Characterization of Responders to Treatment of DME

Combination therapies may benefit patients who do not respond to anti-VEGF agents.

BY JOSÉ CUNHA-VAZ, MD, PHD

Diabetic retinopathy (DR) is a complex disease, a disorder of the retina that develops to one degree or another in almost all people with systemic diabetes mellitus of long duration.[1,2] In its earliest clinically recognizable form, nonproliferative DR, the disease is characterized by retinal vascular abnormalities, including increased vascular permeability leading to the development of diabetic macular edema (DME). Patients with clinically significant macular edema (CSME) are at risk for vision loss and should be considered for treatment.[3]

DR does not evolve in the same way in all individuals. Different modes of evolution can be seen in patients with similar levels of metabolic control and disease duration. Some patients experience disease progression despite good metabolic control, while others with poor control do not progress. Not all patients develop persistent DME, and not all patients develop the neovascularization characteristic of proliferative DR. These differences in the course of the disease suggest that genetics may play a role in its development.

Recognizing and understanding these differences in early, nonproliferative DR could help to identify more effective therapies at a stage when diabetic retinal lesions are still reversible.

DIFFERENT PHENOTYPES

Four types of changes characterize early DR: the development of microaneurysms and retinal hemorrhages, alteration of the blood-retina barrier (leakage), capillary closure (ischemia), and alterations of the neuronal and glial cells of the retina. Our group at the Institute of Biomedical Research on Light and Image at the University of Coimbra, Portugal, has identified and validated three phenotypes of DR in patients with type 2 diabetes based on these four factors (Table 1).[4-6]

These phenotypes can be identified by monitoring a combination of diagnostic information: alterations in fluorescein leakage, retinal thickness, and the number of red dots on fundus images.

Most patients with diabetes fall under phenotype A and experience slow progression of DR. However, we must be concerned about those with phenotype B, in which hemodynamic changes predominate, and phenotype C, in which thrombotic changes predominate. Progression to DME in phenotype A is rare. In a study including 113 patients who progressed to CSME over a 10-year follow-up, only 5.4% of patients with phenotype A developed CSME, whereas large percentages of patients with phenotypes B and C developed CSME (Figure 1).[7,8]

TABLE 1. NONPROLIFERATIVE DIABETIC RETINOPATHY PHENOTYPES

Phenotype A:
- Slow progression (number of red dots/year)
- Accelerated aging process (diabetes)

Phenotype B:
- Rapid progression (number of red dots/year)
- Increased flow
- Alterations of blood-retina barrier (leakage)
- Increased retinal thickness (edema)
- *Hemodynamic changes predominate*

Phenotype C:
- Rapid progression (number of red dots/year)
- Decreased flow
- Foveal avascular zone outline changes
- *Thrombotic changes predominate*

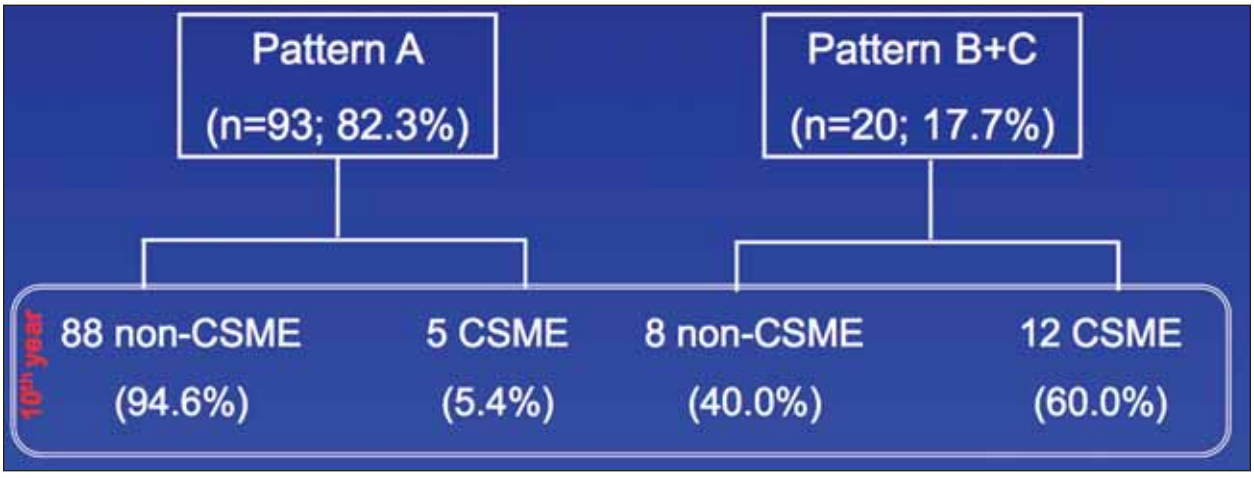

Figure 1. In a study including 113 patients who progressed to CSME over a 10-year follow-up, only 5.4% of patients with phenotype A developed CSME, whereas large percentages of patients with phenotypes B and C developed CSME.

Progression to DME can be monitored by evaluating changes in microaneurysm development and disappearance using fundus photography with the Retmarker (Critical Health, Coimbra, Portugal) software; by assessing increase in retinal thickness with optical coherence tomography (OCT); and by following associated loss of best corrected visual acuity (BCVA), which is an indicator of the patient's photoreceptor status. Vision loss is a key factor because it is what concerns our patients most, and in addition it is one of the clinical endpoints the Food and Drug Administration and other regulators look at in evaluating the efficacy and safety of proposed therapies for DME. Future developments in OCT analysis software will bring us more information about the density of the photoreceptors and the size and location of changes in the photoreceptor layer. This will also be important information in the diagnosis and treatment of DME because it determines the potential for recovery.

CHARACTERIZING RESPONDERS

In characterizing responders to therapy for DME, it is important to keep in mind the predominant disease mechanisms in DR: vascular leakage, inflammation, and ischemia. Leakage can be measured with fluorescein angiography or with OCT analysis indicating the presence of edema. Inflammation is a response to DME disease activity, and it influences the turnover (appearance and resolution) of microaneurysms. Ischemia also clearly plays a role in DME, but most clinical trials in DME exclude patients with ischemia. Therefore, even though ischemia is often present in eyes that have more rapid progression of disease, we have little information about how ischemia affects treatment, and vice versa.

The major pathways of progression in DR are leakage, development of microaneurysms, inflammation, and ischemia. The therapies that we employ for treatment of DME act on one or more of these pathways. The rationale for use of vascular endothelial growth factor (VEGF) inhibitors in DME is the association of the presence of VEGF with vascular leakage; VEGF increases leakage, and anti-VEGF action can control leakage. Anti-VEGF therapy may also have an effect on ischemia, depending on the level of ischemia. Steroids act on both leakage and, especially, inflammation. Although we do not fully understand the mechanism of action of laser, we observe that it stabilizes disease activity in DME.

The current consensus on treatment of DME depends on whether there is center involvement.[3] If there is no center involvement, we treat according to ETDRS guidelines. If there is central involvement, we determine whether there is vision loss or not due to DME; if there is no vision loss we observe or treat according to ETDRS guidelines, and if there is vision loss we employ anti-VEGF monotherapy.

Response to anti-VEGF treatment in DME is generally better than response to any other means of treatment. A randomized controlled trial by the Diabetic Retinopathy Clinical Research Network showed that intravitreal ranibizumab (Lucentis, Genentech) plus prompt or deferred laser resulted in greater visual acuity gain than treatment with either intravitreal triamcinolone acetonide plus laser or laser alone.[9] However, in clinical trials we are always looking at the mean results of a number of patients. In any trial of a proposed DME therapy, there will be good responders who achieve decreased thickness and increased visual acuity in a relatively short period after the initial injections, but there will also be poor responders and nonresponders. It would be helpful to know more about the nonresponders in order to choose alternative treatments to which they might respond better.

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ab groups experienced injection-related endophthalmitis. No evidence of progressive tractional retinal detachment was seen, despite a high percentage of patients with a history of proliferative diabetic retinopathy receiving anti-VEGF treatment.

Almost 60% of eyes in the triamcinolone group underwent cataract surgery over 2 years of follow-up, compared with a 14% incidence of cataract surgery in the ranibizumab groups. In addition, 28% of individuals in the triamcinolone group required intraocular pressure-lowering medications during 2 years of follow-up, compared with roughly 4% in the ranibizumab groups and 5% in the laser.

CONCLUSION

This phase 3 study clearly demonstrated that intravitreal ranibizumab with either prompt or deferred laser provided superior anatomic and functional outcomes in individuals with DME through 2 years compared with the previous gold standard of laser alone.

It is crucial to recognize that the regimens employed in this study require seeing patients with DME frequently and recognizing that, even once treatment is deferred, more often than not patients will relapse and require additional care. It is by being diligent that we can provide the tremendous levels of efficacy and safety achieved in this study.

The combination of triamcinolone plus laser was not superior in efficacy to laser alone and did not approach the efficacy and safety of ranibizumab. An exception to this was seen in eyes that were pseudophakic at study entry; this was a subgroup analysis, so we must be conservative in drawing any substantial conclusions from this finding. ■

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To evaluate response to treatment in DME, retinal thickness measurement with OCT is crucial to evaluate structural changes—decreases in intraretinal or subretinal fluid as markers for reduction of vascular leakage. Visual acuity is also fundamental to evaluate the response to treatment because it determines whether or not we repeat treatments. It does not make much sense to keep injecting a patient whose visual acuity is not improving. Visual acuity also gives clues to the photoreceptor status, which determines the patient's potential for recovery.

For patients with DME who do not respond or respond poorly to anti-VEGF therapy, combination treatments may offer an additional benefit. Applying laser immediately after the first or second injection in the initial stages of anti-VEGF treatment may reduce the number of injections needed and/or improve response. Adding steroid injection or an extended release steroid implant may improve the disease course in patients who do not respond or respond poorly to anti-VEGF monotherapy.

It is crucial to identify responders and nonresponders to therapy for DME. If we can develop mechanisms to recognize early those patients who are not responding to therapy and devise alternative treatment approaches for them, we can be sure we are getting the right treatments to the right patients at the right time. ■

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