Effects of Topically Administered Neuroprotective Drugs in Early Stages of Diabetic Retinopathy: Results of the EUROCONDOR Clinical Trial

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Diabetes 2019;68:457–463 | https://doi.org/10.2337/db18-0682

The primary objective of this study was to assess whether the topical administration of two neuroprotective drugs (brimonidine and somatostatin) could prevent or arrest retinal neurodysfunction in patients with type 2 diabetes. For this purpose, adults aged between 45 and 75 years with a diabetes duration ≥5 years and an Early Treatment of Diabetic Retinopathy Study (ETDRS) level of ≤35 were randomly assigned to one of three arms: placebo, somatostatin, or brimonidine. The primary outcome was the change in implicit time (IT) assessed by multifocal electroretinography between baseline and at the end of follow-up (96 weeks). There were 449 eligible patients allocated to brimonidine (*n* = 152), somatostatin (*n* = 145), or placebo (*n* = 152). When the primary end point was evaluated in the whole population, we did not find any neuroprotective effect of brimonidine or somatostatin. However, in the subset of patients (34.7%) with preexisting retinal neurodysfunction, IT worsened in the placebo group (*P* < 0.001) but remained unchanged in the brimonidine and somatostatin groups. In conclusion, the topical administration of the selected neuroprotective agents appears useful in preventing the worsening of preexisting retinal neurodysfunction. This finding points to screening retinal neurodysfunction as a critical issue to identify a subset of patients in whom neuroprotective treatment might be of benefit.

Diabetic retinopathy (DR) is classically considered a microvascular disease. However, growing evidence suggests that abnormalities in retinal function can be detected in

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Received 19 June 2018 and accepted 21 October 2018

Clinical trial reg. no. NCT01726075, clinicaltrials.gov

This article contains Supplementary Data online at http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db18-0682/-/DC1.

*A list of the participants for the European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR) is included in the Supplementary Data online.

patients without any evidence of microvascular abnormalities (1,2). In addition, that diabetes-induced retinal dysfunction might contribute to the development of microvascular abnormalities has been suggested (2). Therefore, it is reasonable to hypothesize that therapeutic strategies aimed at neuroprotection may also be effective in preventing the development and progression of microvascular disease. In fact, there is experimental evidence to support this concept (3,4).

In the early stages of diabetes, a high proportion of patients present deficiencies such as decreased hue discrimination and contrast sensitivity, delayed dark adaptation, abnormal visual fields, and impairment of vision-related quality of life (5–7). Therefore, neuroprotection itself can be considered a therapeutic target independently of its potential to prevent the development or progression of microangiopathy (8).

A number of therapeutic strategies based on the main pathogenic mechanisms involved in neurodegeneration have been proposed (9). On one hand, systemic administration of drugs blocking these pathways is very unlikely to reach the retina at pharmacological concentrations and, in addition, could have serious adverse effects. On the other hand, if the early stages of DR are the therapeutic target, aggressive treatments such as intravitreal injections would be unacceptable. Topical treatment with neuroprotective agents in the form of eye drops has been neglected as a possible option because of a general assumption that the posterior chamber of the eye cannot be reached by this route. However, there is emerging evidence that several peptides administered by eye drops are able to reach the retina in pharmacological concentrations, at least in animal models (3,10–13). Topical administration has the advantage of concentrating drug action to the eye while potentially minimizing systemic effects.

On this basis we conducted the first clinical trial aimed at evaluating the effects of topically administered neuroprotective agents in patients with diabetes with no or mild DR. The selected drugs were brimonidine and somatostatin, which have already shown their neuroprotective action in preclinical studies (11,14). The primary objective was to assess whether these drugs administered topically would be able to prevent or arrest neurodegeneration as assessed by multifocal electroretinography (mfERG). The main secondary objectives were to evaluate their safety and examine their potential effect on the development or progression of DR in terms of microvascular disease.

RESEARCH DESIGN AND METHODS

Study Design and Participants

In this randomized, placebo-controlled, phase II-III trial of parallel groups, a total of 450 patients with type 2 diabetes were enrolled at 11 European centers belonging to the European Consortium for the Early Treatment of Diabetic Retinopathy (EUROCONDOR) consortium. The trial (NCT01726075) was funded by the European Commission Seventh Framework Programme. The protocol (Supplementary Data) was approved by the local research ethics committee at each site. All participants provided their written informed consent.

Eligibility criteria were age between 45 and 75 years, a diagnosis of type 2 diabetes with a known duration $\geq$5 years, and an Early Treatment for Diabetic Retinopathy Study (ETDRS) level of $\leq$35. Exclusion criteria were previously detailed (15).

Randomization and Masking

Eligible patients (n = 449) (Supplementary Fig. 1) were randomly allocated in a 1:1:1 ratio to placebo, somatostatin 0.1%, or brimonidine tartrate 0.2% (one drop b.i.d. in each eye in all cases). Randomization was based on a minimization algorithm that balanced the three groups, stratified by ETDRS level ($<$20 vs. 20–35).

Procedures

Each patient underwent a comprehensive ophthalmic examination as previously reported (15). Only one eye from each patient was included in the study. If both eyes met the inclusion criteria, one eye was chosen randomly.

mfERG Recording and Analysis

The mfERGs were recorded in the study eye using the RETI-port/scan21 (Roland Consult, Berlin, Germany) visual electrophysiology system. Detailed information regarding the methodology used has been previously reported (15).

Optical Coherence Tomography Imaging and Analysis

Spectral domain–optical coherence tomography (SD-OCT) images were acquired according to standardized protocols by CIRRUS HD-OCT (Zeiss Meditec) or by Topcon 3D-OCT 2000 (Topcon Corporation), henceforth designated as Topcon, depending on the equipment available at each site. A total of 284 patients underwent CIRRUS HD-OCT imaging, and 165 patients underwent Topcon 3D-OCT 2000 imaging. Further details on the methodology have been previously reported (15).

Follow-up, Outcome Measurements, Adverse Events, and Compliance

Patients were monitored and treated during a 96-week period. Study visits were scheduled as detailed in the protocol (Supplementary Data) every 24 weeks.

The presence of neurodysfunction was defined as an eye with six or more altered hexagons for implicit time (IT) (16). An altered hexagon was defined as a hexagon with a z-score of 2 or higher for IT compared with a normative database that was previously created (17).

The primary outcome was the change in the IT assessed by mfERG (between baseline and the end of follow-up).

Secondary outcomes were other neurodegenerative variables (thickness of the retinal nerve fiber layer and ganglion cell layer assessed by SD-OCT), microvascular

variables (microaneurysm turnover assessed by color fundus photography, central retinal thickness assessed by SD-OCT, DR severity assessed by the ETDRS scale, best corrected visual acuity (BCVA) assessed by the ETDRS scale, and visual field defects assessed by the Visual Fields Test.

Safety evaluation included assessment of intraocular pressure, BCVA, conjunctival redness, biomicroscopy, visual fields, blood pressure, heart rate, and laboratory safety variables (i.e., blood count and blood biochemistry). Reported adverse events, such as overall drop discomfort, were also recorded.

A compliance of 60% was considered appropriate for this study. If compliance was below 60% or patients interrupted the study medication for more than 1 month, they were not evaluable for efficacy.

Sample Size Calculation

Assuming that, at the end of the study, the placebo group would present 50% of abnormal mfERG IT vs. 30% in the patients receiving the active drugs, the number of patients required in each group to demonstrate neuroprotection would be 93. However, because the progression of microvascular changes was also going to be analyzed, the progression rate for patients with very early ETDRS stages at study entry needed to be taken into account. Therefore, assuming that 30% of these patients would present some degree of worsening during the follow-up and that active therapy would reduce this figure to 15%, the number of patients required in each arm was 120. These estimates were performed to assess the efficacy of the neuroprotective drugs (somatostatin or brimonidine) versus placebo with a two-sided risk level of 0.05 and a statistical power of 80%. Taking into account a dropout rate of 20%, the final number of patients to be included in each arm would be 150.

Statistical Analyses

For primary analyses (efficacy), we did the analyses per protocol (restricted to participants who completed the study) and by intention to treat. Prespecified analyses for both the prevention and progression of neurodysfunction were performed. No imputations were done for missing data. The safety analysis population included the subjects who received at least one dose of study treatment.

Statistical analysis was performed by TechnoSTAT (www.technostat.co.il) in close collaboration with the statistical team from the Association for Innovation and Biomedical Research on Light and Image (AIBILI) and Vall d'Hebron Institute of Research (VHIR). We used the two-tailed paired or independent samples Student *t* test and ANOVA for continuous variables. Mixed-effect linear regression models adjusted by HbA_{1c} were performed to evaluate IT progression during follow-up. The association between categorical variables was examined with the χ^2 test. Data are expressed as mean ± SD for continuous data and as percentages for categorical data. All analyses were done with SAS 9.4 software under Windows 2008 Terminal.

RESULTS

Baseline Characteristics and Dropouts

Between 5 February 2013 and 6 November 2013, 449 eligible patients with type 2 diabetes were randomized. The characteristics of the treatment groups at randomization were well balanced in age, HbA_{1c}, and cardiovascular risk factors, as previously reported (15).

According to the predefined criteria of this study, we found only 156 patients (34.7%) with mfERG abnormalities at baseline (patients with neurodysfunction).

During the 2 years of follow-up, a 24% (n = 109) dropout rate was observed, occurring mainly in the 1st year (Supplementary Fig. 2). The characteristics of patients included in the analysis of efficacy per protocol according to treatment are reported in Table 1.

Safety

Detailed information of serious adverse events is shown Supplementary Tables 1 and 2. Only one serious adverse event (ocular hyperemia) was considered related to the investigational drugs (brimonidine). The most frequent ocular adverse events are detailed in Supplementary Table 3. Brimonidine had more frequent adjudicated ocular adverse events.

Effectiveness

We did not find any significant effect of brimonidine or somatostatin compared with placebo on the number of abnormal hexagons during follow-up in the whole population when the analysis was performed per protocol (P = 0.75) (Table 2) or by intention to treat (P = 0.24).

Prespecified subanalyses were performed separately to examine the effects of the neuroprotective drugs in preventing neurodysfunction or arresting its progression. When patients without neurodysfunction at baseline were analyzed, we did not find significant differences in the incidence of neurodysfunction at the end of the study. In contrast, somatostatin and brimonidine were both able to arrest the progression of preexisting neurodysfunction. Therefore, in those patients in whom some degree of neurodegeneration was already present (six or more abnormal hexagons at the baseline), somatostatin and brimonidine were effective in preventing the increase of the mean IT that was observed in the placebo group (Fig. 1*A*). However, when patients were analyzed by intention to treat, a clear tendency to increasing the IT in the placebo group was also observed but did not reach statistical significance (P = 0.06) (Fig. 1*B*).

It is worth mentioning that there were no differences between the groups regarding the mean HbA_{1c} during the trial. Therefore, our findings are not influenced by differences in glycemic control (Supplementary Tables 4 and 5).

Table 1—Baseline characteristics of patients with type 2 diabetes included in the analysis per protocol

	Placebo n = 123	Brimonidine n = 97	Somatostatin n = 120
Age (years)	62.4 ± 7.1	63.7 ± 6.0	62.6 ± 6.6
Male sex	66.1	66.0	65.0
BMI (kg/m^2)	30.8 ± 5.6	30.8 ± 5.3	31.1 ± 5.4
Diabetes duration (years)	11.6 ± 5.8	11.1 ± 5.5	11.4 ± 5.5
Diabetes treatment			
Diet	4.8	2.1	4.2
Oral agents	65.3	76.3	73.3
Oral agents + insulin	24.2	21.6	20.8
Insulin	5.6	0.0	1.7
HbA_{1c} (%)	7.21 ± 0.97	7.22 ± 1.09	7.11 ± 0.92
Hypertension	71.0	73.2	71.7
Dyslipidemia	69.4	67.0	67.5
Micro/macroalbuminuria	19.3	22.7	19.1
Cardiovascular disease	19.4	14.4	21.7
ETDRS			
<20	42.7	38.1	43.3
20–35	57.3	61.9	56.7
BCVA letter score	85.9 ± 5.2	86.1 ± 5.2	85.7 ± 4.6

Data are presented as mean ± SD or as the percentage of subjects.

Regarding the main prespecified secondary objectives, we did not find any effect of brimonidine or somatostatin in preventing or arresting microvascular disease.

Analyses of SD-OCT data revealed no difference in retinal thickness between the placebo, brimonidine, or somatostatin arms at study entry or during follow-up (Table 3).

DISCUSSION

The concept of DR as microvascular disease has evolved into that of a more complex diabetic complication in which neurodegeneration plays a significant role (8). In fact, the American Diabetes Association recently defined DR as a highly specific neurovascular complication (18). This is the first clinical trial using neuroprotective drugs for treating DR. We found that eye drops containing neuroprotective agents (brimonidine or somatostatin) did not exert any apparent effect in terms of primary prevention of neurodysfunction or in modulating the appearance and progression of microvascular disease, at least over 2 years of follow-up and using the methodology previously described. In the subgroup of patients with preexisting retinal dysfunction, the agents tested were able to arrest the progression of IT only in patients who completed the study without any major protocol violations (per protocol). Overall, our results suggest that topical administration of somatostatin or brimonidine failed in achieving the primary end point of this clinical trial. However, the subset of patients with neurodysfunction could be envisaged as a promising target population in future clinical trials designed to elucidate this issue. The lack of effectiveness in preventing neurodysfunction could be attributed to the short follow-up (2 years) and to the excellent metabolic control of the patients included in the study.

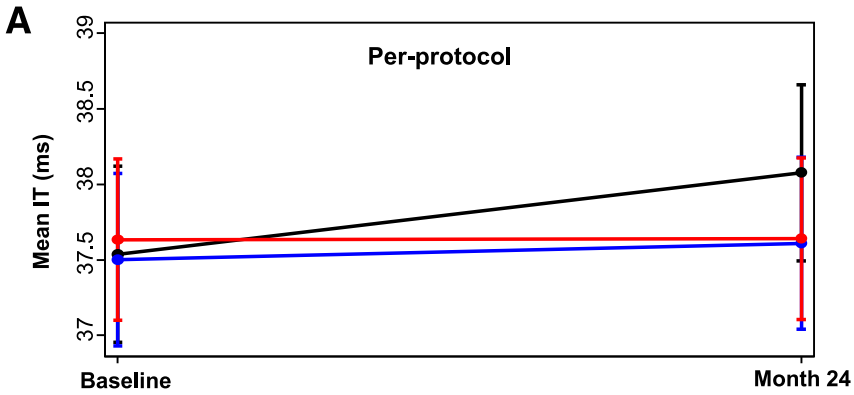
Table 2—Effect of the investigational drugs on the number of abnormal hexagons assessed by mfERG

	n	Patients in whom abnormal hexagons did not increase compared with baseline	Patients in whom abnormal hexagons increased compared with baseline
Placebo	123	69 (56.1)	54 (43.9)
BRIM	97	48 (49.5)	49 (50.5)
SST	120	55 (45.8)	65 (54.2)

Data are presented as n (%). BRIM, brimonidine; SST, somatostatin. BRIM vs. placebo: P = 0.29; SST vs. placebo: P = 0.11.

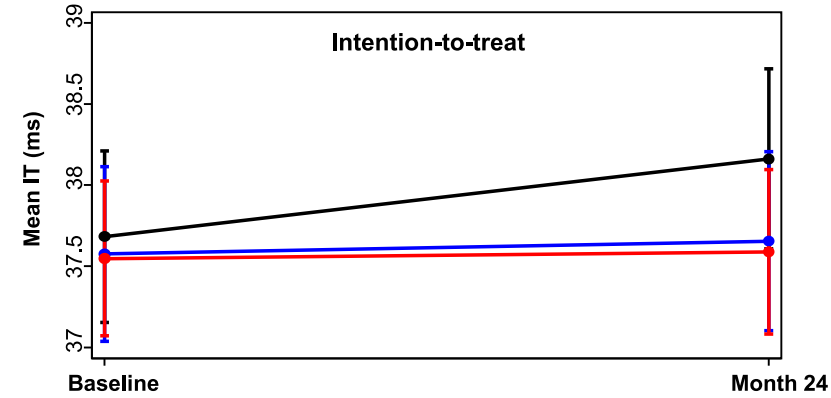
The mechanisms by which brimonidine and somatostatin arrest the progression of neurodysfunction remain to be fully elucidated. Brimonidine has been shown to effectively promote the survival and function of retinal ganglion cells in a variety of animal models unrelated to diabetes (14). This is the first study showing that topical administration of brimonidine arrests the progression of retinal neurodysfunction in patients with type 2 diabetes.

Somatostatin is abundantly produced by the human retina, the main source being the retinal pigment epithelium (19). Somatostatin exerts relevant functions in the retina (20). In the diabetic retina, a significant downregulation of somatostatin production has been reported (21–23). Therefore, a replacement treatment by the



	Difference	95% Confidence Interval	p-value
Placebo (n= 39)	0.539 (0.264)	0.021 ; 1.057	0.04
BRIM (n= 39)	0.006 (0.242)	-0.468 ; 0.481	0.97
SST (n= 41)	0.108 (0.258)	-0.398 ; 0.614	0.67

SD of Random effect =1.46



	Difference	95% Confidence Interval	p-value
Placebo (n= 49)	0.479 (0.259)	-0.028; 0.987	0.06
BRIM (n= 60)	0.041 (0.236)	-0.422; 0.501	0.86
SST (n= 47)	0.078 (0.254)	-0.421; 0.577	0.76

SD of Random effect =1.49

Figure 1—Progression of IT (ms) during follow-up in patients with preexisting neurodysfunction: analysis per protocol (*A*) and analysis by intention to treat (*B*). Black, placebo group; red: brimonidine (BRIM) group; blue: somatostatin (SST) group. Difference (change in IT) from baseline to month 24 is expressed as mean (SD).

topical route can be envisaged as a reasonable approach for treating DR. The main reasons by which systemic administration of somatostatin analogs failed in arresting progression of DR were recently reviewed (20), but one of the most important is their inability to cross the blood-retinal barrier.

Our results point to screening for retinal neurodysfunction as a critical issue to identify those patients in whom neuroprotective treatment might be of benefit. In this regard, mfERG is probably not a good option because it is a cumbersome and time-consuming method and should therefore be reserved for clinical trials. In addition, mfERG reflects only macular cone photoreceptor function and does not assess broader retinal integrity. Apart from mfERG, other methods addressed to measure retinal function have been proposed (9). Among these methods, fundus-driven microperimetry is a very sensitive, reliable, and rapid method and, consequently, can be

Table 3—Changes in retinal thickness measured by SD-OCT

	Baseline (μm)	24 months (μm)	*P*
Placebo	255.14 ± 25.93	253.63 ± 25.16	0.06
BRIM	255.94 ± 27.03	255.30 ± 29.13	0.64
SST	256.20 ± 28.23	257.14 ± 29.73	0.31

Data are presented as mean ± SD. BRIM, brimonidine; SST, somatostatin.

a useful tool to screen for neurodysfunction in clinical practice (24,25).

Our study has several limitations. First, we found a lower prevalence of neurodysfunction than expected. Second, a low progression rate of microvascular disease was found. The inclusion by design of 43% of patients without any microvascular abnormalities at study entry, the short follow-up (2 years), and the excellent HbA_{1c} and blood pressure levels throughout were the main factors accounting for this low rate of DR progression. Third, the dropout rate was higher than anticipated (24% vs. 20%), but the number of patients who completed the study was higher than required to achieve the primary end point. Finally, there was no way to determine quantitatively whether somatostatin and brimonidine reached the human neurosensory retinas in meaningful concentrations.

In conclusion, we did not find any significant effect of topical administration of brimonidine or somatostatin in preventing or arresting neurodysfunction and microvascular disease in the whole population included in this study. However, these neuroprotective agents could play a role in reducing the progression of preexisting neurodysfunction. Further studies using new technologies and with longer follow-up addressed to confirm the neuroprotective effects in this population subset with type 2 diabetes and whether they result in reduction of microvascular disease are needed.

Acknowledgments. The authors thank the patients and the EUROCONDOR Investigators for participating in this study (a complete list of the participants can be found in the Supplementary Data).

Funding. This project has received funding from the European Union's Seventh Framework Programme for research, technological development, and demonstration under grant agreement No. 278040.

Duality of Interest. B.P. is an employee of BCN Peptides, which holds the intellectual property related to the use of ocular somatostatin to treat diabetic retinopathy. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. R.S. and J.C.-V. contributed to the study design, discussion, and reviewed the manuscript. C.H. and M.Â.C. analyzed the data, wrote the first draft, and edited the manuscript. M.P., F.B., J.G., S.P.H., S.J.A., C.E., U.F.-O., J.G.-A., J.G., G.E.L., R.L., P.M., E.M., B.P., L.R., P.S., and C.L. researched data, contributed to the discussion, and reviewed the manuscript. R.S. and J.C.-V. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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