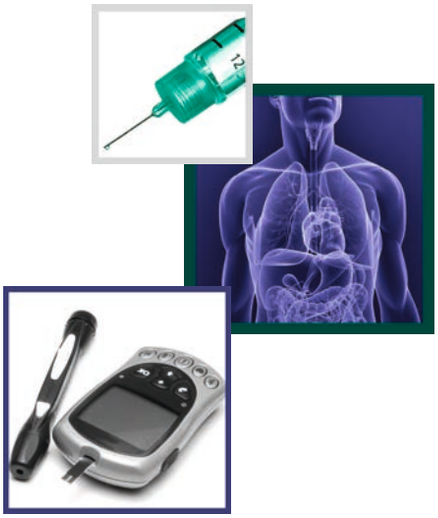

# Treating diabetic retinopathy: developments and challenges



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**Q What features are characteristic of diabetic retinopathy & how does this disorder develop?**

■ **Bandello, Lattanzio & Zucchiatti**

The pathophysiology of diabetic retinopathy (DR) is extremely complex and involves all the cell types in the retina: blood vessels, cellular components, glial cells, neurons and microglia [1]. Proinflammatory mediators such as VEGF are also believed to play a key role.

The clinical finding of DR can range in severity according to the degree of retinal vascular abnormalities [2]. The early stage is a mild nonproliferative DR characterized by increased retinal vascular permeability, mycroaneurysms, intraretinal hemorrhages and cotton wool spots. This can progress to severe proliferative DR (PDR), the most destructive stage, where new vessels form at the surface of the retina and extend into the vitreous.

Diabetic macular edema (DME) may be present at any stage of DR with occurrence increasing with DR severity. The criteria to define clinically significant DME are quite old and poorly defined when compared to clinical practice. Some authors propose the differentiation between focal and diffuse presentation to employ different treatment regimens for DME, but this issue is controversial.

**Q What is the prevalence of diabetic retinopathy among diabetics and why is this population at such high risk?**

■ **Lanzetta**

Diabetic retinopathy has a substantial socio-economic burden as it is the major cause of new-onset blindness in the adult population aged 20–70 years. This condition is the most important microvascular complication for diabetics and its frequency and progression is strictly related to the duration of the disease. In the WESDR study, among younger-onset diabetic persons, the prevalence of diabetic retinopathy varied from 17 to 97.5% in patients with diabetes for less than 5 years and 15 or more years, respectively. In individuals aged 30 years or more with diagnoses of diabetes, the prevalence of diabetic retinopathy varied from 28.8% in patients who had been diagnosed with diabetes for less than 5 years to 77.8% in patients who had lived with the disease for 15 years or longer. Higher levels of glycosilated hemoglobin and poor metabolic control, presence of proteinuria and higher diastolic blood pressure are well-known risk factors for severity and progression of diabetic retinopathy.

■ **Bandello, Lattanzio & Zucchiatti**

Recent estimates from the extensive body of literature on the epidemiology of DR show that its prevalence, especially with intensive therapy, is lower than that reported historically [3]. The estimated prevalence of DR among adult US diabetics is 28.5%, with 4.4% having vision-threatening DR [4]. In particular, the risk of PDR and the incidence of visual impairment are declining and less prevalent in more recently diagnosed patients [5]. However, blindness is still a common complication in diabetic patients and DME is the leading cause. Estimates of the prevalence of DME vary, but it is higher among Type 2 diabetics compared with Type 1 diabetics [6,7].

Projected estimates suggest that the number of people in the USA with diabetes will triple by 2050, indicating a major health burden in the coming decades that will substantially impact the employed population [8].

**Q In your opinion, is DR well managed clinically? What is the current standard therapy?**

**■ Lanzetta**

The management of DR is still part of secondary and even tertiary prevention of diabetes with methods to diagnose and treat the disease in the early stages before it causes significant morbidity, loss of function and severe complications. After the Diabetes Control and Complication Trial it was known that optimal glycemic control delays the onset and slows the progression of DR. For years, laser photocoagulation and metabolic control have been the only treatment possibilities to face both DME and PDR. While the importance of glycemic control is now widely recognized, the current role of laser photocoagulation as first-line therapy for DME is under debate following the advent and approval of anti-VEGF therapy. However, despite a reduction of its use in this condition, laser photocoagulation remains pivotal in the treatment of proliferative DR.

**■ Bandello, Lattanzio & Zucchiatti**

Visual impairment could be substantially reduced in diabetics by effective control of serum glucose and blood pressure as well as through early DR detection and timely treatment. Detection and treatment of DR to prevent visual loss are in fact cost effective and may result in well-established cost savings; but only 50–70% of diabetic patients receive guideline-recommended levels of eye care [9]. Laser treatment has been the mainstay of DR treatment for a quarter of a century, with vitrectomy an option for patients not responding to photocoagulation. More recent approaches include agents targeting key proteins in DR pathogenesis, such as VEGF (ranibizumab, bevacizumab, pegaptanib and VEGF Trap-Eye), which have demonstrated efficacy in the treatment of DME [10] and in some cases of PDR [11].

**Q What progress has been made recently in managing DR?**

**■ Lanzetta**

As mentioned previously, intravitreous anti-VEGF therapy has recently been validated for the treatment of DME. Although repeated injections of medication are needed, especially during the first year, visual acuity improvements after anti-VEGF therapy are immediate and sustained and are usually superior to those achieved with focal or grid laser photocoagulation. Moreover, positive outcomes have been reported both in focal and diffuse DME, the latter typically responding poorly to laser photocoagulation. Apart from the availabilty of newer therapies, progress has been made in the field of classification and pathogenesis of DME, especially owing to the use of optical coherence tomography. True retinovascular or tractional DME can be differentiated and targeted with the most appropriate approach, either medically or via a laser surgically. Regarding PDR, newer and less invasive surgical techniques are now available when scatter laser photocoagulation is not efficacious. Panoramic viewing systems and transconjunctival small gauge vitrectomy are now routinely used during surgery.

**■ Bandello, Lattanzio & Zucchiatti**

The gold standard DR treatment should be based on a good systemic metabolic control. Despite this being essential, sometimes in clinical practice, an optimum blood glucose control may be insufficient as soon as DR and DME appear. Additional measures have been proven to be essential in order to avoid the subsequent visual loss. While laser treatment has been the only efficient treatment option in preventing vision loss so far, it has been inadequate in chronic cases. Intravitreal agents have recently demonstrated their safety and efficacy and have emerged as an increasingly common treatment that often replaces the standard of care to best manage this complex disease. In particular, anti-VEGF therapies have shown impressive promise in not only maintaining but also improving visual acuity, although we should assess whether they must be used as monotherapy or in combination with laser treatment and vitreoretinal surgery. Visual benefits of intravitreal triamcinolone have not been so robust; however, it has a role in treating refractory DME. The economic and social burden of DR is ever changing, as new and improved therapies are continuously developed and evaluated.

**Q How effective are early screening interventions in diagnosing DR?**

**■ Lanzetta**

Past experiences have clearly shown that well-established and -conducted screening campaigns

can significantly decrease the incidence of blindness, severe visual loss and disability due to DR. This also results in saved resources that can be reinvested. Screening activities should be part of every country's healthcare program.

■ **Bandello, Lattanzio & Zucchiatti**

Prevention plays an essential role in the management of DR. Screening interventions enable effective prevention of the development and progression of DR, monitoring for early detection and treatment of microangiopathy and supervising all DR-related complications. Patients should perform routine ophthalmological evaluations in order to early detect the first signs of retinopathy early and as soon as this sight-threatening complication is detected, a strict follow-up is required.

**Q Would you recommend multidisciplinary intervention in the treatment of DR?**

■ **Lanzetta**

As diabetes is a very complex disease involving various organs, a multidisciplinary approach is mandatory in order to reduce the burden of complications. With regard to DR, its treatment is not only based on laser photocoagulation or intravitreal therapy but quite importantly on the level of disease control. Therefore, the active participation of different professionals, such as ophthalmologists and diabetologists can contribute to reducing the morbidity caused by diabetes. Additionally, educational programs specifically dedicated to diabetes, and its complications and their management, represent an important step.

■ **Bandello, Lattanzio & Zucchiatti**

DM is a chronic disease with short-and long-term complications, including micro- and macro-vascular damage. A multidisciplinary team approach is essential for the successful prevention and management of this chronic illness and its dramatic complications, including DR, neuropathy, nephropathy and cardiovascular disease.

The DCCT Research Group first established the basis for the development of multidisciplinary coordinate care teams [12]. An expert team of diabetologists, pediatrics, cardiologists and highly trained diabetes nurses, dieticians, educators and behavioral specialists should be involved, not only to optimize diabetes control, but also to help educate the patient to allow them to better accept and live this chronic illness. This coordinate disease management approach may not only improve DR, but also the health-related quality of life, thus reducing the risk of earlier mortality.

**Q How would you select a certain method of treatment for an individual patient?**

■ **Lanzetta**

Recently, a better knowledge of DR has become available. Optical coherence tomography has allowed the identification of different DME subtypes that may respond differently to various therapeutic approaches. In addition, newer treatment modalities, other than laser photocoagulation, can be considered.

DME may or may not involve the foveal center. In addition, laser treatment can be differentiated as focal or diffuse with a retinovascular origin. Laser photocoagulation can still be the first choice treatment option in cases of focal edema, mainly due to the lower costs as compared with anti-VEGF therapy. In cases of diffuse macular edema, anti-VEGF therapy is now the mainstay. In specific cases, grid laser photocoagulation can be added once the central retina has flattened with the aim of limiting the number of intravitreal injections. Intravitreal steroids can also be considered. Tractional macular edema should be treated with a surgical approach and sometimes combined or not with intravitreal therapy, depending on the individual patient. Forms of proliferative retinopathies should be treated with scattered laser photocoagulation, surgery and the adjunct of intravitreal anti-VEGF agents in selected cases. Anti-VEGFs may increase the efficacy of panretinal photocoagulation in high-risk eyes, such as those with florid DR, or may reduce the risk of vitreous hemorrhage when a surgical approach is considered.

■ **Bandello, Lattanzio & Zucchiatti**

Focal/grid laser photocoagulation [13] and intravitreal anti-VEGF [14,15] are currently the main treatment options for the treatment of DME. However, some patients can be refractory to both treatments and a different individual therapeutic approach should be offered, including intravitreal steroids.

Thus, a treatment algorithm has been proposed to identify an individual patient-centered option in the management of DME [16]. First, DME should be classified as a focal, diffuse or tractional form. In the case of focal DME, laser photocoagulation should be performed as a first

choice option, based on the ETDRS guidelines. In nonresponders, focal DME may be treated with anti-VEGF injections. In the case of diffuse DME, intravitreal injections of anti-VEGF or steroids should be performed and later combined with laser treatment if a good recovery is observed. In nonresponders, diffuse DME may be treated with intravitreal steroids combined with laser photocoagulation as a second choice treatment option. Finally, in the case of tractional DME, surgery combined with anti-VEGF therapy or steroid injections is the main treatment option.

### Q What have the RESTORE and RESOLVE studies revealed?

#### ■ Bandello, Lattanzio & Zucchiatti

The RESTORE and RESOLVE studies are two multicenter, randomized, double-masked, 12-month clinical trials, both designed to evaluate the therapeutic effect and the safety of intravitreal ranibizumab in the management of DME [14,17].

The RESOLVE study is a sham-controlled clinical trial that first proved the efficacy and safety of ranibizumab in the treatment of DME. At month 12, a gain of ≥10 letters in the best-corrected visual acuity (BCVA) score from baseline occurred in 60.8% of ranibizumab and 18.4% of sham eyes.

The RESTORE study is a laser-controlled clinical trial that demonstrated the superiority of ranibizumab monotherapy or in combination with laser photocoagulation. At month 12, the proportion of patients who had a BCVA letter score ≥15 letters was 22.6% in the ranibizumab monotherapy group and 22.9% in ranibizumab and laser group, respectively.

The results of these [14,17] and other [15,18,19] clinical trials revealed, for the first time, that treating DME with intravitreal ranibizumab can statistically improve the visual acuity, while the previous results of the ETDRS [13] demonstrated that focal grid laser photocoagulation was only effective in the prevention of the visual acuity decline.

#### ■ Lanzetta

In the RESOLVE study, 151 patients were assigned to two different doses of ranibizumab (0.3 or 0.5 mg) or sham injection. There was an option to double the dose of anti-VEGF after 1 month of follow-up, depending on treatment response. Patients received three initial mandatory doses at monthly intervals and from month 3, treatment was administered on demand, depending on success, futility and safety criteria. Laser photocoagulation could be given after three initial injections if needed. At 1 year, 102 eyes treated with either dose of ranibizumab significantly improved in visual acuity by 10.2 letters compared with baseline, with an average of ten ranibizumab injections, whereas the control group decresased in visual acuity by 1.4 letters.

In the RESTORE trial, 315 patients with visual impairment due to DME were randomized 1:1:1 to sham injection and active laser, ranibizumab 0.5 mg injection and active laser and ranibizumab 0.5 mg and sham laser. Patients received three consecutive injections and thereafter were switched to an individualized regimen with retreatment as needed, based on stopping and reinitiation criteria. In the ranibizumab arm and the ranibizumab and laser arm, there was rapid improvement in BCVA scores up to month 3, followed by stabilization up to month 12 with a 6.8 and 6.4, letters gain, respectively, following an average of 7 and 6.8 injections, respectively. In the laser arm, there was maintenance of the baseline BCVA scores approximately +1 letter over the 12-month study period. Two hundred and twenty patients completed the 24-month visit. During the second year, patients initially assigned to laser treatment could receive ranibizumab treatment as needed. Safety analysis at this time point showed neither new adverse events nor new safety risks. The mean BCVA gain was maintained with an average of 3.9 and 3.5 ranibizumab injections in the ranibizumab and the ranibizumab plus laser group, respectively. The retinal thickness decreased with ranibizumab treatment that was observed during the first year was also maintained at month 24. In patients treated with laser only during the first year, visual acuity improved to +5.4 letters at month 24 with an average of 4.1 ranibizumab injections in the second year. Therefore, in the second year, an average of 3.8 ranibizumab injections was sufficient to maintain (ranibizumab/ranibizumab plus laser) or improve (laser) BCVA scores and retinal thickness outcomes. The adverse events reported over 2 years were consistent with the published safety profile of ranibizumab in DME.

The take-home messages from the two studies are that in patients with DME, visual acuity gain can be obtained with a frequent rate of ranibizumab injection during the first year of therapy.

The number of injections significantly decrease by half during the second year and visual acuity gains are maintained. At this time, adding laser photocoagulation to ranibizumab treatment does not seem to increase visual acuity benefit or reduce the number of injections needed.

### Q Which therapeutic agents are currently in clinical trials and what have been the most promising results so far?

**■ Lanzetta**

Many other anti-VEGF compounds are being studied for the treatment of DME. Pegaptanib has completed a 2-year Phase II/III study. Two hundred and sixty patients received 0.3 mg pegaptanib or laser treatment every 16 weeks. At the end of follow-up the total number of injections was 16 in the pegaptanib group. Visual acuity improved by 6.1 letters in the anti-VEGF-treated eyes and by 1.3 letters in the laser group. However, at week 102, the improvement in visual acuity of ten or more letters was not significantly different in the two groups (38.3% pegaptanib and 30% laser). Aflibercept, a VEGF-Trap, has shown encouraging results in the DA VINCI study. Two hundred patients were randomized to receive focal laser, or three groups treated with VEGF-Trap (0.5 mg every 4 weeks, 2.0 mg every 4 weeks, 2.0 mg every 8 weeks or 2.0 mg *pro re nata* [PRN]). Three monthly mandatory initial injections were given in the aflibercept group, whereas the laser group received one laser treatment at baseline followed by PRN laser from week 16. Over a 6-month period, the aflibercept PRN group received a median of four treatments and the laser group a median of two photocoagulations. Visual acuity gain was +2.5 letters in the laser group, +11.4 letters in the 2 mg/month group, +10.3 letters in the PRN group, +8.5 letters in the 2 mg/bimonthly group and +8.6 letters in the 0.5 mg/month group. While VEGF is a well-known component in the pathogenesis of DME, it is also known that this condition is associated with an overexpression of inflammatory cytokines. On this basis, off-label intravitreal steroids have been extensively used.

A dexamethasone biodegradable implant with a slow-release formulation is also being studied with promising preliminary results. Intravitreal fluocinolone in a non-erodible implant has also been evaluated with encouraging results in chronic DME and some safety issues with respect to cataract development and elevated intraocular pressure.

Recently, newer, less invasive modalities of laser treatment have been proposed. In a randomized 12-month trial, high-density micropulse photocoagulation provided a visual acuity improvement of 0.25 logMAR. Whether the combination of less destructive laser applications and intravitreal pharmacotherapies will be the future in the treatment of DME it is still to be fully elucidated.

**■ Bandello, Lattanzio & Zucchiatti**

Currently, most of the studies regarding DME are evaluating the frequency of retreatment and the efficacy of intravitreal ranibizumab in a longer follow-up period. These studies are evaluating the best treatment strategy, within a fixed regimen of monthly ranibizumab or PRN injections. The results of these trials are encouraging and offer hope to establishing the optimum interval retreatment, as a useful scheduling approach in everyday clinical practice.

Nevertheless, new drugs have become available for the treatment of DME. Several studies are ongoing to assess the safety and efficacy of known anti-VEGF injections, such as VEGF Trap-Eye [20], or new agents targeting proteins, such as TNF-α and protein kinase C-β2, or anti-inflammatory agents (e.g., NSAIDS and corticosteroids).

However, statistically significant results are needed to establish which treatment or combination of treatments is the most appropriate in this deluge of data. Head-to-head comparisons are currently ongoing to evaluate whether intravitreal anti-VEGF or slow-release steroids are better as the first-line treatment for DME.

### Q What can diabetics do to decrease their risk of DR?

**■ Lanzetta**

Optimal glycemic and arterial pressure control are well-known measures that can decrease the risk of both incidence and progression of DR. In addition, regular visits with fundus examination are crucial in order to promptly intervene when necessary.

**■ Bandello, Lattanzio & Zucchiatti**

Diabetics should try to reach and maintain the optimum blood glucose control and to avoid serious episodes of hypoglycemia, based on an individualized approach and a multidisciplinary

strategy. The DCCT [12] and the ACCORD [21] studies revealed that intensive glycemic regimen was effective in reducing the rate of progression to DR, even if patients and clinicians were very careful to avoid the risk of dangerous hypoglycemic episodes. Antihypertensive and lipid-lowering therapies are also required to further prevent the development and progression of the diabetic microangiopathy.

### Q What challenges are currently faced in the field & where do you see research progressing in the next 10 years?

#### ■ Lanzetta

Major advances in the management of DR have been obtained in the last decade. Laser photocoagulators can now be used less invasively and intravitreal anti-VEGF agents are now applied routinely in the treatment of DME. There are still many limitations in the current approaches. The incidence of the disease *per se* is fast increasing in developing countries due to the changing lifestyles. Therefore, there is an urgent need for screening and educational campaigns in those countries where diabetes is an epidemic emergency. Regarding DR, newer therapies have expanded the treatment armamentarium but at same time have caused a significant burden. Studies on anti-VEGF drugs have shown that they have limited duration and multiple injections are needed to maintain efficacy. More action is needed in the field of newer drugs, but more importantly in the field of delivery systems.

#### ■ Bandello, Lattanzio & Zucchiatti

Currently, the approved therapeutic options and the new promising strategies include intravitreal agents. These treatment are effective, not only in the prevention of visual loss, but also allow visual acuity recovery. Nonetheless the major limitation of these treatment options is their short duration and, thus, multiple intravitreal injections are required, increasing the risk of injection-related adverse events. In the future, researchers should focus their efforts to assess new therapeutic agents with a more lasting effect and reduced risk of recurrences, such as slow-release drug delivery devices. The use of combination therapy may also give encouraging results, as diabetes is a chronic illness and patients require long-term care.

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