

The Evolving Treatment of Diabetic Retinopathy


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Purpose: To review the current therapeutic options for the management of diabetic retinopathy (DR) and diabetic macular edema (DME) and examine the evidence for integration of laser and pharmacotherapy.

Methods: A review of the PubMed database was performed using the search terms diabetic retinopathy, diabetic macular edema, neovascularization, laser photocoagulation, intravitreal injection, vascular endothelial growth factor (VEGF), vitrectomy, pars plana vitreous surgery, antiangiogenic therapy. With additional cross-referencing, this yielded 835 publications of which 301 were selected based on content and relevance.

Results: Many recent studies have evaluated the pharmacological, laser and surgical therapeutic strategies for the treatment and prevention of DR and DME. Several newer diagnostic systems such as optical coherence tomography (OCT), microperimetry, and multifocal electroretinography (mfERG) are also assisting in further refinements in the staging and classification of DR and DME. Pharmacological therapies for both DR and DME include both systemic and ocular agents. Systemic agents that promote intensive glycemic control, control of dyslipidemia and antagonists of the renin-angiotensin system demonstrate beneficial effects for both DR and DME. Ocular therapies include anti-VEGF agents, corticosteroids and nonsteroidal anti-inflammatory drugs. Laser therapy, both as panretinal and focal or grid applications continue to be employed in management of DR and DME. Refinements in laser devices have yielded more tissue-sparing (subthreshold) modes in which many of the benefits of conventional continuous wave (CW) lasers can be obtained without the adverse side effects. Recent attempts to lessen the burden of anti-VEGF injections by integrating laser therapy have met with mixed results. Increasingly, vitreoretinal surgical techniques are employed for less advanced stages of DR and DME. The development and use of smaller gauge instrumentation and advanced anesthesia agents have been associated with a trend toward earlier surgical intervention for diabetic retinopathy. Several novel drug delivery strategies are currently being examined with the goal of decreasing the therapeutic burden of monthly intravitreal injections. These fall into one of the five categories: non-biodegradable polymeric drug delivery systems, biodegradable polymeric drug delivery systems, nanoparticle-based drug delivery systems, ocular injection devices and with sustained release refillable devices. At present, there remains no one single strategy for the management of the particular stages of DR and DME as there are many options that have not been rigorously tested through large, randomized, controlled clinical trials.

Conclusion: Pharmacotherapy, both ocular and systemic, will be the primary mode of intervention in the management of DR and DME in many cases when cost and treatment burden are less constrained. Conventional laser therapy has become a secondary intervention in these instances, but remains a first-line option when cost and treatment burden are more constrained. Results with subthreshold laser appear promising but will require more rigorous study to establish its role as adjunctive therapy. Evidence to support an optimal integration of the various treatment options is lacking. Central to the widespread adoption of any therapeutic regimen for DR and DME is substantiation of safety, efficacy, and cost-effectiveness by a body of sound clinical trials.

Keywords: diabetes, retina, diabetic retinopathy, diabetic macular edema, neovascularization, laser photocoagulation, intravitreal injection, vascular endothelial growth factor, vitrectomy pars plana vitreous surgery, antiangiogenic therapy

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Plain Language Summary

With the recent expansion of management options for diabetic retinopathy, optimal sequences of treatment application and combination in specific clinical situations are under investigation. A review and synthesis of the ophthalmologic literature on treatment of diabetic retinopathy was performed to provide perspective on the relative prioritization of the various treatments in the contexts seen in clinical practice. In general, pharmacotherapy is ascendant, particularly with the anti-VEGF class, while laser treatment continues to have lesser roles in specific situations and under certain economic constraints. Surgical intervention continues to be reserved for those situations which fail to respond to pharmacotherapy, laser or combination therapy. Ongoing refinements in the systemic management of both hyperglycemia and hyperlipidemia continue to demonstrate significant benefits for both diabetic retinopathy and diabetic macular edema. Recent developments involving newer retinal diagnostics are proving beneficial in optimizing both initiation and maintenance of therapy. As well, recent advances in novel pharmaceutical agents and ocular drug delivery methods show promise in better controlling the disease as well as reducing the burden of treatment.

Introduction

With the increasing global incidence of diabetes mellitus (DM) in both developed and developing countries, diabetic retinopathy (DR) has likewise increased in prevalence. Recent estimates suggest that approximately 486 million people worldwide have DM and that roughly one-third demonstrate evidence of DR, including diabetic macular edema (DME).^{1–5} In the working adult population, DR remains a major cause of blindness in the US, causing 12,000–24,000 new cases each year. Approximately 30 million people or 9.4% of the US population in 2017 had DM.⁶ With DR consuming roughly 40% of the total cost of DM care in the US, this translates approximately to \$120 billion annually in economic burden, not only from direct disease management costs but also from lost worker productivity.⁷

Methods

A systematic search of English-language articles in the PubMed database was performed using the medical subject headings (MeSH) search terms “diabetic retinopathy”, “diabetic macular edema”, “retinal neovascularization”, “laser photocoagulation”, “intravitreal injection”, “vascular endothelial growth factor” (VEGF), “vitrectomy”, “pars plana vitreous surgery”, “antiangiogenic therapy”. The date range of the search was restricted to a period from January 1st, 1965 to May 1st 2019. The initial retrieved search was followed by a manual search of reference lists of selected major review articles. Randomized controlled trials (RCTs) with more than 6

months of follow-up and meta-analyses were included. Case reports and “grey literature” articles were excluded. Only indexed, peer-reviewed articles were included and with additional cross-referencing, this yielded 839 publications of which 305 were selected based on content and relevance to the main search term “diabetic retinopathy”.

Historical Background

In the 1950s DR was the leading cause of blindness and visual disability in the United States. Perhaps because of a dearth of alternative therapies, photocoagulation had gained widespread use in clinical practice in spite of inadequate evidence as to its benefit. Begun in 1971 and completed in 1975, the landmark Diabetic Retinopathy Study (DRS) demonstrated that scatter laser photocoagulation was beneficial in reducing the risk of progression to “severe visual loss” (SVL) in eyes with “high-risk characteristics (HRC).” Reflecting the dismal prognosis of the era, the primary outcome was not VA gain but rather the reduction of SVL (<5/200 (VA) at two consecutive 4-month visits).⁸

The minimum degree of retinopathy for patients enrolled in the DRS was “severe nonproliferative diabetic retinopathy (NPDR).” As no patients with “mild to moderate NPDR” were studied, the results did not guide clinicians as to when to apply scatter photocoagulation in such eyes. The clinical question arose as to whether earlier application of scatter photocoagulation prior to the development of proliferative diabetic retinopathy (PDR) would help to reduce the risk of progressing to PDR and thus help reduce the risk of progressing to SVL. To answer this question, the Early Treatment Diabetic Retinopathy Study (ETDRS) was formulated. Patients were randomized to either a pattern of full panretinal laser photocoagulation (PRP) (1200–1600 burns of 500 μ m spot size) or mild PRP (400–650 burns of 500 μ m spot size).^{9,10} Although full PRP reduced the risk of developing HRC by 50% and mild PRP reduced the risk of developing HRC by 25%, the rates of developing SVL were low as long as patients could be followed closely with laser applied after HRC developed.¹¹ As such, the timing of the application of scatter photocoagulation the ETDRS did not significantly alter the recommendations of the DRS.

A second major question posed by the ETDRS was whether photocoagulation was effective in the treatment of DME. When patients with DME, defined initially as thickening of the retina within one disc diameter of the center of the macula, were treated with focal laser, there was no significant VA benefit.¹² However, when a more restrictive definition of “clinically significant macular edema” (CSME) was used as

a treatment criteria, focal photocoagulation was shown to reduce the risk of progression to “moderate visual loss” (defined as loss of 15 or more ETDRS letters).⁹ The protocol laser parameters were to treat microaneurysms from 500–3000 μ m from the center of the fovea directly with burns of 50–100 μ m spot size; 0.05–0.1 seconds duration; with power sufficient to whiten or darken the microaneurysm. Either color change indicates that the microaneurysm has been changed by the absorption of laser energy, and usually leads to involution and reduction or cessation of leakage. A grid treatment of <200 μ m spot size with mild intensity and a 0.05–0.1 second duration was applied to areas of diffuse leakage and non-perfusion.

CSME was defined as 1) retinal thickening at or within 500 μ of the center of the macula 2) hard exudates at or within 500 μ of the center of the macula if associated with thickening of the adjacent retina 3) retinal thickening of at least one disc area in size if at least part of that retinal thickening was within one disc diameter of the center of the macula.¹² If CSME persisted at the 4 month follow-up visits then treatable lesions received additional direct and grid photocoagulation. As with the DRS, the ETDRS goals of laser therapy were to help prevent visual loss. As the authors commented, “treatment is less effective at improving vision than in preventing further visual loss.”¹¹

In 1991 the American Academy of Ophthalmology established a long-term educational project, “Elimination of Preventable Blindness from Diabetes by the Year 2000.”¹³ Somewhat akin to John F. Kennedy’s pledge to place a man on the moon by the end of the decade of the 1960s, this program was termed “Diabetes 2000” with the goal of disseminating the results of the DRS and the ETDRS such that early recognition and timely treatment of diabetic retinopathy could prevent visual loss. Experience with the Diabetes 2000 program illustrated the need for new strategies capable of improving accessibility to high-quality eye care, increasing involvement of primary care physicians in DR screening and encouraging at-risk individuals to seek testing.¹⁴

In 2002, the collaborative Diabetic Retinopathy Clinical Research Network (DRCR Network) was formed to facilitate multicenter clinical research of diabetic retinopathy, diabetic macular edema and associated conditions. Whereas the DRS and ETDRS involved primarily academic institutions, the DRCR.net has a majority of community-based sites participating in their trials. Simultaneous with the formation of the DRCR Network in the last decade, was the increasing use of intravitreal pharmacotherapy for the management of DR and DME. The DRCR Network has conducted multiple clinical

trials addressing various diagnostic and therapeutic approaches to the management of DR and more recently DME.^{15–21}

Along with advances in retinal diagnostics, the last two decades have also seen advances in vitreoretinal surgical techniques and instrumentation. When first introduced in 1970, vitrectomy for proliferative diabetic retinopathy was reserved for severe vitreous hemorrhage which had not cleared by one year or for traction retinal detachment involving the macula. Increasingly, surgical techniques are employed for less advanced stages of the disease. The development and widespread use of smaller gauge instrumentation along with intraoperative wide-field viewing systems and advanced anesthesia agents have been associated with a trend toward earlier intervention for diabetic retinopathy. There is need for a large, prospective trial to determine if the threshold for surgical intervention in both DR and DME can be reduced in comparison to the criteria established by the Diabetic Vitrectomy Study thirty years ago. The Diabetic Retinopathy Vitrectomy Study (DRVS) was done to evaluate vitrectomy in the setting of proliferative diabetic retinopathy and enrolled patients from 1976 to 1978. Group N was designed to yield information on the conventional management of eyes with very severe PDR. This information was then used to define eligibility criteria for Group NR which included eyes with retinopathy severe enough to justify randomization to either early vitrectomy or conventional management. Group H included eyes with severe vitreous hemorrhage for less than 5 months combined with reduction in visual acuity to 5/200 or worse which were randomized to either early vitrectomy or deferral of vitrectomy for one year. Early vitrectomy resulted in visual acuity of 10/20 or better in 25% of eyes versus deferral of vitrectomy which resulted in visual acuity of 10/20 or better in 15% of eyes. In Type I diabetes, early vitrectomy resulted in visual acuity of 10/20 or better in 36% of eyes whereas deferral of vitrectomy resulted in 10/20 or better visual acuity in 12% of eyes. There was no advantage of early vitrectomy found in Type 2 diabetes patients.^{22,23}

The dramatic increase in diagnostic and therapeutic options available to the clinician managing DR and DME has made more pressing the question of the optimal integration of these treatment modalities for specific situations.

Recent Developments in Systemic Management of DM

The basis for the medical management of diabetic retinopathy consists of intensive medical control of blood glucose, blood pressure and blood lipids. The Diabetes Control and

Complications Trial (DCCT) demonstrated that intensive insulin therapy over an average of 6.5 years in Type I diabetes resulted in a reduction of clinically important retinopathy (34–76%), need for laser photocoagulation (34%) and first appearance of retinopathy (27%) over four years.²⁴ The Epidemiology of Diabetes Intervention and Complications Study, an extension of the DCCT showed that the beneficial effects persist for an additional 4–10 years and more recently out to 23 years.^{25,26} The relative risk reduction at 10 years was 53–56% (95% CI 45–66, $p=0.001$) and at 23 years the risk reduction of any diabetes-related eye surgery was 48% (95% CI 29–63, $P<0.001$).²⁶ The UK Prospective Diabetes Study in Type II diabetes also showed similar results and for every 1% decrease in hemoglobin A1C, there was a 35% reduction in the risk of microvascular complications.^{27–29} Similarly, results from the DRCR Network's Protocol T trial demonstrated a correlation of visual acuity (VA) improvement in patients receiving anti-VEGF therapy with lower hemoglobinA1c levels.³⁰

The Actions to Control Cardiovascular Risk in Diabetes (ACCORD) Study was designed to test three separate strategies to reduce cardiovascular disease in those with Type II diabetes including intensive glycemic control vs standard, intensive blood pressure control vs standard and intensive therapy of blood lipids/lipoproteins vs placebo and simvastatin.³¹ The study examined the effect of adding fenofibrate 160 mg/d in diabetic patients with normal glomerular filtration rate (GFR) or 54 mg/d in patients with reduced GFR to simvastatin. Over four years, the progression of retinopathy was reduced by 40% in the fenofibrate group.³² The study showed that intensive glycemic, blood pressure and lipid control did not significantly reduce cardiovascular disease.^{32,33} Tight glycemic control increased mortality (5% vs 4%) and tight blood pressure control reduced strokes.^{32,34} The ACCORD Eye Study showed that intensive glycemic control, control of dyslipidemia with fenofibrate and simvastatin reduced the proportion of eyes that had progression of retinopathy by one-third. Intensive blood pressure control did not have a statistically significant effect.^{32,33,35} The results of the optical coherence tomography substudy of ACCORD, which will illuminate the effects on DME, have not been published yet. In order to determine whether there is a “memory imprint” for intensive glucose or lipid control, the 8 year follow-up data was recently published and demonstrated that prior intensive glycemic control continued to reduce DR progression, despite similar A1C levels; however, the benefit of fenofibrate did not persist. Likewise, intensive blood pressure control had no effect on DR progression.³⁶

Simultaneous with the ACCORD study, the fenofibrate intervention and event lowering in diabetes (FIELD) study concluded that a potential therapeutic role existed for fenofibrate in the prevention of retinopathy alongside intensive management of hyperglycemia and high blood pressure.^{37,38} The FIELD study showed that oral fenofibrate 200 mg/d was associated with a statistically significant reduction in a composite endpoint of 2-step progression of retinopathy grade, macular edema, or laser treatment for either DME or proliferative retinopathy. The hazard ratio for the fenofibrate group compared to placebo was 0.66, 95% confidence interval 0.47–0.94, $P=0.022$. It is not known how the DME component of the composite outcome was affected by the fibrate therapy. Newer fibrates such as the selective peroxisome proliferator-activated receptor alpha modulator (SPPARM- α), pemafibrate, may have even more significant impact on ameliorating DR than older agents in this class.³⁹ In general, studies with fibrates have been shown to have a protective effect on DR progression and possibly reduction in risk of DME development; however, their effect on preserving vision as well as retinal hard exudate formation is marginal.³⁸

Studies with statins and their role in delaying the onset and severity of DR have yielded similar results to those obtained with the fibrates.^{40,41} The recent results from the prevención con dieta Mediterránea (PREDIMED) trial have demonstrated that dietary modification involving consumption of long-chain omega-3 polyunsaturated fatty acids (LC ω 3PUFAs) decreases the risk of DR development.⁴² Further support for dietary supplementation benefit in DR was provided by the diabetes visual function supplement study (DiVFuSS). The DiVFuSS was a 6 month randomized trial involving subjects with Type 1 and 2 DM for at least 5 years and a VA of 20/30 or better with no retinopathy to mild or moderate NPDR. Subjects were randomized to placebo or a twice-daily oral supplement containing xanthophyll pigments, antioxidants and botanical extracts, specifically: vitamins C, D3 and E (d- α tocopherol), zinc oxide, eicosapentaenoic acid, docosahexaenoic acid, α -lipoic acid (racemic mixture), coenzyme Q10, mixed tocotrienols/tocopherols, zeaxanthin, lutein, benfotiamine, N-acetyl cysteine, grape seed extract, resveratrol, turmeric root extract, green tea leaf and Pycnogenol. Visual function tests including contrast sensitivity, color error score and visual field mean sensitivity and macular pigment optical density showed statistically significant improvements in the treatment group compared to placebo.⁴³

Newer adjunctive therapies such as Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are increasingly being employed to better regulate serum glucose fluctuations in

DM and also appear to confer some benefit in severity reduction of DR.^{44,45}

Ultimately, effective resolution of DR will depend on permanent correction of the underlying systemic abnormality for both type 1 and 2 DM. Although there are encouraging results from recent and limited trials of diabetic cell therapy, particularly stem cell transplantation, it is still too early for these new therapies to be applied in large-scale trials.^{46–49} Likewise, recent advances in artificial pancreas development hold promise for better control of both DM and DR progression.^{50–54}

Current Role of Laser Therapy in the Management of Diabetic Retinopathy

In the past decade, new approaches in pharmacotherapeutic management of DME have overshadowed developments in laser therapy. The initial clinical trial of the DRCR Network published in 2007 illustrates the modest evolution of laser techniques for management of diabetic macular edema.⁵⁵ The “modified-ETDRS” pattern involved less intense power such that a change in the microaneurysm color was not required for direct treatment and for the grid treatment the burn intensity was to be “barely visible.” The “mild macular grid photocoagulation” varied from the ETDRS pattern of grid treatment in that the intensity was “barely visible” and also that the area of treatment was to both thicken and un-thicken retina within the macula.

The results of some clinical trials have demonstrated that supplementing pharmacotherapy with laser therapy both as focal and grid application for macular edema and as PRP application for proliferative disease may provide a more durable response.^{56–59} However, conventional, continuous wave (CW) or photocoagulative laser destroys some retinal cells and often results in permanent scotomas in the visual field.^{12,60–62} PRP can worsen night vision and delay light-to-dark adaptation.^{63–66}

A newer mode of laser, termed subthreshold, involves grid type application of non-photocoagulative laser spots to “photo-stimulate” outer retinal tissues, primarily the retinal pigment epithelium (RPE), to either increase production of metabolites that inhibit neovascularization and reduce vascular permeability activity or to downregulate production of mediators that increase vascular permeability and neovascularization.^{67–76} In subthreshold laser, many of the benefits of CW lasers can be obtained without the adverse side effects. There are now several laser manufacturers providing subthreshold lasers (STL)

systems such as the Micropulse laser™ (Iridex Corp.; Quantel Medical), Endpoint Management™ (Topcon), Microsecond Pulse (Navilas OD OS) and 2RT® (Ellex), all of which can be safely applied over the fovea without visible damage. Several small and often uncontrolled studies have shown the benefits of subthreshold lasers in treating diabetic macular edema either alone or in combination with pharmacotherapy, yielding results comparable to those obtained with conventional laser but with no tissue damage or scotomas.^{77–85} To date however, a definitive advantage of these alternative laser therapies over the ETDRS established delivery method has not been borne out for PDR.⁸⁶

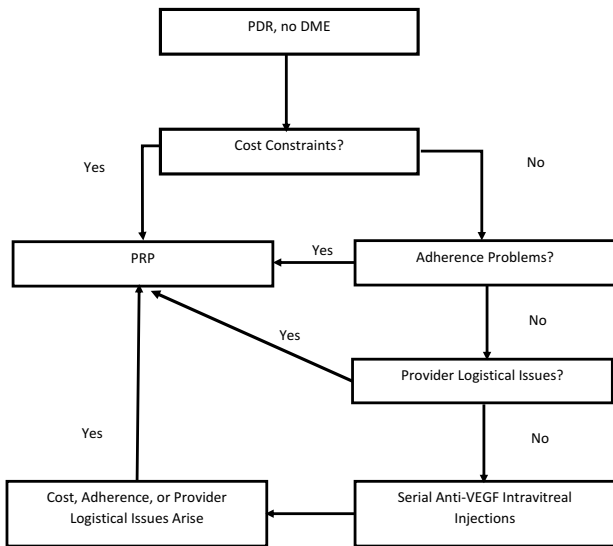
Another new development in retinal laser therapy is a fundus camera-based photocoagulation system that is integrated with retinal eye-tracking technology (NAVILAS).^{87–89} This technique allows the ophthalmologist to take an image of the retina of a patient with DR or DME, digitally encircle the areas requiring treatment and have the device automatically deliver the laser spots to the specified areas. Higher accuracy of laser delivery compared with conventional, manually operated lasers can be achieved.⁹⁰ In managing patients with proliferative disease, this system is able to deliver a “navigated” pattern PRP which is selectively applied to areas of ischemia identified by wide-field fluorescein angiography. Fewer, more uniform laser burns are delivered in shorter time and with less discomfort. Although all treatments ultimately depend on the specifics of the clinical situation, [Figure 1](#) shows suggested guidelines from the authors for the relationship of laser treatment and pharmacologic treatment for DME, PDR, and combined situations that are commonly encountered.

Recent, uncontrolled studies have demonstrated that when used in combination with pharmacotherapy, the patients receiving NAVILAS guided focal laser required fewer injections of anti-VEGF agents than would otherwise have been required in order to maintain remission of the macular edema.^{91,92} Analogous attempts to lessen the burden of anti-VEGF injections in the setting of DME by integrating peripheral PRP have met with mixed results.^{93–95} Recent data from protocol V of the DRCR Network examining timing of therapy initiation in patients with center-involved DME and good VA demonstrated that focal macular laser fared equally well as anti-VEGF (aflibercept) therapy at 2 years.^{96–98} In addition, the same protocol validated a “watchful wait” approach to managing patients with mild DME.

In summary, the use of laser therapy for managing diabetic-related retinal disease will continue to play a role. Situations which preclude the use of pharmacotherapy in

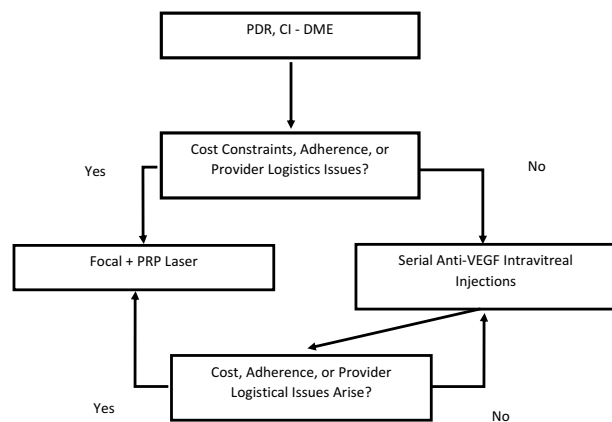
A

Suggested Treatment Decision Tree for the Clinical Scenario of Proliferative Diabetic Retinopathy without Diabetic Macular Edema



B

Suggested Treatment Decision Tree for the Clinical Scenario of Proliferative Diabetic Retinopathy with Center-Involved Diabetic Macular Edema



C

Suggested Treatment Decision Tree for the Scenario of Clinically Significant Diabetic Macular Edema

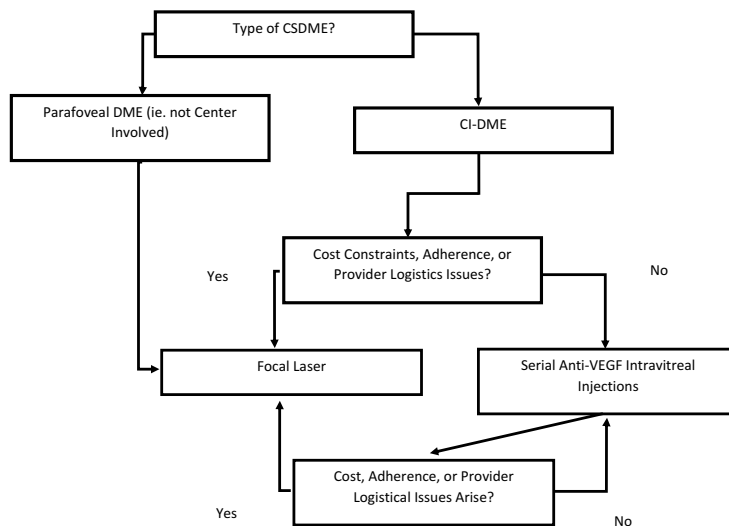


Figure 1 (A) Suggested treatment decision tree for the clinical scenario of proliferative diabetic retinopathy without diabetic macular edema. (B) Suggested treatment decision tree for the clinical scenario of proliferative diabetic retinopathy with center-involved diabetic macular edema. (C) Suggested treatment decision tree for the scenario of clinically significant diabetic macular edema. CSDME=clinically significant diabetic macular edema, which falls into 3 subcategories: edema of 1 disc area or more within 1 disc diameter of the fovea; foveal or parafoveal hard lipid with adjacent macular thickening; or foveal thickening. Focal laser means modified focal-grid laser in the manner outlined by the diabetic retinopathy clinical research network. Subthreshold laser may eventually gain a place in this block, but currently, the evidence is not strong enough to merit commensurate standing with focal laser.

Abbreviations: PDR, proliferative diabetic retinopathy; DME, diabetic macular edema; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor; CI-DME, center-involved diabetic macular edema.

DME & DR, such as unreliable patient visit compliance, pregnancy or anti-VEGF non-responders, would be best managed by laser therapy. Large, prospective comparative trials are needed to determine if the newer subthreshold and navigated laser techniques are superior to conventional laser methods.

Pharmacotherapy in Diabetic Retinopathy and Diabetic Macular Edema

When the results of the ETDRS were published in 1985, focal laser for DME became established as the standard of care for

the next 30 years.¹² However, it was evident during this era that more effective therapy was needed.⁸ Pharmacological and surgical therapies were subsequently investigated.^{99–101}

Pharmacotherapy for both DR and DME can be subdivided by class of drugs and methods of delivery as shown in Table 1. The most important class of drugs is the anti-vascular endothelial growth factor (anti-VEGF) agents, followed by the corticosteroids. Much less important are systemic angiotensin receptor blockers and fibrates. Topical nonsteroidal anti-inflammatory drugs have so far proven futile in long-term DME management.

Anti-VEGF Therapy

The first anti-VEGF drug used to treat DME was pegaptanib, which selectively blocks the 165 isoform of VEGF.¹⁰² Its promise was superseded by superior results obtained with anti-VEGF drugs that blocked all isoforms of VEGF. The efficacy of bevacizumab and ranibizumab was proven in randomized-controlled clinical trials in 2010 and that of aflibercept in 2014.^{6,7,18,103–105} Conbercept may prove to be a fifth effective anti-VEGF agent, but a level I randomized clinical trial has not yet been published. A prospective, randomized, comparative effectiveness trial of bevacizumab, ranibizumab, and aflibercept showed no difference in efficacy of the three drugs in eyes with center-involved DME and VA of 20/40 or better at one or two years of follow-up. However, in eyes with VA of 20/50 or worse, aflibercept was superior to ranibizumab and bevacizumab at one year (Table 2), whereas at two years aflibercept was no longer superior to ranibizumab, but remained superior to bevacizumab.^{21,106}

Approaches aimed at increasing the intravitreal concentration of anti-VEGF agents have not proved beneficial. The READ-3 clinical trial examining two doses of ranibizumab (0.5 and 2.0 mg) in DME showed that at 1 year there were no significant differences between the two groups.^{107–109} Focal laser added from the outset to anti-VEGF does not improve VA outcomes relative to its use in a deferred manner if incomplete drying of the macula occurs with anti-VEGF therapy.¹¹⁰ As a result, in 2019, serial anti-VEGF intravitreal injection monotherapy has become the standard of care. Unlike clinical trials, real-world data have demonstrated that a significant portion of patients in clinical practice are undertreated with anti-VEGF and have subsequently lower best corrected visual acuity (BCVA).¹¹¹ In DME patients, post hoc analysis of data from Protocol I of the DRCR Network demonstrated that the initial macular response to three injections of a particular anti-VEGF agent was predictive of long-term outcome.¹¹² Accordingly, poor responders might potentially benefit from a switch in therapeutic agents.

Intravitreal ranibizumab injections given monthly for DME increase the proportion of 2 or 3 step improvement in the severity of diabetic retinopathy, reduce the proportion of eyes with 2 or 3 step worsening in severity of diabetic retinopathy, and reduce the proportion of eyes progressing to proliferative diabetic retinopathy.^{113,114} More recently, preliminary results from the Phase III PANORAMA trial demonstrated significant regression of DR severity with intravitreal aflibercept in comparison to sham injections.¹¹⁵ Also, recent subgroup analysis from both the RIDE and RISE trials demonstrated significant

Table 1 Pharmacotherapy of Diabetic Retinopathy and Macular Edema

Administration Route	Class of Drugs					
	Anti-VEGF ^a	Corticosteroids	ACE Inhibitors ^b	Angiotensin Receptor Blockers	Fibrates	NSAIDs ^c
Intravitreal	Bevacizumab, Aflibercept, Ranibizumab, Pegaptanib, Conbercept	Dexamethasone, Fluocinolone, Triamcinolone	N/A ^d	N/A	N/A	Diclofenac
Periocular	N/A	Triamcinolone	N/A	N/A	N/A	N/A
Topical	N/A	N/A	N/A	N/A	N/A	Nepafenac, Ketorolac
Oral	N/A	N/A	Enalapril	Losartan, Candesartan	Fenofibrate	N/A

Notes: ^aVascular endothelial growth factor; ^bAngiotensin-Converting Enzyme Inhibitors; ^cNonsteroidal anti-inflammatory drugs; ^dNot applicable.

Table 2 Anti-VEGF Therapy for Diabetic Macular Edema: Selected Studies

Study	n ^a	Duration (Years)	Subgroup	Mean BL ^b BCVA ^c	Mean BL CST ^d	# Injections	ΔBCVA	ΔCST	Persistent Edema (%)
RISE ^e	377	2	Sham	20/80	467	0	2.6	-133	
			0.3R monthly	20/80	475	24	12.5	-251	26
			0.5 R monthly	20/80	464	24	11.9	-253	24
BOLT ^f	80	2	1.25B 6 weekly	20/80	501	13	8.6	-146	NG ^j
			Focal	20/80	478	0	-0.5	-118	NG
VIVID ^g and VISTA ^h	872 (pooled)	1	2A monthly	20/63	485/502	11.8/12.2	12.5/10.5	-186/-195	NG
			2A q2 months	20/63	479/518	8.4/8.7	10.7/10.7	-183/-192	NG
			Focal	20/63	483/540		0.1/1.2	-73/-66	NG
DRCR ⁱ Protocol T	660	1	2A monthly	20/32	373	9	8.0	-210	38
			1.25B monthly	20/40	363	10	7.5	-135	66
			0.3R monthly	20/40	384	10	8.3	-176	40
			2A monthly	20/80	452	9	18.9	-129	30
			1.25B monthly	20/80	467	10	11.8	-67	61
			0.3R monthly	20/80	431	10	14.2	-119	44

Notes: ^aSample size; ^bBaseline; ^cBest corrected visual acuity; ^dCentral subfield thickness; ^eRanibizumab Injection in Subjects with clinically significant macular Edema; ^fBevacizumab or Laser Therapy in the management of diabetic macular edema; ^gVEGF Trap-Eye in Vision Impairment due to DME; ^hStudy of Intravitreal Administration of VEGF Trap-Eye in Patients with Diabetic Macular Edema; ⁱDiabetic Retinopathy Clinical Research Network; ^jNot given.

benefit in improvement of DR severity with ranibizumab use in mild and moderate NPDR.¹¹⁶

Despite safety concerns that intravitreal anti-VEGF drugs could raise the risk of cardiovascular complications in patients with diabetes, there is no consistent evidence that this is the case. Recent meta-analysis of anti-VEGF therapy in DME found that aflibercept, ranibizumab and bevacizumab did not differ regarding the occurrence of systemic serious adverse events.¹¹⁷ Likewise, the concern that in already ischemic vascular beds, additional anti-VEGF therapy could further compromise the macula has not been borne out by recent data from the RESTORE study.⁵⁹ In fact, post hoc analysis of data from the VIVID and VISTA trials involving aflibercept in DME demonstrated that patients with macular nonperfusion had improvement in macular perfusion status as well as visual and anatomic improvements following treatment.^{118,119} In 2019, the data consensus suggests that for eyes with mild DME in terms of both retinal thickness and VA loss, treatment with either aflibercept, bevacizumab or ranibizumab will be equally efficacious. When there is moderate or worse VA loss, aflibercept is more efficacious.¹²⁰ Bevacizumab remains more cost-effective than ranibizumab or aflibercept.¹²¹

For PDR management, the role of anti-VEGF and laser therapy is different than that for DME. Protocol S of the DRCR Network was a randomized prospective clinical trial, comparing standard PRP with intravitreal ranibizumab 0.5mg for eyes with proliferative diabetic retinopathy.¹²² In

this multicenter randomized, non-inferiority trial, 305 patients with PDR were enrolled and randomly assigned to treatment requiring follow-up for 2 years. The results of this study showed that patients in the non-laser ranibizumab group gained 10 or more letters in approximately 42% of eyes compared to approximately 35% in the laser-treated arms at 2 years follow-up. Similarly, the rates of 10 letter score worsening were higher in the laser group at approximately 13% compared to 10% in the laser-treated arms at 10 years. In addition, the VA change area under the curve analysis favored the ranibizumab eyes over the 2-year course, which may have artificial been partially explained by relative undertreatment of DME with intravitreal ranibizumab injections compared to expectations set by the results of protocol I. Specifically, the patients in the baseline DME subgroup of the PRP arm of the trial received a median of 9 ranibizumab injections over 2 years compared to 13 injections over two years for patients in the ranibizumab plus deferred focal laser arm of protocol I.¹⁹ A further limitation of the study was the fact that 53% of the PRP group also received intravitreal ranibizumab for DME at baseline or newly developed DME during the follow-up period. Therefore, the PRP group may have been assisted by the application of ranibizumab in half of the study eyes. In terms of complications, there was a higher rate of vitrectomy and any vitreous hemorrhage in the PRP group compared to the ranibizumab group. Interestingly, the recently published 5-year data from this protocol demonstrated

equivalent VA outcomes between both groups at 5 years and progressive visual field reduction was also present in both groups.¹²³

The CLARITY study compared three monthly intravitreal aflibercept injections followed by as needed injections with PRP in the treatment of PDR. With a primary outcome at 52 weeks and 116 patients in each arm of the study, aflibercept was superior with a mean best corrected VA difference of 3.9 letters [95% CI 2.3–5.6], $p < 0.0001$, fewer vitreous hemorrhages, better visual fields, and higher patient satisfaction.¹²⁴ In light of the RISE, RIDE and other studies, the traditional view of PRP being a truly “one and done” therapy for PDR is inaccurate.¹²⁵ For now, management of PDR will more likely be guided by both cost of therapy as well as patient-specific factors such as visit compliance. Over the coming two years, data analysis from protocol W of the DRCR Network, examining the role of aflibercept in the prevention of PDR and center-involving DME will shed more light on the optimal timing of anti-VEGF therapy in DR and DME.

Corticosteroid Therapy

Corticosteroids were first used to treat DME in 2001.¹⁰⁰ Triamcinolone, dexamethasone, and fluocinolone have been used in many forms, including particulate suspensions, viscoelastic mixtures, and solid slow-release devices.^{100,126–128} Topical difluprednate for persistent DME has demonstrated short-term improvement in both VA and reduction in macular thickness, but this has been accompanied by an incidence of approximately 20% increase in intraocular pressure.^{129–131} Many dosages and intervals between injections have also been tried.¹³² Although enthusiasm for serial intravitreal triamcinolone injection was initially high, protocol B of the DRCR Network proved that focal laser led to superior VA outcomes at 3 years relative to either triamcinolone 1 mg or 4mg.^{16,133} Since the results of that large, prospective, randomized-controlled clinical trial were published, therapy with corticosteroids has taken a secondary role to anti-VEGF therapy, often used in cases refractory to, or with incomplete responses to, first-line anti-VEGF therapy.^{134,135}

The availability of corticosteroids in the form of sustained release implants has potential benefits in terms of durability of therapy in vitrectomized eyes.¹³⁶ Results from protocol U from the DRCR Network demonstrated that in the short term, combination intraocular steroid in the form of a dexamethasone implant plus anti-VEGF therapy (ranibizumab) in comparison with that of continued anti-VEGF therapy alone in eyes with persistent center-involved DME

and VA impairment despite previous anti-VEGF treatment, had modest improvement in visual gain despite significant reductions in retinal thickness on OCT.¹³⁷ In phakic eyes receiving continuous anti-VEGF therapy for DME, the addition of intravitreal corticosteroids did not result in significant visual improvements.^{138,139} Recent reports summarizing observational studies investigating dexamethasone implants in DME have reported similar final VA outcomes when compared to anti-VEGF monotherapy, but superior visual gains in real-life practice.^{140–142} There appears to be a predictive correlation between the early response to anti-VEGF therapy with the visual and anatomical outcomes following a switch to intravitreal corticosteroids. Those with poor responses to anti-VEGF demonstrated a more robust increase in BCVA.¹⁴³ Side effects of cataract in phakic eyes and intraocular pressure elevation without regard to lens status have accompanied all steroids studied, although to varying degrees.^{144–149} However, there may be a role for long-acting intraocular corticosteroids in reducing overall treatment burden in DME as early data from both the TYBEE and PALADIN studies have recently demonstrated.^{150–152} Likewise, intravitreal triamcinolone 4 mg injections for DME reduced 2 step progression in severity of diabetic retinopathy compared to focal/grid laser at 3 years.¹¹⁰ Similar data obtained from the DR-Pro-DEX Study and others demonstrated that the dexamethasone and fluocinolone implants significantly delayed the progression and reduced the severity of DR over a 24-month study period.^{153,154}

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) for DME have not been studied in depth, but available investigations suggest that they have little role in its management. Protocol R of the DRCR Network was a prospective, masked, randomized clinical trial of topical nepafenac 0.1% three times per day versus placebo over 12 months in eyes with non-center-involved DME and good VA.¹⁵⁵ No differences in VA outcomes were found. Meta-analyses examining the role of NSAIDs in the prevention of post-cataract extraction cystoid macular edema in patients without or with diabetes have come to opposite conclusions.^{156,157} Topical bromfenac in short-term trials has similarly yielded moderate macular thickness reductions with no significant gain in VA.¹⁵⁸ One small randomized trial used intravitreal diclofenac 500 µg in one of the treatment arms for patients with DME. DME improved, but VA did not.¹⁵⁹ In another small case series, there was no effect on macular edema or VA.¹⁶⁰

No further testing has been undertaken. As such, there is currently scant evidence for a benefit of NSAIDs in the treatment or prevention of DME.

Systemic Drug Therapy

Systemic drug therapy for DME and DR has also been relatively under-investigated. Drugs that block the rennin-angiotensin pathway have been one focus. The RASS study showed that the odds of retinopathy progression by two steps or more after 5 years of follow-up in patients with type 1 diabetes was reduced by 65% with enalapril, an angiotensin-converting enzyme inhibitor, and by 70% with losartan, an angiotensin receptor blocker, independently of changes in blood pressure.¹⁶¹ The DIRECT-Prevent 1 trial compared candesartan to placebo in type 1 diabetics without retinopathy with a median follow-up of 4.7 years. A post hoc analysis showed that the adjusted hazard ratio for a three-step increase in incidence of retinopathy was 0.71, 95% CI 0.53–0.95, $p=0.046$.¹⁶² Angiotensin-converting enzyme inhibition with captopril or lisinopril did not reduce the risk of incident diabetic retinopathy in patients with type 1 diabetes, but did retard progression of diabetic retinopathy.^{163–165} Conversely, in patients with type 1 diabetes, angiotensin II receptor antagonists reduced the risk of incident diabetic retinopathy but did not reduce diabetic retinopathy progression.^{162,165} High levels of diacylglycerol seen in DM patients have been known to promote activation of protein kinase C (PKC) leading to increased levels of VEGF in retinal vascular tissues. Subsequently, compounds such as Ruboxistaurin have been developed to inhibit the beta isoform of PKC and have shown some efficacy in reduction of vision loss in several large, multi-center, randomized clinical trials.^{166–168}

The US Food and Drug short-term studies of lipoprotein-associated phospholipase A2 inhibitors such as Darapladib have demonstrated only modest improvements in DME reduction and VA gains.¹⁶⁹

To summarize, pharmacotherapy for DME has produced the most significant progress in the treatment of the condition compared to laser or surgical therapy. Newer approaches based on other metabolic pathways involved in the pathogenesis of DME and combination approaches targeting multiple pathways simultaneously or sequentially hold promise. Controlling the cost of applying these treatments is a challenge as the burden of DME is increasing with the global rise in obesity and type 2 diabetes mellitus. In situations of incomplete or no response of DME to first-line treatment,

recourse is often made to focal laser, intravitreal corticosteroids, and vitrectomy.

Integration of Laser Therapy & Pharmacotherapy

To date, there have been very few clinical trials examining whether integration of laser therapy, either conventional, targeted or in subthreshold mode, with pharmacotherapy can result in a reduced treatment burden for the patient while achieving optimal clinical efficacy. In PDR, some reports have suggested that combination treatment with anti-VEGF and PRP may be superior to monotherapy in terms of NV regression and treatment burden.^{170–172} As indicated earlier, recent data from protocol S of the DRCR Network demonstrated that both PRP and intravitreal ranibizumab were similar in the prevention of severe visual loss and other complications in PDR suggesting that patient-specific factors such as compliance and financial impact be considered primarily in management decisions.^{123,173} Protocol I of the DRCR Network demonstrated that there was little short-term benefit in combining prompt macular laser with anti-VEGF therapy for center-involved DME.¹⁷⁴ However in that same protocol, patients who were treated with deferred laser therapy achieved the best outcome in terms of sustained visual improvement.

Protocol T of the DRCR Network was a comparative effectiveness trial utilizing bevacizumab, ranibizumab or aflibercept.²¹ As part of the protocol, laser treatment was mandated for persistent centrally involved macular edema at the 24-weeks follow-up examination following monthly initial treatment by 1 of the 3 agents. At the 1-year follow-up examination, 50% of eyes in the study had received laser treatment because of persistent macular edema. There was a slightly higher percentage of patients receiving laser in the bevacizumab group and a lower percentage in the aflibercept-treated group compared to the 2 other agents. In addition, deferred macular laser was still required in over 30% of study eyes with center-involved DME receiving ranibizumab in the RISE and RIDE studies.¹⁷⁴ These studies emphasize the beneficial influence of specific targeted focal and grid laser treatment in eyes not responding initially to anti-VEGF agents alone. In addition, the same trial demonstrated that regardless of the anti-VEGF agent used, there was nearly a 50% reduction in the frequency of needed injections in the subsequent year.¹⁰⁶ It remains to be seen if supplemental laser treatment might reduce this treatment burden further. Preliminary data from the DAVE trial examining widefield

targeted PRP in conjunction with intravitreal ranibizumab for DME, have demonstrated no significant reduction in the frequency of PRN injections.^{93,94} Combination therapy with intravitreal corticosteroids has likewise yielded mixed results in terms of both VA stabilization or improvement and reduction in overall treatment burden.^{175–178} Further studies to explore potential benefits of combination treatment are planned, perhaps involving widefield imaging-guided peripheral laser to ischemic retina and subthreshold technique. Notwithstanding, there are ongoing attempts at publishing guidelines for the integration of laser and pharmacotherapy in DME management in particular.^{179–181}

Surgical Management of Diabetic Retinopathy and Diabetic Macular Edema

Currently, vitrectomy continues to play a critical role in the management of certain scenarios in DR. These include non-clearing vitreous hemorrhages, tractional retinal detachment in PDR, and vitreoretinal interface abnormalities impeding macular edema resolution. Numerous reports over the past 40 years have clearly established the beneficial effect of vitrectomy in these settings.^{182–191}

In theory, the removal of the majority of the vitreous body along with the hyaloid membrane during surgical vitrectomy has been shown to improve retinal oxygenation, increase intraocular cytokine turnover and remove mechanical barriers to the egress of fluid and metabolites as well as removing impediments to the intraretinal penetration of intravitreal administered medications. Debate still exists as to the necessity of ILM removal during vitrectomy for DME. In theory, the removal of the diabetic ILM with its altered histology would be beneficial to the bidirectional flow of chemokines and pharmacological agents within the retina. However, studies to date have not definitively supported that conclusion.^{192–194} With regards to the use of preoperative anti-VEGF therapy to minimize intraoperative and postoperative hemorrhages, the majority of studies do demonstrate a benefit.^{195–202} In addition, reduction in operating time and a trend toward better postoperative VA have also been demonstrated in smaller case series.^{181,203–205} Initial concerns regarding the potential adverse effect of vitrectomy on the durability of intravitreally administered anti-VEGF agents have not been borne out by recent studies.^{206–209}

The exact role of vitrectomy in the management of DME, however, remains incompletely defined at present. Several

studies over the past 3 decades have established the anatomical improvements following vitrectomy in recalcitrant DME cases.^{101,209–216} VA improvements however have not been as consistent and as significant as the reduction in retinal thickness following the procedure.^{192,203,217–234} This discrepancy between anatomical and functional results of vitrectomy for DME may be due to the inherent postoperative ocular sequelae, such as cataract formation that can confound VA interpretations. Also, surgical intervention continues to be reserved for those cases that have had chronic and severe forms of DME when retinal damage is irreversible thereby biasing the results. Despite these limitations, vitrectomy for DR and DME may be beneficial for certain diabetic patients with specific systemic risk factors.^{235–237} In addition, vitrectomy for DR and DME is widely used in regions of the world where economic resources are more constrained and even in relatively affluent nations for underinsured patients. The procedure improves VA in certain cases, but its broader role relative to serial anti-VEGF injections has never been established in a randomized-controlled clinical trial.

Future Trends Diagnostics

New treatments often arise from insights gained with new imaging techniques. Ultra-widefield imaging has allowed clinicians to assess the severity of peripheral ischemia and new software in development is aimed at automatically quantifying and monitoring retinopathy progression in affected areas. As a result, there is an increasing need for revising the existing DR classification system.²³⁸ Newer developments in OCT imaging including swept source OCT (SS-OCT) enhanced depth imaging OCT (EDI-OCT), adaptive optics (AO) and OCT angiography (OCTA) are increasingly being used in the management of DR.^{239–241} These allow for more detailed and rapid imaging of both the retinal and choroidal vasculature. Increasing application of artificial intelligence (AI) techniques such as “Deep Learning” for fundus and OCT images facilitates cost-effective, widespread, diabetic eye screenings via telemedicine.^{242–245}

Newer fundus imaging techniques, such as flavoprotein fluorescence (FPF) may allow the detection of metabolic improvements that precede structural improvements in DME patients receiving anti-VEGF injections.²⁴⁶ Functional testing of macular sensitivity utilizing microperimetry and electroretinography is also being increasingly used in both DR and DME to assess both disease severity and response to therapy.^{247–262} These provide new indices to explore, seeking

prognostic value for response to therapy. In light of recent data demonstrating the incomplete correlation of VA and macular thickness on OCT imaging, non-anatomic diagnostics of macular function will play an increasing role in management of DME.^{263,264} These new diagnostic modalities will necessitate a redefining of universal DR and DME severity classification beyond the DRS and ETDRS definitions established nearly three decades ago. To that end, several investigators have proposed the inclusion of both temporal and spatial factors, as well as integration of multimodal biomarkers towards the formation of a more comprehensive, and clinically useful classification of DR.²⁶⁵

Therapeutics

Concomitant with the progress in diagnostics has been progressing in therapeutics for DR and DME. Despite the effectiveness of the current anti-VEGF agents in reducing progression of diabetic retinopathy and DME, protocol T of the DRCR Network demonstrated the incidence of persistent DME at 24 weeks to be 65.6% for bevacizumab, 31.6% for aflibercept, and 41.5% for ranibizumab.²⁶⁶ In clinical practice, an analysis of Medicare claims data indicates that approximately 50% of DME patients will have persistent edema after 1 year of anti-VEGF treatment.²⁶⁷ These rates of persistent DME in conjunction with the concomitant need for continuous monitoring call into question the long-term sustainability of such strategies. As such, there is currently a robust amount of research conducted on developing new therapies to deal with these recalcitrant cases. Newer pharmacological agents of potentially increased efficacy and durability are in clinical trials for DR and DME (Table 3).^{268–270} Also emerging are novel gene therapies for DR management that are in early clinical trial phases.²⁷¹ Novel anti-VEGF therapies that may be more effective, durable and cheaper than current agents such as conbercept are currently in trial for DME.²⁷² Other agents involving combination therapy, such as Genentech's anti-VEGF/ANG-2 (RG7716), have yielded favorable efficacy and durability data in recent Phase II studies.²⁷³ In addition, optimal strategies for combining anti-VEGF and corticosteroid treatment are still undergoing investigation despite the recent marginal results provided by protocol U of the DRCR network.

Alternate, non-VEGF strategies for DR and DME management are also being developed at a rapid pace. Among these are drugs targeting a central regulator, such as Raf kinase, mammalian target of rapamycin (mTOR) and the RTP 801 gene.^{274–276} A Phase I/II study of an ankyrin

repeat protein that binds VEGF reduced DME when injected intravitreally in several patients with a duration of effect of 8–12 weeks but had a tendency to cause iritis.²⁷⁷ A modified version designed to eliminate the problem of iritis is undergoing further clinical testing.

Platelet-derived growth factor (PDGF) inhibitors are also being currently investigated as potential DR therapies.²⁷⁸ A monoclonal antibody directed against the receptor-binding site of human placental growth factor (PLGF) developed by Thrombogenics (THR-317) is currently being investigated for DME treatment in the THR-001 study. Recent results from this Phase I/II study appear promising. Stealth Biotherapeutics has also explored subcutaneous injection, among other methods of delivery, of elamipretide, a mitochondrial therapy.

Anti-integrin therapeutic agents, such as Allegro Ophthalmics peptide, risuteganib (Luminate) and SciFluor Life Sciences's SF0166, inhibit the oxidative stress process that is responsible for initiating DME and are also undergoing clinical trials in this setting.

Anti-Inflammatory Agents

Chronic inflammation contributes to the pathophysiology of both DR and DME. To that end, several novel therapeutic targets have been identified for this disease targeting those processes that release cytokines and chemokines. These include direct and indirect antagonism of interleukins, proteases, chemokines, tumor necrosis factor (TNF), angiopoietin-2 (ANGPT-2) and kallikrein. Currently, there are no active clinical trials for DR and DME involving interleukins or proteases. One of the potent mediators of both inflammation and breakdown of the blood retinal barrier is the chemokine ligand, CCL2.²⁷⁹ A CCR2/5 receptor antagonist (Pf-04634817) (Pfizer) was recently tested in patients with DME.²⁸⁰ Another compound implicated in many systemic inflammatory diseases as well as DR is TNF. A clinical trial with infliximab, the monoclonal antibody antagonist of alpha (TNF- α), in patients with persistent DME demonstrated significant improvement in both VA and overall reduction in retinal thickening.^{281,282}

Angiopoietin-2 is another potent mediator of increased vascular permeability in DR. This growth factor achieves most of its biological effect by binding to the endothelial cell receptor tyrosine kinase Tie-2. A Phase I investigation of a competitive inhibitor of vascular endothelial-protein tyrosine phosphatase that promotes Tie2 activation and reduces vascular leakage in animal models showed no safety signal of concern and led to reduction in DME in a few cases.²⁸³ A Phase II trial is planned. A recent study

Table 3 Current Investigational Pharmacotherapy for Diabetic Retinopathy and Diabetic Macular Edema⁽¹⁻⁴⁾

Pharmacological Agent	Mechanism Category	Administration Route	Trial Phase	Sponsor
Abicipar pegol	DARPin	IVit	II	Allergan
AKB-9778	Tie2 agonist	SC	II	Aerpio Therapeutics
ALG-1001	Integrin receptor antagonist	IVit	II	Allegro Ophthalmics
Alpha lipoic acid	Antioxidant	PO	III	Ludwig-Maximilians University of Munich
Aminoguanidine	AGE Inhibitor	PO	I	University of Minnesota
AR-13503	Rho kinase & Protein kinase C inhibitor	IVit	I	Aerie Pharmaceuticals
ASP8232	Vascular adhesion protein I inhibitor	PO	II	Astellas Pharma
Bevasiranib (Cand5)	siRNA silencing of VEGF mRNA	IVit	II	Opko Health, Inc.
Betamethasone (DE-102)	Corticosteroid	ST	III	Santen Pharmaceutical Co.
BI 1026706	Bradykinin I Antagonist	PO	II	Boehringer Ingelheim
BI 1467335	SSAO (VAP-I) Inhibitor	PO	Ila	Boehringer Ingelheim
Brimonidine	Neuroprotection	Top	III	European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR)
Brolucizumab	Anti-VEGF	IVit	III	Novartis Pharmaceuticals
Bromocriptine,	Dopaminergic	PO	I/II	University of Southern California
Candesartan	Angiotensin receptor blocker	PO	III	AstraZeneca
Celecoxib	COX-2 inhibitor	Top	I	University of Coimbra
Choline fenofibrate	Triglyceride reduction	PO	II	Abbott
Conbercept	Anti-VEGF Anti-PlGF	IVit	III	Chengdu Kanghong Biotech Co
Danazol	Androgenic vascular permeability modulator	PO	II/III	Ampio Pharmaceuticals
Darapladib	Phospholipase CA2 inhibitor	PO	II	GlaxoSmithKline
Dextromethorphan	NMDA receptor antagonism, insulinogenic	PO	II	NEI
Diclofenac	NSAID	IVit	Ila	Shahid Beheshti University of Medical Sciences
Doxycycline	Anti-inflammatory	PO	I/II	NEI
DS-7080a	Anti-angiogenic mAb	IVit	I/II	Daiichi Sankyo, Inc.
EBI-031	Anti-interleukin-6 antibody	IVit	I	Eleven Biotherapeutics (Sesen Bio)
Emixustat	RPE65 inhibition	PO	II	Acucela Inc.
Empagliflozin	SGLT2 inhibitor	PO	IV	Hannover Medical School

(Continued)

Table 3 (Continued).

Pharmacological Agent	Mechanism Category	Administration Route	Trial Phase	Sponsor
Faricimab	Anti-VEGF & Ang-2 inhibitor	IVit	II	Roche/Genentech
Fasudil	Rho-kinase inhibitor	IVit	II	Shahid Beheshti University of Medical Sciences
Fenofibrate	PPARalpha agonist	PO	IV	University of Padova
Folic acid, B6, B12	Antioxidant	PO	IV	University of Catania
FOV2304	Kinin β 1 receptor Antagonist (anti-angiogenic)	Top	II	Fovea Pharmaceuticals
GB-102	pan-VEGF inhibitor	IVit	Ila	Graybug Vision
iCo-007	Anti-sense c-RAFkinase	IVit	II	iCo Therapeutics
Infliximab	Anti-TNF alpha mAb	IVit	I	Retina Research Foundation
Ketorolac	NSAID (coxib)	Top	I	Roche
KP-121	Corticosteroid	Top	II	Kala Pharmaceuticals
KSI-301	Anti-VEGF Biopolymer	IVit	Ib	Kodiak Sciences
KVD001	Plasma kallikrein inhibitor	IVit	II	Kalvista Pharmaceuticals
Levosulpiride	Dopamine D ₂ receptor blocker	PO	III	National University of Mexico (UNAM)
LKA651	Anti-erythropoietin	IVit	I	Novartis
Luminate (Risuteganib)	Integrin receptor antagonist	IVit	III	Allegro Ophthalmics
Mecamylamine	nACh antagonist	Top	II	CoMentis
Minocycline	Anti-microglial (anti-inflammatory)	PO	III	NEI
MTP-131	Mitochondrial cardiolipin promoter	Top	I/II	Stealth Biotherapeutics
Nutritional supplements	Anti-oxidative stress	PO	II	Mid-Atlantic Retinal Consultants
Ocriplasmin	PVD Induction	IVit	I	ThromboGenics
Octreotide	GH inhibitor	SC	III	Novartis
OC-10X	Tubulin inhibitor	Top	I	OcuCure Therapeutics
Opt-302	VEGF-r/Fc-fusion	IVit	II	Opthea
PAN-90806	VEGF ₂ R tyrosine kinase inhibitor	Top	II	PanOptica
Pemafibrate	PPARalpha agonist	PO	III	Jaeb Center for Health Research
PF-04523655	siRNA against RTP801 (antiangiogenic)	IVit	II	Quark Pharmaceuticals

(Continued)

Table 3 (Continued).

Pharmacological Agent	Mechanism Category	Administration Route	Trial Phase	Sponsor
REGN910-3 (nesvacumab)	Anti-angiopoietin 2 mAb	IVit	II	Regeneron/Bayer
RO6867461	bi-specific anti-VEGF /antiangiopoietin 2	IVit	II	Hoffman-LaRoche
Ruboxistaurin	PKC- β inhibitor	PO	III	Chromaderm, Inc. & Eli Lilly & Co
SF0166	alphaVbeta3 integrin inhibitor	Top	I/II	SciFluor
Sirolimus	Anti-IL-2 (mTOR inhibitor)	IVit/SConj	II	Santen Pharmaceutical & NEI
Somatostatin	Neuroprotection	Top	III	European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR)
Sorbinil	Aldose Reductase inhibitor	PO	III	NEI
Squalamine	Anti-angiogenic	Top	II	Elman Retina Group
Sulodexide	Glycosaminoglycan analogue	PO	II	DRESS Research Group
Teprotumumab	IGF-1 receptor antagonist	IV	I	River Vision Development Corporation
TG100801	Anti-angiogenic	Top	I	TargeGen
THR-149	Plasma kallikrein inhibitor	IVit	I	Oxurion (ThromboGenics)
THR-317	Anti-PlGF mAb	IVit	II	Oxurion (ThromboGenics)
Tocilizumab	Anti-IL-6	IVit	II	University of Nebraska
Ubiquinone	Antioxidant	PO	Ila	University of Guadalajara, Mexico
Ziv-aflibercept	Anti-VEGF	IVit	II	Shahid Beheshti University of Medical Sciences

Abbreviations: IV, Intravenous; IVit, Intravitreal; PO, Oral; SC, Subcutaneous; SConj, Subconjunctival; ST, Sub-tenons; Top, Topical.

of the Tie-2 activator AKB 9778 (Aerpio Therapeutics) in conjunction with ranibizumab demonstrated significantly greater reduction in retinal thickening in patients with DME than that seen with suppression of VEGF alone.²⁸⁴ Another important mediator of increased vascular permeability in DR and DME is activation of the plasma kallikrein-kinin pathway.²⁸⁵ Recent results from a Phase I study of the plasma kallikrein inhibitor KVD001 (KaVista Pharmaceuticals) for the treatment of central involved DME showed that not only was the compound well tolerated but also it had significant effects on VA improvement and retinal thickening reduction.²⁸⁶

Drug Delivery Strategies

In an attempt to decrease the therapeutic burden of monthly intravitreal injections, several novel strategies are currently

being examined. These mainly fall into one of five categories: non-biodegradable polymeric drug delivery systems, biodegradable polymeric drug delivery systems, nanoparticle-based drug delivery systems, ocular injection devices and sustained release refillable devices. Non-biodegradable polymeric drug delivery systems include such devices as the Iluvien[®] and Retisert[®] implants which can release fluocinolone acetonide in the vitreous cavity for up to 3 years.²⁸⁷ Also in this category is the encapsulated cell technology (ECT) Renexus[™] device, which utilizes recombinant RPE (NTC-200) cell lines to continuously secrete antibodies, fusion proteins and growth factors in the vitreous cavity. Recently, an ECT system utilizing genetically engineered ARPE-19 cells secreting soluble vascular endothelial growth factor receptor 1 (sVEGFR1) was developed with the hope of reducing intravitreal VEGF

levels for an extended period.²⁸⁸ Another novel device in development in this category is the ODTx™ (On Demand Therapeutics) implant which is an intravitreally injected rod containing multiple reservoirs of drugs that are each able to be separately activated using a laser beam. This allows for a long-term, noninvasive, control of drug delivery within the eye for a period of several months.

Biodegradable polymeric drug delivery systems such as the dexamethasone containing Ozurdex™ (Allergan) implant have now been in use for several years in the management of DME. An increasingly popular approach for sustained drug delivery is the use of drug-laden microspheres. Currently, the betamethasone containing DE-102 (Santen) and the ranibizumab (Genentech) containing microspheres are in various stages of clinical trials for DME.

Nanoparticle-based drug delivery systems include entities such as liposomes, microspheres, nanospheres, emulsions and dendrimers. Bevacizumab encapsulated liposomes have been demonstrated to have significant sustained drug release at nearly 2 months following injection. Micro- and nanospheres are synthetic biodegradable polymers that allow for a slow, controlled release of the bound medication. Microparticles incorporating ranibizumab have been developed allowing therapeutic levels of the drug to be present for up to 6 months following a single administration.^{289–291} Emulsion-based drug delivery involves the admixture of a lipid-soluble agent with a drug of interest to extend its duration within the intravitreal space. One example of this approach is the Verisome drug-delivery platform (Icon Bioscience) which involves mixtures of triamcinolone acetate or ranibizumab injected intravitreally. So far this has only been tested in CME from retinal vein occlusions and as adjunctive therapy in ARMD. The Cortiject™ (Santen Pharmaceutical) system involves an injectable dexamethasone prodrug emulsion. Studies of both these agents for DR and DME are still pending.

Another interesting emulsion based, drug delivery system, is the topically applied, antisense oligonucleotide, aganirsen (GS-101, GeneSignal International SA). This inhibitor of insulin receptor substrate-1 expression is able to achieve effective VEGF inhibition at the retinal level for as long as 8 hrs following a single application. Dendrimers, so named because of their unique “hub and spoke” structure of a central core with radiating side chain moieties “dendrons” are very effective hydrophobic drug carriers. So far, they are still being tested at the *in vitro* stage for inhibition of VEGF expression with intravitreally administered antisense oligonucleotide compounds.^{292–296}

Novel ocular injection devices, such as the iTrack microcatheter (iScience Interventional), allow the administration of various medications in the suprachoroidal space to allow for a sequestered, sustained release of drug. Recently, a combination of bevacizumab and triamcinolone was delivered via the iTrack device to the submacular area in a pilot study of patients with chronic ME and HEs.²⁹⁷ There was a significant and sustained improvement in both VA and in resolution of both the ME and HEs in the majority of subjects, with no significant complications for at least 1 year of the start of the study. Another sustained delivery, nonbiodegradable device for triamcinolone is the I-vation intravitreal implant (Surmodics Inc.) with a duration of 2 years. Other approaches to injecting medications into the suprachoroidal space involve devices employing 0.5–1 mm length microneedles such as the CLS1001 (Clearside Biomedical Inc.). An ongoing clinical trial of this device utilizing triamcinolone acetonide is being conducted in patients with noninfectious, uveitic, retinal vein occlusion related ME as well as DME.^{298,299}

Sustained release, refillable devices hold the promise of a more steady and sustained intravitreal drug delivery via an infrequently replenished reservoir. Currently, there are 2 systems being investigated for retinal disease, the Posterior MicroPump™ (Replenish Inc.) and the Port Delivery System (PDS) (ForSight Vision 4 Inc.). Although these devices are currently being investigated for treatment of ARMD, as of yet, there are no ongoing preclinical trials for DR or DME.^{300,301}

Conclusion

New imaging techniques and the ability to identify and quantitate aspects of DR will influence when to initiate treatment and when to re-treat. Pharmacotherapy, both ocular and systemic, has become the primary mode of intervention in the management of DR and DME. Conventional laser therapy has become a secondary intervention in DME, and perhaps will take that role for PDR. Subthreshold laser treatment has promising characteristics, but requires more rigorous investigation. What remains lacking is the optimal integration strategy for these treatment modalities. The goal remains to achieve the greatest reduction in clinical disease, in the shortest time, with the least amount of side effects, with the greatest duration and in the most cost-effective fashion. Testing hypothetical strategies will require sound clinical trials conducted by a consortium of large, independent entities such as the DRCR network.

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