acuity: anti-VEGF agents (ranibizumab and aflibercept) or dexamethasone intravitreal implant.

A first-line treatment with monthly anti-VEGF injections will be proposed in patients with DME reaching the macula center associated with a decrease in visual acuity,

- Especially if severe peripheral retinal ischemia, and *a fortiori* rubeosis iridis, is present
- in the absence of contraindications to anti-VEGFs: recent cardiovascular history (myocardial infarction, stroke that theoretically occurred within the last 3 months), pregnancy
- but, provided that a monthly monitoring, essential during the first year, is possible
- this treatment will also be proposed when Ozurdex® is contraindicated

The choice between the 2 anti-VEGF agents available, Lucentis® and Eylea®, will be left at the prescribing ophthalmologist's discretion, since no data is available on the direct comparison between both treatments at doses marketed in Europe.

Injections of dexamethasone intravitreal implant (Ozurdex®) may be proposed as a first-line therapy, according to the AMM label:

- in pseudophakic patients
- in phakic patients when non-corticosteroid therapy is not suitable, especially when a monthly monitoring is not possible (travel difficulties, poorly compliant patients or patients who do not want to consult every month), or when anti-VEGF treatment is contraindicated. Young patients whose lens is clear should be informed of the risk of cataract.
- this treatment is contraindicated in patients with advanced or uncontrolled glaucoma, aphakia, iris implant or who underwent large peripheral iridectomy, patients with history of ocular infections (herpes, toxoplasmosis...).

Laser therapy may secondarily be associated with intravitreal injections on persistent perifoveal areas of the ME, in compliance with the above-mentioned precautions.

If the initial intravitreal treatment is ineffective, it is possible to switch to one of the other molecules, in compliance with the respective contraindications.

Finally, treatment with ILUVIEN® may be proposed in patients who do not respond to anti-VEGF therapy. As it is a long-term treatment, it makes sense to propose it in patients for whom the efficacy of short-term intravitreal corticosteroids has already been demonstrated, and who have not experienced severe ocular hypertonia during previous treatments with corticosteroids. Nevertheless, it could also be tested after failure of Ozurdex®.

3/ Dosing regimen and monitoring

Treatment with Lucentis®: it will be administered according to the following scheme

- induction therapy with 3-4 monthly injections,
- if the visual acuity improves and/or the macular thickness decreases at the end of this phase, the treatment will be continued on a monthly basis until achieving the maximum visual acuity and maximum reduction in macular thickening, i.e. until there are no more changes in visual acuity and central macular thickness during three consecutive monthly assessments.
- After this phase, two strategies are possible: monthly monitoring (ProReNata, PRN), and resumption of injections if the visual acuity decreases and /or the macular thickness increases or "Treat and Extend" strategy, including scheduled injections carried out with increasing intervals and resumption of more frequent injections in patients with relapsing DME.
- If no visual acuity gain and no decrease in macular thickness are observed after the induction phase, the treatment with Lucentis® will be discontinued and a treatment with another molecule may be initiated.

Treatment with Eylea®: it will be administered according to the set label scheme. At the time of treatment initiation, Eylea® is injected once a month for 5 consecutive months followed by one injection every 2 months. The label of Eylea® states that no monitoring visits are required between injections during the first year. It is however recommended to ensure that a functional and/or anatomical response to the treatment is achieved after 3-4 injections. Subsequently, it may be useful depending on the clinical context to perform an additional functional and morphological assessment between the injections.

If no visual acuity gain and no decrease in macular thickness are observed after the induction phase, the treatment with Eylea® will be discontinued and a treatment with another molecule may be initiated.

After the first 12 months of treatment with Eylea®, the time between two injections may be extended depending on visual and anatomical outcomes.

Treatment with Ozurdex®: after the first injection, monitoring visits at 1, 2 and 4 months are recommended to verify the efficacy of the treatment and monitor the IOP. In patients with ocular hypertonia >21 mmHg upon treatment initiation, an additional monitoring is recommended within 15 days after injection, only after the 1st injection. Subsequently, longer monitoring intervals will be possible. If no visual acuity gain and no decrease in macular thickness are observed after the first injection or if uncontrollable severe ocular hypertonia occurs, the treatment with Ozurdex® will be discontinued and a treatment with another molecule may be initiated.

Treatment with Iluvien®: monitoring visits at 1, 2 and 4 months are recommended to verify the efficacy of the treatment and monitor the IOP. In patients with ocular hypertonia >21 mmHg upon treatment initiation, an additional monitoring is recommended at day 7. Thereafter, the IOP will be monitored every three months.

4/ Special cases

- Pregnancy: DME may occur during pregnancy, when DR worsens. It may occur at the end of the second trimester of pregnancy, in particular when the pregnancy was not

planned and a rapid blood glucose control was necessary. It is recommended not to treat DME during pregnancy since it disappears after childbirth in most cases. Anti-VEGF treatments should be avoided during pregnancy.

- Florid diabetic retinopathy and DME: florid DR is a rare but serious form of DR occurring in young diabetic patients, remarkable for its very rapid evolution. It is characterized by severe retinal ischemia, which may very rapidly be complicated by neovascularization, which may even reach the posterior pole. Rapid panretinal photocoagulation (PRR) is indicated in these serious forms of florid DR. DME is usually found in patients with rapid DR worsening. In this case, DME is mainly related to severe retinal ischemia and therefore probably to the high level of growth factors in the vitreous. If the visual acuity is normal or moderately decreased, PRP alone may allow DME resorption, although PRP is performed more rapidly and the risk is reduced when PRP is combined anti-VEGF injection. If the visual acuity is severely reduced, the treatment of choice is the administration of anti-VEGF intravitreal injections. When fibrosis is associated with neovascularization, care should be taken regarding the risk of fibrosis retraction induced by anti-VEGF therapy.
- Cataract surgery may worsen a preexisting DME. The worsening generally occurs about 6 weeks after surgery. When a preexisting DME reaches the central area, a treatment with intravitreal injections of anti-VEGFs or Ozurdex® will be initiated before surgery and continued postoperatively. If a DME reaching the central area appears post surgery, the treatment of choice is Ozurdex® when it is not contraindicated, due to the inflammatory component.
- Vitrectomized eye: due to the absence of vitreous gel, a faster clearance of the products injected into the vitreous may be observed. For dexamethasone implant, the studies have shown equivalent dexamethasone concentrations in the vitreous of vitrectomized and non-vitrectomized eyes (23). Little data is available on anti-VEGF therapy.

Factors influencing treatment choice

Besides controlling systemic factors, the choice of treatment will depend on:

- visual acuity and functional discomfort experienced by the patient, taking into account the professional requirements, including the need to drive
- type of DME: location and leakage sources (microaneurysms...)
- presence of a tractional component associated with the DME
- severity of associated retinal ischemia, including rubeosis iridis
- lens condition: clear lens, cataract, pseudophakia, iris implant, aphakia
- IOP and existence of glaucoma
- possibility of the patient to consult every month, patient compliance
- existence of contraindications to the various treatments, including recent cardiovascular history, pregnancy, history of ocular infections (herpes, toxoplasmosis...)

		MONITORING	LASER	ANTI-VEGFs	OZURDEX®
No visual loss					
	Moderate ME		+		
	Severe ME, microaneurysms remote		+		

	from the center				
	Severe ME, limited number of microaneurysms or microaneurysms near the center	+			
Significant visual loss					
	Absence of cataract			+	+/-
	Pseudophakia			+	+
	Monthly monitoring not possible				+
	Advanced or uncontrolled glaucoma			+	
	Severe retinal ischemia			+	
	Recent cardiovascular history				+
	Pregnancy	+			
	Pre and post-cataract surgery			+/-	+
	History of ocular infections (herpes, toxoplasmosis...)			+	
	Vitrectomized eye			+/-	+

Main factors influencing the choice of first-line treatment for DME

Conflict of interest:

Pascale Massin: consultant or clinical investigator or speaker for Alimera, Allergan, Bayer, Novartis

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