Oral Dextromethorphan for the Treatment of Diabetic Macular Edema: Results From a Phase I/II Clinical Study

David J. Valent¹, Wai T. Wong², Emily Y. Chew¹, and Catherine A. Cukras¹

¹ Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Bethesda, MD, USA
² Unit on Neuron-Glia Interactions in Retinal Disease, National Eye Institute, National Institutes of Health, Bethesda, MD, USA

Correspondence: Catherine A. Cukras, Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Bethesda, MD 20892, USA. e-mail: cukrasc@nei.nih.gov

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Purpose: The activation of microglia, the primary innate immune cell resident in the retina, produces inflammatory mediators, which underlie changes in diabetic retinopathy including increased vascular permeability. This study evaluates the safety and efficacy of dextromethorphan, a drug capable of inhibiting microglial activation, in the treatment of diabetic macular edema (DME).

Methods: A single-center, prospective, open-label phase I/II clinical trial enrolled five participants with macular involving DME who received oral dextromethorphan 60 mg twice daily for 6 months as monotherapy. Main outcome variables included central retinal subfield thickness (CST), best-corrected visual acuity (BCVA), macula sensitivity, and late leakage on fluorescein angiogram (FA).

Results: The study drug was well tolerated. At the primary end point of 6 months, mean CST decreased by \(6.3\%\) and BCVA increased by \(0.6\) letters. Late leakage on FA was scored as improved in four of five study eyes. These findings were not correlated with changes in hemoglobin A1c (HbA1c), creatinine, or blood pressure.

Conclusions: In this proof-of-concept study, dextromethorphan administration as the primary treatment for DME was associated with decreased vascular leakage, suggesting possible therapeutic effects. Additional studies investigating the modulation of microglial activation is warranted.

Translational Relevance: These findings highlight microglial modulation as a potentially useful therapeutic strategy in the treatment of diabetic macular edema.

Introduction

The Centers for Disease Control and Prevention estimates that 29.1 million people in the United States carry a diagnosis of diabetes.¹ Diabetic retinopathy (DR), a common complication of the disease, has an estimated prevalence of 28.5% among diabetics, with 4.4% having vision-threatening DR.² In this latter category, one cause of significant vision loss is diabetic macular edema (DME), a thickening of the retina involving or approaching the center of the macula. Approximately 20% of diabetic patients develop DME within 15 years of diagnosis³ and, if untreated, can lead to irreversible vision loss.⁴,⁵

While the etiology of DR is incompletely understood, there is increasing evidence that inflammatory processes within the retina play an early role in driving disease progression, commencing prior to the onset of pathogenic vascular changes,⁶,⁷ and which can exacerbate the later stages of the disease.⁸ Previous studies have demonstrated that in diabetic eyes, levels of inflammatory mediators are elevated in the aqueous⁹–¹¹ and vitreous.¹²–¹⁴ These mediators are thought to originate principally from the activation of microglia, the primary innate immune cell resident in the retina.¹⁵ These retinal microglial cells have been found in increased numbers in the activated state in human diabetic retinas¹⁶,¹⁷ and animals model of DR.¹⁸–²² Microglial activation in the context of DR has been thought to be triggered by hyperglycemia.²³,²⁴ and the formation of advanced glycation end-products.²⁵,²⁶

The implication of microglial activation in the pathogenesis of DR has led to the concept of
microglial modulation as a therapeutic strategy. Preclinical studies in animal models have demonstrated that modulating microglial activation and reducing inflammatory biomarkers can decrease measures associated with DR progression. As a consequence, approved drugs, such as minocycline and doxycycline, which are capable of inhibiting microglia activation, have been recently evaluated in early phase proof-of-concept clinical trials as therapies that may decrease DR progression or improve DME.

The interest in the therapeutic strategy of microglial modulation has prompted the evaluation of other approved drugs that have been demonstrated to suppress microglial activation, both in retinal diseases, as well as other central nervous system (CNS) diseases in which microglial activation has been associated with neurodegenerative changes. Dextromethorphan, a medication with favorable safety profile and approved as an over-the-counter cough suppressant, has been demonstrated to have anti-inflammatory properties related to the modulation of microglial activation. Dextromethorphan administration in animal models of CNS diseases in which microglial activation features, including Parkinson’s disease, neuropathic pain, traumatic brain injury, multiple sclerosis, and vascular dementia, has shown therapeutic effects associated with decreased microglial activation. Dextromethorphan has also been evaluated in clinical trials for the treatment of Rett syndrome (NCT01520363), a disease featuring aberrant microglia, and neurogenic Retinopathy Study (ETDRS) visual acuity score of 34 letters or better (i.e., 20/200 or better); (2) definite retinal thickening due to DME, based on clinical examination that is not refractory to further therapy based on the investigator’s clinical judgment; (3) retinal thickening due to DME within 3000 µm of the center of the macula, as detected on spectral-domain optical coherence tomography (SD-OCT); and (4) media clarity, pupillary dilation, and patient cooperation sufficient for adequate fundus photographs. Eyes that met any of the following criteria also were excluded from enrollment: (1) macular edema arising from a cause other than DME; (2) presence of an ocular condition that in the opinion of the investigator can limit the improvement of visual acuity, even with the resolution of macular edema; (3) presence of an ocular condition (other than DR) that in the opinion of the investigator might influence macular edema or visual acuity during the course of the study; (4) substantial cataract judged as likely to decrease visual acuity ≥ three lines; (5) history of panretinal scatter photocoagulation (PRP) within 4 months of study enrollment; (6) history of pars plana vitrectomy within 6 months of study enrollment; (7)
history of major ocular surgery within 3 months of study enrollment; (8) history of yttrium aluminum garnet (YAG) laser capsulotomy performed within 2 months of study enrollment; and (9) history of treatment with any drug that has not received regulatory approval within 3 months of study enrollment.

Both eyes of each enrolled participant were evaluated in the study to determine eye eligibility. If only one eye in a participant fulfilled the eye-specific criteria, then that eye was designated the “study eye.” If both eyes met eligibility criteria, the treatment-naive eye was designated as the “study eye,” and the other eye designated the “qualifying fellow eye.” If both eyes were naïve to treatment, the eye with the higher visual acuity score was designated as the “study eye.” Data from all study eyes and qualifying fellow eyes were analyzed.

Study Drug

Dextromethorphan hydrobromide (USP Powder; Ruger Chemical Co., Inc, Warren, NJ) was obtained by the NIH Clinical Center Pharmacy. The NIH Clinical Center Pharmacy compounded the drug to formulate a capsule containing 60 mg dextromethorphan and included the inactive ingredients microcrystalline cellulose, NF (Avicel PH 102, FMC BioPolymer, Philadelphia, PA) and croscarmellose sodium, NF (Ac-Di-Sol, JRS Pharma, LP, Patterson, NY). Participants were instructed to take one capsule orally two times a day, once in the morning and once in the evening approximately 12 hours apart. The exception to this was on the day of the baseline visit, in which participants took only the evening pill.

Study drug compliance was monitored during the study. Participants were asked to record study drug administration using a “pill diary” and to return any unused study medication. Compliance data were measured from a review of the pill diary at each study visit and from study drug accounting of unused medication. Unused study drug was returned to the NIH Research Pharmacy.

Study Design and Procedures

Five participants with DME were enrolled into the study according to the study eligibility criteria and were treated with dextromethorphan 60 mg orally twice daily for up to 24 months. Study visits were scheduled at baseline, month 1, month 2, and every 2 months thereafter until month 24. Additional ad hoc visits were permitted as clinically warranted. Participants were evaluated at the baseline study visit with a medical history, review of systems, medication assessment, and serum blood analysis including HbA1c, complete blood count, electrolyte analysis, and liver function tests. Serum blood analyses were repeated at month 2 and every 4 months thereafter. Review of systems, AE assessment, and urine pregnancy testing (for female participants of childbearing age) were performed at each study visit. Participants were evaluated at each study visit with a complete ophthalmic examination that included bilateral assessment of best-corrected visual acuity (BCVA), intraocular pressure measurement, and stereoscopic fundus examination. Best-corrected distance visual acuity was assessed using a standard ETDRS protocol and scored using the ETDRS logarithm of the minimum angle of resolution (logMAR) visual acuity chart.

SD-OCT imaging (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA) was obtained in both eyes of each participant at each study visit using the 512 × 128 scan pattern with the center of the 6 × 6-mm scanning area positioned at the center of the macula. Quantitative longitudinal scan analysis was performed by first aligning the scans spatially using functions provided within the OCT instrument software (Carl Zeiss Meditec) and manually verified. The accuracy of automated delineations of the inner and outer retinal boundaries was also manually verified and corrected if needed. OCT retinal thickness measurements in the macula were analyzed using a circular ETDRS-type grid positioned on the center of the fovea. Mean thickness measurements for the central subfield (central circle of diameter 1 mm) and for the four “inner” quadrants (circumscribed by a circle 3 mm in diameter, concentric to the central region and divided into superior, inferior, nasal, and temporal quadrants) were calculated. The volume of the retina summed over all five subfields, termed central macular volume (CMV), was also computed in units of cubic millimeters.

Microperimetry was performed using the MP-1 microperimeter (NAVIS software, version 1.7.1; Nidek Technologies, Fremont, CA). Assessments were performed as previously described in the study eye only. The follow-up testing feature in the testing software (NAVIS software, version 1.7.1; Nidek Technologies) was used in testing following baseline visit. Macular mean sensitivity (dB) of all responding points (central circle radius 10°) as well as all testing points in the central radius of 5° was calculated in the study eye. Imaging by color fundus
photography and fluorescein angiography (FA) was obtained using a standard digital imaging system (Ophthalmic Imaging Systems, Inc., Sacramento, CA) in both eyes of each participant at baseline and at month 6, month 12, month 18, and month 24.

Study Outcomes

The primary outcome of the study is the change in retinal thickness as measured by OCT at month 6 compared to baseline. Secondary outcome measures include changes in BCVA, changes in mean macular sensitivity as measured by microperimetry, and changes in fluorescein leakage in the macula as demonstrated by FA. Participant’s late (~10 minutes) baseline and month 6 fluorescein angiograms were assessed for change by three of the authors (W.W., E.C., and C.C.) who had been masked to image assignment.

Beginning at the month 4 visit, participants were assessed for worsening disease defined as loss of ≥15 ETDRS letters of vision compared to baseline or a ≥50% increase in total CST as measured by OCT. Additionally, beginning at the month 6 visit, study eyes were eligible for treatment, with either focal laser or anti-VEGF injections (bevacizumab or ranibizumab) if they had center-involving macular edema. Fellow eyes were eligible to receive standard of care therapy for DME at any point during the study.

Results

Baseline Characteristics of Study Participants

Five participants were enrolled between July 2012 and December 2013 who completed scheduled study visits up to month 6. An additional two participants were enrolled but had withdrew <2 months following enrollment for reasons unrelated to any IP-associated adverse events (AEs). The baseline demographic and medical characteristics are summarized in Table 1. Participants ranged in age from 47 to 64 years (56.8 ± 6.5 years, mean ± SD) and had been diagnosed with diabetes for an average of 21.6 years (3–50 years, range) at study baseline. Baseline HbA1c values ranged from 6.7% to 9.9% (7.96% ± 1.19%, mean ± SD). Four of five participants had a history of hypertension, four of the five were on insulin therapy, and four of the five had a history of hypercholesterolemia.

Baseline ocular characteristics of study participants are summarized in Table 2. Visual acuity in study eyes ranged from 65 to 85 letters (approximately 20/20 to 20/50), with a mean of 75.0 ± 9.8 letters (Snellen equivalent 20/32). Three of the five study eyes had previously been treated with focal laser; four of five eyes had received prior treatment with intravitreal bevacizumab; one of five eyes had received prior treatment with intravitreal ranibizumab, three of five eyes had been treated with panretinal photocoagulation (PRP); and one of five eyes received a subtenon triamcinolone injection. All previous treatments were administered at least ≥3 months prior to baseline visit. For the three participants who had previously been treated with focal laser: participant 2 received treatment with focal laser at 7 months prior to entering the study, participant 3 received focal laser 4 months prior to entering the study, and participant 5 received focal laser 18 months prior to entering the study. Mean central retinal thickness (CST) at baseline in the study eye
ranged from 298 to 438 µm (335 ± 67.8 µm, mean ± SD).

**Follow-up of Study Participants During the Study**

Study eyes were treated solely with IP through month 6 and did not meet criteria for adjunctive treatment. In the fellow eyes of study participants, participant 2 had a prior history of a central retinal vein occlusion, which required treatment with an intravitreal triamcinolone injection at the month 2 study visit, while participant 1 required an intravitreal injection of bevacizumab at the month 4 study visit in the fellow eye owing to a worsening of DME present at baseline. Both of these fellow eyes were excluded from analysis at the month 6 primary outcome time point. The remaining five study eyes and three qualifying fellow eyes had no adjunctive treatment up to the month 6 time points and were included in subsequent qualifying-eye analyses.

**Ocular and Systemic Safety of Study Drug**

The study drug was generally well tolerated. A total of 14 AEs were recorded between the baseline to month 6 visits (Supplementary Table S1). All but two AEs were mild in severity: one moderate AE involved an episode of hypoglycemia, and one severe AE involved a vitrectomy for a nonclearing vitreous hemorrhage in a study eye. Both AEs were considered
Changes in OCT Macular Thickness

The primary outcome measure of the study was change in macular thickness as measured by OCT at month 6 relative to baseline. The central horizontal B-scans traversing the fovea are shown for all study visits from baseline to month 6 (Fig. 1). The retinal thickness maps for baseline and month 6 are compared for all eyes analyzed. Three of five study eyes demonstrated a clear decrease in macular thickness; one study eye showed increased edema, and one study eye showing a redistribution of areas of edema (Fig. 1). Macular thickness measurement changes at month 6 in the fellow qualifying eyes were varied, with eyes showing both improvement and worsening (Fig. 2).

We also performed macular thickness analysis on areas of macular edema beyond the five central subfields of the ETDRS grid. Study eyes of participants 2 and 4 had areas of macular edema in the temporal macula that were followed quantitatively between baseline and month 6 by repositioning the ETDRS grid to center on the area of temporal macular edema (Fig. 3). The area of temporal macular edema in the study eye of participant 2 demonstrated improvement and participant 4 showed mild reductions in thickness.

Figure 1. Longitudinal record of central macular thickness in study eyes (*n* = 5) as evaluated by SD-OCT. (Upper panels) Horizontal B-scans traversing the center of the fovea are shown for all study visits from baseline to month 6. (Lower panels) Topographic maps of macular thickness at baseline and month 6 with a superimposed ETDRS grid centered on the fovea. The numbers in the grid depict mean retinal thickness in each subfield in micrometers. Study eyes in participants 1, 3, and 5 demonstrated a decrease in overall macular thickness at month 6 relative to baseline. The study eye in participant 2 showed in redistribution in the position of macular edema, while that in participant 4 showed an increase in central edema.

unrelated to the study drug. No other ocular AEs were reported.
Quantitative longitudinal changes in CST from baseline are depicted in Figure 4. Of the eight study $(n = 5)$ and qualifying fellow eyes $(n = 3)$, four eyes showed decreased CST while four eyes demonstrated increased CST from baseline (Figs. 4A, 4C). Participants 1 and 5 showed decreases in CST in their study eyes at all study visits up to month 6. Participant 3 showed a decrease in CST in their fellow eye at all visits up to month 6. Two of the five study eyes showed a 15% or greater improved in CST at 6 months when compared with baseline and no study eye had a 15% or great worsening in CST at 6 months when compared with baseline. Mean percentage change in CST from baseline were also averaged across all study eyes $(n = 5)$ and all qualifying eyes $(n = 3)$ (Fig. 4B). Results showed a general decrease across all time points for study eyes and minimal overall changes for all qualifying eyes. At month 6, the mean percentage change in CST from baseline was $-6.3\% \pm 6.8\%$ (mean $\pm$ SEM) for the study eyes and $+0.1\% \pm 6.2\%$ (mean $\pm$ SEM) for all qualifying eyes. We also analyzed changes in macular edema beyond the central 1-mm subfield. Mean percentage change from baseline in CMV, defined as the overall retinal volume within the 3-mm diameter circle of the ETDRS grid, was computed for all time points up to month 6 (Fig. 4D). Changes in CMV were similar in trend as those for CST, with a mean percentage change in CMV from baseline in the study eye of $-1.8\% \pm 3.6\%$ (mean $\pm$ SEM) and $-0.1\% \pm 2.3\%$ (mean $\pm$ SEM) in qualifying eyes.

**Changes in BCVA**

Figure 5A shows the change in BCVA from baseline in both the study eyes and fellow eyes at each study visit through month 6. Participant 1 had...
an improvement in BCVA in the study eye at all study visits from baseline. All other study eyes and qualifying fellow eyes had either no change or a mild decrease in BCVA at month 6 relative to baseline. Altogether, one of the five study eyes had a greater than 15 letter visual acuity gain at month 6 when compared with baseline and no study eyes or qualifying fellow eye lost greater than 15 letters in BCVA at 6 months when compared with baseline.

Figure 5B illustrates the mean change in BCVA relative to baseline. At month 6, the mean change in BCVA from baseline was \(0.6 \pm 5.11\) (mean \(\pm\) SEM) letters for study eyes \((n = 5)\), \(-0.33 \pm 1.85\) (mean \(\pm\) SEM) letters for fellow eyes \((n = 3)\) and \(+0.25 \pm 3.12\) letters (mean \(\pm\) SEM) for all qualifying eyes \((n = 8)\).

Changes in Macular Sensitivity As Measured by Microperimetry Testing

Microperimetry was followed in the study eye at baseline and month 6. Changes in the mean sensitivity for the entire central radius \(10^\circ\) and the central radius \(5^\circ\) at 6 months compared to baseline is shown in Figure 6. Mean sensitivity changes were small (less than 2 dB) for most participants except participants 3 and 5, which demonstrated changes in both mean changes greater than 2 dB (Fig. 6A). Participant 3 who demonstrated the largest drop in mean sensitivity was noted to have a vitreous hemorrhage at his month 6 study visit.

Changes in Retinal Vascular Permeability on FA

FA was obtained in all study participants at baseline and at month 6. Late phases (at \(\sim 10\) minutes) of the angiograms compared and analyzed in study eyes and qualifying fellow eyes between baseline and month 6 (Fig. 7). The change in the area of late leakage at month 6 was graded by three masked graders as being either: (1) decreased, (2) increased, or (3) unchanged from baseline. Four of the five study eyes were graded as having decreased leakage; the remaining study eye in participant 3 had developed a vitreous hemorrhage, and could not be graded. In the three qualifying fellow eyes, one eye (participant 4) was graded as having decreased leakage. In the remaining two eyes, grades were nonuniform; one (participant 3) was graded as unchanged by two out of three graders, while the other (participant 5) was graded as being decreased in leakage by two out of three graders.

Correlation of OCT Changes to Other Patient Characteristics

Changes in systemic measures and their relationship to changes in BCVA and OCT CST are tabulated in Supplementary Table S2. Mean chang-
Figure 4. Changes in macular thickness measurements from baseline in study and qualifying fellow eyes. (A) Percentage changes in CST (measured in the 1-mm diameter central subfield) from baseline are shown for individual study eyes (left, n = 5) and qualifying fellow eyes (right, n = 3). Each histogram column shows the percentage change in CST at all study visits (months 1, 2, 4, and 6) arranged in consecutive order. (B) Mean percentage change in CST for all study eyes (left, n = 5) and all qualifying eyes (right, n = 8) at all study visits. (C) CST (measured in the 1-mm diameter central subfield) are shown for individual study eyes (left, n = 5) and qualifying fellow eyes (right, n = 3). Each histogram column shows the CST at all study visits (baseline, months 1, 2, 4, and 6) arranged in consecutive order. (D) Mean percentage change in CMV (measured in the 3-mm diameter central subfields) for all study eyes (left, n = 5) and all qualifying eyes (right, n = 8) at all study visits. Column heights indicate means and error bars indicate standard error.

Figure 5. Change in BCVA from baseline in study and qualifying fellow eyes. (A) Changes in BCVA (letters) from baseline are shown for individual study eyes (left, n = 5) and qualifying fellow eyes (right, n = 3). Each histogram column shows the percentage change in CST at all study visits (months 1, 2, 4, and 6) arranged in consecutive order. (B) Mean change in BCVA for all study eyes (left, n = 5) and all qualifying eyes (right, n = 8) at all study visits. Column heights indicate means and error bars indicate standard error.
es from baseline to month 6 in serum creatinine
($-0.03 \pm 0.2 \text{ mg/dL, mean} \pm \text{SD}$), HbA1c ($0 \pm 0.4\% \text{, mean} \pm \text{SD}$), and diastolic blood pressure
($+0.4 \pm 4.1 \text{ mm Hg, mean} \pm \text{SD}$) were minimal. Changes in systolic blood pressure measurements
($+5.2 \pm 17.5 \text{ mm Hg, mean} \pm \text{SD}$) were more
varied; participant 1 had a 24 mm Hg decrease in systolic blood pressure at 6 months when compared with baseline. All other participants had an increase in systolic blood pressure at month 6 when compared with baseline. There was no consistent trend relating the CST changes to changes in

![Figure 6](image)

**Figure 6.** Changes in macular sensitivity measured using MP-1 microperimetry. (A) Changes of mean sensitivity from baseline to month 6 for each study eye (central radius 10°, dark column; central 5°, white columns). (B) The average change in macular sensitivity from baseline to month 6 for all study eyes (central radius 10°, dark column; central 5°, white columns).

![Figure 7](image)

**Figure 7.** Changes in retinal vascular leakage in late phase fluorescein angiograms from baseline and month 6 in study and qualifying fellow eyes. Late phases fluorescein angiograms in (A) study eyes ($n = 5$) and (B) qualifying fellow eyes ($n = 3$) were obtained and compared at baseline and month 6.
systemic findings of HbA1c, serum creatinine, or blood pressure measurements.

Discussion

This prospective phase I/II proof of concept study achieved a high drug adherence rate (97.6 ± 2.5%, mean ± SD, range 94.1%–100.3%) among study participants treated with oral dextromethorphan at doses of 60 mg twice daily. The study drug appeared to be well-tolerated, with minimal drug-related AEs. The one ocular complication was a vitreous hemorrhage and was felt to be unrelated to the study medication, but rather a result of disease progression. At month 4, no study participants met criteria for disease worsening, and they were thus treated with dextromethorphan as monotherapy for the 6 months of follow-up. Two participants required adjuvant therapy in the fellow eye, one for worsening DME and the other for macular edema related to a central retinal vein occlusion that occurred prior to study enrollment.

From baseline to month 6, the primary outcome measure of mean central macular thickness decreased in three study eyes and remained similar or redistributed in the other qualifying eyes. Visual acuity improved 15 letters in one study eye but, on average, there was little change in visual acuity. Visual acuity improvement in both study and fellow eyes may have been difficult to achieve due to excellent baseline visual acuity (mean of 75.0 letters [≈20/32]). Three of the five study eyes were 20/25 or better at baseline and all three qualifying fellow eyes treated only with oral dextromethorphan had a baseline visual acuity of 20/25 or better.

Masked grading of the fluorescein angiograms demonstrated the most consistent findings of decreased leakage with four out of the five study eyes and six out of the eight qualifying eyes graded as having a decrease in late leakage at 6 months. When examining study eyes, improvement of late leakage on FA was associated with modest improvements in central subfield thickness on OCT. However, these changes did not correlate improvements on visual acuity testing. In qualifying eyes, improvement on late FA leakage was not associated with significant improvements on mean central subfield thickness or mean change in BCVA at 6 months.

Increases in vascular permeability have been related to a number of inflammatory mediators, many of which can be produced by activated retinal microglial.20,52–54 The observation of reduced late leakage in many eyes may be related to the potential ability of the study drug to reduce abnormal vascular permeability in the setting of DME. In a similarly designed study, orally administered minocycline was investigated as a proof of concept intervention also targeting microglial activation in the setting of DME.33 In that pilot study, oral minocycline also appeared to have potential efficacy in associated with a decrease in vascular leakage as determined by FA and was also was associated with increasing visual acuity and reducing macular edema in a progressive time dependent manner.33 These changes were not associated with concurrent changes in systemic factors and were suggestive of a treatment effect that was secondary to the study drug.

As this study represents a small, uncontrolled, proof-of-principle study, an obvious limitation is a lack of a comparison control group. Historical controls provide some context to view and interpret the data presented here. In the safety and efficacy of ranibizumab in DME with center involvement (RE-SOLVE) study, a sham group of 49 eyes was included and followed over 12 months with rescue laser available after 3 months with 35% of the eyes receiving one to two laser treatments.55 A planned interim analysis at 6 months included 17 eyes from the sham group. Over 6 months, these eyes demonstrated an increase in central macular edema from 4% to 15%. Over 12 months, the 49 sham eyes demonstrated a mean change in visual acuity of −0.1 ± 9.8 letters. The macular edema reduced over 12 months by −48.4 ± 153.4 microns (approximately 10% of baseline values).

The sham groups from the pair of phase III studies, ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus (RISE) and the phase III study of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus (RISE) provide additional data from control groups for consideration. In the RISE study, 127 eyes were randomized to sham treatment and in RIDE, 130 eyes were randomized to sham treatment. The eyes were eligible for macular focal/girdle rescue laser treatment and did receive on average 1.8 laser treatments. In RISE, the study eyes demonstrated an improvement of central macular thickness (by 133 microns) over 24 months and eyes in the sham group in RIDE demonstrated a reduction by 125.9 microns, with visual acuity gains of 2.6 and 2.3 letters, respectively.56 The strategy of microglial modulation in the
treatment of DR has now been investigated for doxycycline, minocycline, and now dextromethorphan. While large and comprehensive treatment effects have not been observed in these studies, some modest signal involving improvements in functional and anatomical measures was detected. Larger randomized clinical trials will be required to substantiate these effects. These anti-inflammatory treatments, administered systemically on a daily basis, were well-tolerated and were associated with fewer AEs than anti-inflammatory treatment in the form of local administration of steroid medications. Anti-VEGF therapy for DME can improve anatomical and functional outcomes by neutralizing VEGF-driven effects, but are unlikely to address the continued production of increased VEGF in the eye. As such, ancillary anti-inflammatory approaches in a combinatorial approach with anti-VEGF agents may help optimize outcomes.

While the mechanisms through which dextromethorphan exerts in vivo neuroprotective effects are incompletely elucidated, they have been related to its ability to act as an antagonist to N-methyl-D-aspartate (NMDA) receptors and voltage-gated calcium channels, and as an agonist to sigma-1 receptors. These molecular effects may provide protection directly by acting on neurons or oligodendroglia, but multiple studies have indicated that they may do also via the modulation of microglial activation, although individual reports differ on whether the above agonist/antagonist actions are involved. Other in vitro studies have indicated that dextromethorphan may indeed act directly on microglia cells via direct inhibition of NFKB signaling, reducing microglial production of proinflammatory factors (tumor necrosis factor alpha (TNFα), interleukin 1 beta (IL-1β), interleukin 6 (IL-6)), and NO, thereby conferring neuroprotective effects. Additional studies have also described the ability of dextromethorphan to inhibit superoxide production via the suppression of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase activity, possibly by inhibiting voltage-gated proton currents.

The general therapeutic strategy of modulating microglial activation in retinal disease has been a topic of increasing recent interest, with particular consideration of its application in the treatment of DR. However, the specific approaches to microglial modulation are varied, ranging from a generalized blunting of microglial activation with agents such as steroids, to the targeting of specific molecular pathways underlying microglial function (e.g., translocator protein [TSPO] signaling) or microglial effector functions (e.g., specific forms of cytokine signaling). The choice of the ideal approach will likely arise from a deeper understanding of the role that microglia play in each pathologic context, and early clinical trial data regarding the safety and potential efficacy of candidate agents.

The limitations of the current study include its small size, its open-label design, and the presence of unrelated complicating findings in some of the study participants. The potentially therapeutic effects observed in the study may also have been limited by the bioavailability of dextromethorphan in the retina related to its administration. In the repurposing of dextromethorphan for the treatment of pseudobulbar effect in patients with CNS disorders, the bioavailability of dextromethorphan in the CNS was increased by the co-administration of quinidine sulfate, which inhibited the rapid first-pass metabolism of dextromethorphan, and produced superior therapeutic effects compared to dextromethorphan administered alone. This drug combination, which is now approved for the treatment of pseudobulbar effect, may be considered for evaluation in future DME trials.

In summary, the findings of this pilot proof of concept study indicate a therapeutic effect on abnormal retinal vascular permeability evident as late leakage on FA in patients treated with dextromethorphan monotherapy for six consecutive months. Additional studies into anti-inflammatory approaches involving the modulation of microglial activation may be of benefit in discovering combinatorial treatment paradigms for DME that optimize outcomes and decrease treatment burden.

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