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Thiazolidinedione use and retinal fluid in the comparison of age-related macular degeneration treatments trials

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Abstract

Background—Thiazolidinediones, commonly used antidiabetic medications, have been associated with an increased risk of development of diabetic macular oedema and increased vascular endothelial cell permeability. Macular neovascularisation in age-related macular degeneration (AMD) and associated fluid leakage may be influenced by thiazolidinediones. This study aims to determine the association between thiazolidinedione usage and retinal morphological outcomes or visual acuity (VA) in patients treated with bevacizumab or ranibizumab for neovascular AMD (nAMD).

Methods—Secondary analysis of data from the Comparison of Age-related Macular Degeneration Treatments Trials. Participant self-reported diabetes status and thiazolidinedione usage at baseline. VA, intraretinal, subretinal and subretinal pigment epithelium fluid, and foveal thickness of retinal layers were evaluated at baseline and during 2-year follow-up. Comparisons

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Competing interests ED is a consultant to Novartis International AG. MGM serves on a data and safety monitoring committee for Genentech/Roche. GJ has a consultancy relationship with Alcon/Novartis, Genentech/Roche, Neurotech, EyePoint Pharmaceuticals and Adverum. G-SY is a consultant to Chengdu Kanghong Biotech, Ziemer Ophthalmic Systems AG and Synergy Research.

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Patient consent for publication Consent obtained directly from patient(s)

Ethics approval The trial protocol was approved by the institutional review boards of all clinical centres participating in the CATT, and patients provided written, informed consent for participation.

of outcomes between thiazolidinedione usage groups were adjusted by macular neovascularisation lesion type in multivariable regression models.

Results—Patients taking thiazolidinedione (n=30) had lower adjusted mean VA score at baseline (difference −6.2 letters; p=0.02), greater proportion with intraretinal fluid (IRF) at year 2 (75% vs 50%, adjusted OR 2.8; p=0.04), greater mean decrease in subretinal tissue complex thickness from baseline at year 1 (difference −75.1 um; p=0.02) and greater mean decrease in subretinal thickness at year 1 (difference −41.9 um; p=0.001) and year 2 (difference −43.3 um; p=0.001).

Conclusions—In this exploratory analysis, patients with diabetes taking thiazolidinediones and treated with bevacizumab or ranibizumab for nAMD had worse baseline mean VA, greater reductions in subretinal and subretinal tissue complex thickness from baseline, and greater proportions with IRF comparing to patients not taking thiazolidinediones.

Trial registration number—ClinicalTrials.gov NCT00593450.

INTRODUCTION

Thiazolidinediones, such as rosiglitazone and pioglitazone, improve glycaemic control in patients with diabetes through activation of the gamma isoform of the peroxisome proliferator-activated nuclear receptor (PPARγ), which improves insulin sensitivity and alters transcription of genes regulating systemic glucose levels.[1] PPARγ activity has been observed in vascular endothelial cells and is thought to increase vascular endothelial permeability.[1] These drugs produce numerous physiologic effects such as increasing endothelial cell permeability,[1] increasing serum VEGF levels, reducing suppressor-of-cytokine-signalling-3 (SOCS3), tumour necrosis factor alpha (TNF-α) and C reactive protein (CRP) levels, upregulating insulin-growth-factor-binding-protein-3 (IGFBP-3) and inhibiting diabetes-induced apoptosis in retinal neurons.[2–4] Considering these myriad effects, there are multiple potential pathways by which thiazolidinediones could prove either beneficial or detrimental to the retina of people affected by diabetes or other types of neovascular disease.

An association between thiazolidinedione use and an increased risk of diabetic macular oedema has been reported.[5 6] It is not known whether the off-target effects of thiazolidinediones might influence neovascular conditions other than diabetic retinopathy such as neovascular age-related macular degeneration (nAMD). This information would be important given the general prevalence of diabetes and its association with nAMD, which has been consistently observed in cross-sectional studies.[7] Potential effects of thiazolidinediones on AMD have been studied with in vitro or in situ models but not in patients.[8] Therefore, we assessed the association of thiazolidinedione usage with retinal morphology and visual acuity (VA) in participants with diabetes who received antivascular endothelial growth factor (anti-VEGF) treatment for nAMD in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

METHODS

This study is a secondary analysis of data from a cohort within a randomised clinical trialThe trial was conducted in accordance with the tenets of the Declaration of Helsinki and

the Health Insurance Portability and Accountability Act. Detailed descriptions of the design and methods of the CATT are provided in previous reports.[5]

We use the term nAMD so as to include retinal angiomatous proliferation (type 3 macular neovascularisation, characterised by intraretinal neovascularisation), in addition to types 1 and 2 macular neovascularisation (defined by the presence of choroidal neovascularisation) in place of choroidal neovascularisation, which was used in previous CATT reports.[9] Macular atrophy is used in place of geographic atrophy to describe areas of well-circumscribed retinal pigment epithelium (RPE) atrophy.[10] CATT enrolment criteria were age of 50 years or older, treatment-na'fve, active nAMD in the study eye with absence of foveal macular atrophy, and study eye VA of 20/25–20/320. The nAMD activity was determined by leakage on fluorescein angiography and fluid within or beneath the retina or beneath the RPE on time-domain optical coherence tomography (OCT). Baseline medical history and medication use were self-reported by the patient. Only patients reporting a diagnosis of diabetes mellitus were included in this analysis.

Masked, certified readers at the Duke University OCT Reading Center independently evaluated OCT scans for the presence and location (foveal vs extrafoveal) of intraretinal fluid (IRF), subretinal fluid (SRF) and sub-RPE fluid. Thickness of retinal layers at the foveal centre were measured. Characteristics of macular neovascularisation such as lesion type and area were determined based on fundus photographs and fluorescein angiogram by readers in the reading centre. A senior reader resolved discrepancies between readers.

Baseline participant characteristics including age, gender, smoking status, hypertension and macular neovascularisation lesion characteristics were compared between participants taking vs not taking thiazolidinediones. Proportions with fluid, mean thickness of retinal layers and mean VA (ETDRS letters) at the baseline, year 1 and year 2 visits were compared between patients taking vs not taking thiazolidinediones and adjusted by baseline macular neovascularisation lesion type in logistic regression models for binary outcomes and linear regression models for continuous outcomes. Statistical analysis was performed with SAS V.9.4 (SAS Institute) and R (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p values <0.05 were considered statistically significant.

RESULTS

Among 1185 participants in the CATT, 207 (17.5%) had diabetes at baseline and 30 (14.5%) of them were taking thiazolidinediones. Baseline demographic and macular neovascularisation lesion characteristics were similar between participants taking vs not taking thiazolidinediones (all $p \leq 0.12$; table 1). Participants taking thiazolidinediones had lower baseline VA score (55.2 vs 61.4 letters, p=0.02), and the difference remained significant after adjustment by macular neovascularisation lesion type (mean difference −6.2 letters; 95% CI (−11.2 to −0.8); p=0.02). Among 112 participants assigned anti-VEGF treatment as-needed, those taking (N=22) and not taking thiazolidinediones (N=90) received a similar mean number of injections through year 1 (6.1 vs 6.9; p=0.36) and year 2 (10.1 vs 11.8; p=0.30).

Adjusted VA score (letters) and change in VA were similar between thiazolidinedione takers versus non-takers at years 1 and 2 (all p≤0.27; table 2). Presence of SRF and sub-RPE fluid were similar at years 1 and 2 between takers versus non-takers (all p≤0.06). Proportions with IRF were higher in thiazolidinedione takers at both year 1 (64% vs 44.2%, p=0.10) and year 2 (75% vs 50%, p=0.04) and after adjustment for lesion type at year 2 (adjusted OR 2.8; 95% CI (1.0 to 8.0); p=0.04). Retinal, subretinal and subretinal tissue complex thicknesses at years 1 and 2 were similar between takers versus non-takers (all p≤0.13, table 2). Thiazolidinedione usage was associated with a greater decrease in SRF thickness at year 1 (adjusted mean difference −41.9 um; 95% CI (−66.7 to −17.0); p=0.001) and year 2 (adjusted mean difference −43.3 um (−69.5 to −17.2); p=0.001). Thiazolidinedione usage was associated with a greater mean decrease in subretinal tissue complex thickness at year 1 (difference −75.1 um; 95% CI (−139.8 to −10.4); p=0.02) and year 2 (difference −67.0 um; 95% CI (−135.4 to 1.4); p=0.06). The changes in SRF and subretinal tissue complex thickness from week 24 to year 2 were similar between thiazolidinedione takers versus non-takers (figure 1). Between year 1 and year 2, mean retinal thickness increased slightly in participants taking thiazolidinediones while remaining stable in non-takers.

DISCUSSION

We observed several differences in retinal anatomy among patients with diabetes taking thiazolidinediones when compared with patients with diabetes not taking them. Participants taking thiazolidinediones had similar mean SRF and subretinal tissue complex thicknesses at baseline compared with non-takers but had greater reductions in SRF and sub-RPE fluid thickness after anti-VEGF therapy initiation. Participants taking thiazolidinediones had worse mean baseline VA score, but similar VA score at year 1 and year 2 compared with non-takers. Finally, thiazolidinedione usage was associated with an increased risk of IRF at year 2.

Studies investigating the role of PPAR-γ signalling in AMD are sparse and focused on in vitro or in situ models. Herzlich *et al* found that human retinas with wet and dry AMD have increased PPAR-γ expression compared with age-matched healthy retinas and higher VEGF levels. These results were replicated in vitro when ARPE19 cells, a human RPE cell line commonly used as a model to study AMD, were exposed to H2O2-induced oxidative stress.[8] While the clinical effects of TZDs on eyes with nAMD are unstudied, usage of this drug class has previously been associated with diabetic macular oedema (DME). Fong *et al* found that patients with diabetes taking thiazolidinediones were more likely to develop DME in a cohort study of 996 cases of new-onset DME after adjusting for age, glycaemic control and insulin usage.[5] A larger retrospective cohort study of the Health Improvement Network database involving 103 368 patients with type 2 diabetes found an association between thiazolidinedione usage and DME following adjustment for confounding factors known to influence diabetic retinopathy at both 1-year and 10-year follow-ups.[6] It must be noted, however, that the association between thiazolidinedione usage and DME has not been replicated in other retrospective analyses, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study.[11] Thiazolidinediones have multiple effects which may predispose to a greater amount of vascular leakage or promote angiogenesis. Rosiglitazone has been found to increase VEGF expression and vascular permeability in human umbilical

vein endothelial cells in vitro.[12] Systemically, thiazolidinediones increase serum levels of VEGF and expand the plasma volume.[13 14] Through VEGF-induced augmentation of vascular permeability and altered haemodynamics, thiazolidinediones could induce greater amounts of leakage from a persistent or recurrent neovascular membrane, leading to the greater incidence of IRF at follow-up observed in the CATT. Given that IRF has been associated with poor VA and increased risk of macular atrophy in large-scale clinical trials of anti-VEGF therapy for nAMD,[15–17] a greater incidence of IRF among participants taking thiazolidinediones may herald later poor visual and anatomic outcomes.

Interestingly, thiazolidinediones have been shown in some studies to produce antiangiogenic rather than proangiogenic effects. In endometrial cells, thiazolidinediones inhibited VEGF gene promoter activity and expression.[18] Thiazolidinediones administered intravitreally in animal models have inhibited VEGF-induced proliferation and migration of choroidal endothelial cells and retinal pigment epithelium.[19] Whether thiazolidinediones act as an inhibitor or promoter of angiogenesis may depend on cell type, and it is unclear which effect, if any, predominates in vivo for the retinal tissues of patients with diabetes or nAMD. The greater reductions in fluid thickness from baseline observed in CATT participants taking thiazolidinediones suggest that their nAMD lesions are equally or more responsive to initiation of anti-VEGF therapy. If thiazolidinediones did hypothetically synergise with anti-VEGF therapy, resulting in a greater drying of the retina, the higher incidence of IRF we observe with their usage could result from degenerative cystic change rather than ongoing leakage. In the CATT and IVAN trials, greater fluctuations in the combined foveal centre point thicknesses (FCPT) of the retinal, subretinal and sub-RPE compartments have been correlated to poorer VA and the development of macular atrophy and fibrosis.[20] The greater reductions in subretinal and subretinal tissue complex thickness observed in participants taking thiazolidinediones could promote retinal damage and cystic degeneration via greater FCPT fluctuations over time.

Thiazolidinediones might also influence macular neovascularisation lesions by anti-inflammatory effect, as demonstrated by in vitro and in vivo studies. Decreased circulating levels of the pro-inflammatory cytokine TNF-α have been found in patients treated with pioglitazone, while diabetic atherosclerotic plaques in patients treated with rosiglitazone contained lower concentrations of TNF-α and other inflammatory cytokines.[21 22] TNF-α increases VEGF secretion by human RPE cells and choroidal fibroblasts and may therefore play a role in initiating retinal neovascularisation.[23] Although TNF-inhibiting therapy for the treatment of nAMD has not been well tolerated,[24] thiazolidinediones may nevertheless dampen the inflammatory milieu involved in the pathogenesis of nAMD and thereby alter the disease course. Overall, the effects of thiazolidinediones are numerous, complex and not well understood. Additional studies should be conducted to characterise their risk-benefit profile in the setting of nAMD as well as other diseases involving neovascularisation.

This study has several limitations. The analysis is post hoc and observational rather than based on randomised assignment to drug exposure or placebo group and cannot establish causality between thiazolidinedione usage and the reported findings. All OCT scans acquired in the first year of the CATT were time-domain and only a minority (22.6%) acquired in the second year were spectral-domain. Due to the lower resolution

of time-domain OCT images, it is possible that some small collections of fluid may have been missed during grading, or that similarly appearing but distinct anatomic features such as outer retinal tubulations may have been misinterpreted as retinal fluid.[25] The number of patients taking thiazolidinediones at the study baseline was small, limiting the statistical power of the analysis. Lastly, measurement of fluid thickness and retinal thickness was performed only at the foveal centre.

CONCLUSIONS

In this exploratory analysis, CATT participants with diabetes taking thiazolidinediones at baseline had greater reductions in SRF and subretinal tissue complex thickness from baseline, worse baseline VA and a greater proportion with IRF after 2 years of treatment. Additional studies are warranted to confirm these findings and characterise the effects of thiazolidinediones in neovascular ocular diseases.

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Data availability statement

Data is available at the following website: https://hyperprod.cceb.med.upenn.edu/catt/catt_index.php

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Key messages

What is already known on this topic

- Thiazolidinediones have been associated with an increased risk of development of diabetic macular edema and may increase vascular endothelial cell permeability.

What this study adds

- In this post-hoc analysis of participants with diabetes in the Comparison of Age-related Macular Degeneration Treatments Trials, we found thiazolidinedione usage was associated with worse baseline visual acuity, greater decreases in subretinal fluid and subretinal tissue complex thickness, and a greater proportion with intraretinal fluid at 2 years.

How this study might affect research, practice or policy

- Additional studies are warranted to confirm these findings and characterize the effects of thiazolidinediones in neovascular ocular diseases.

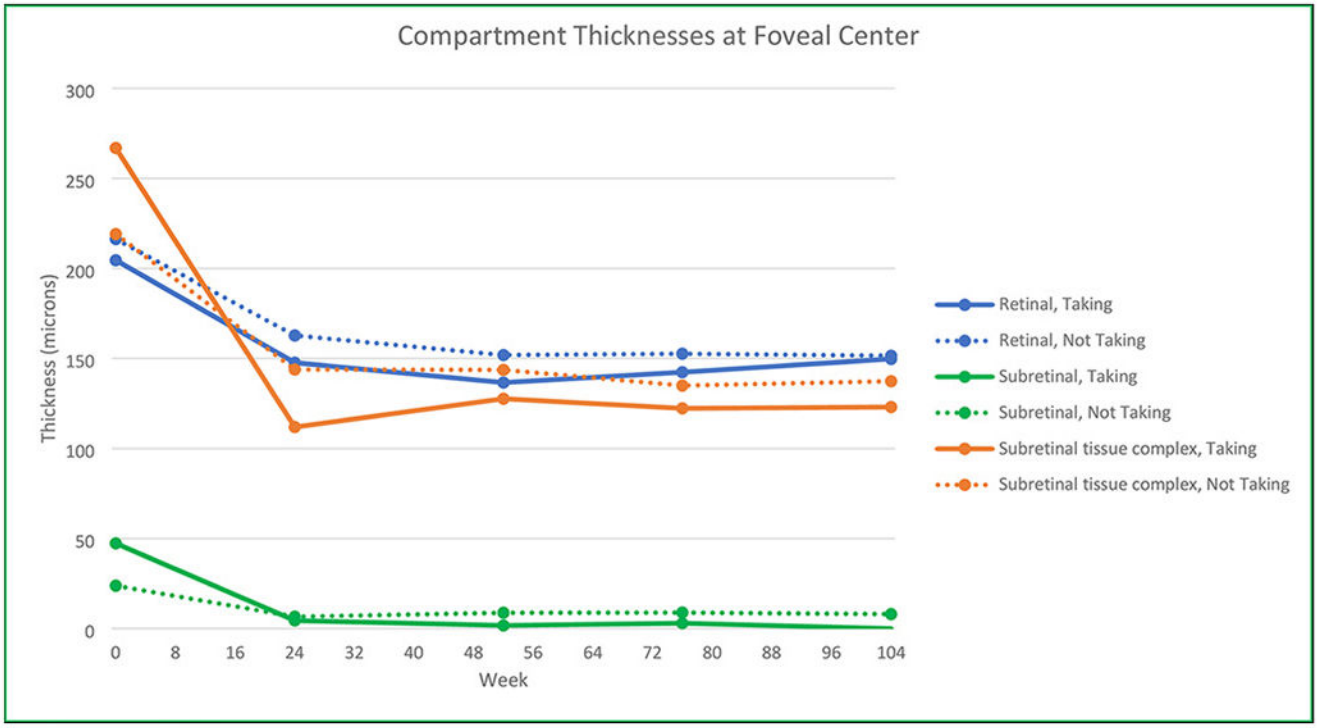

Figure 1.

Retinal, subretinal fluid and subretinal tissue complex thickness at the foveal centre over time stratified by baseline use of thiazolidinedione. Mean thickness values of the retina, subretinal fluid and subretinal tissue complex compartments at the foveal centre are shown for key timepoints from baseline to week 104. Mean thickness values are stratified by patients taking (solid lines, N=151) and not taking thiazolidinediones at baseline (dashed lines, N=26).

Table 1

Baseline demographic and ocular characteristics in patients with and without baseline thiazolidinedione use

	Thiazolidinedione usage at baseline		
Baseline characteristics	**No (N=177)**	**Yes (N=30)**	**P value***
Age (years), mean (SE)	77.6 (0.5)	77.9 (1.3)	0.81
Gender, female (%)	88 (53.0)	16 (61.5)	0.42
Hypertension (%)	133 (80.1)	23 (88.5)	0.42
Cigarette smoking			0.53
Never	71 (42.8)	14 (53.8)	
Quit	83 (50.0)	11 (42.3)	
Current	12 (7.2)	1 (3.8)	
Area (disc area) of macular neovascularisation, mean (SE)	1.5 (0.1)	2.1 (0.4)	0.13
Presence of retinal angiomatous proliferation, n (%)	19 (10.7)	4 (13.3)	0.75
Macular neovascularisation type, n (%)			0.33
Predominantly or minimally classic	58 (33.3)	7 (24.1)	
Occult only	116 (66.7)	22 (75.9)	
IRF presence, n (%)	119 (69.6)	20 (66.7)	0.75
SRF presence, n (%)	149 (85.1)	29 (96.7)	0.14
Sub-RPE fluid presence, n (%)	92 (56.8)	16 (55.2)	0.87
Retinal thickness at foveal centre (μm), mean (SE)	216.3 (8.6)	204.6 (20.9)	0.61
SRF thickness at foveal centre (μm), mean (SE)	23.8 (4.6)	47.3 (11.1)	0.12
Subretinal tissue complex thickness at foveal centre (μm), mean (SE)	219.1 (13.6)	266.9 (32.9)	0.34
Visual acuity (letters): mean (SE)	61.4 (1.0)	55.2 (2.4)	0.02

* P value calculated based on χ^2 test Fisher's exact test and two-sample t-test as appropriate.

IRF, intraretinal fluid; RPE, retinal pigment epithelium; SRF, subretinal fluid.

Table 2

Associations between baseline use of thiazolidinedione with fluid status, retinal thickness and visual acuity at year 1 and year 2

	Year 1				Year 2			
Outcomes at year 1 or 2	**Not Taking (N=166)**	**Taking (N=26)**	**Adjusted OR (95% CI)***	**P value**	**Not Taking (N=151)**	**Taking (N=26)**	**Adjusted OR (95% CI)***	**P value***
IRF presence, n (%)	72 (44.2)	16 (64.0)	2.1 (0.9 to 5.0)	0.10	74 (50.0)	18 (75.0)	2.8 (1.0 to 7.5)	0.04
SRF presence, n (%)	56 (34.6)	5 (21.7)	0.5 (0.2 to 1.6)	0.25	58 (40.3)	5 (20.0)	0.4 (0.1 to 1.1)	0.06
Sub-RPE fluid presence, n (%)	54 (34.6)	5 (23.8)	0.6 (0.2 to 1.7)	0.31	56 (40.0)	10 (41.7)	1.2 (0.5 to 2.8)	0.75
			Adjusted Difference (95% CI)*	**P value**			**Adjusted Difference (95% CI)***	**P value**
Retinal thickness at foveal centre (μm), mean (SE)	151.9 (4.1)	136.6 (10.2)	−13.2 (−35.0 to 8.5)	0.23	151.5 (5.1)	149.8 (12.4)	1.3 (−25.6 to 28.1)	0.93
SRF thickness at foveal centre (μm), mean (SE)	8.8 (2.3)	1.8 (5.9)	−7.5 (−20.2 to 5.2)	0.25	8.1 (2.1)	0.0 (5.1)	−8.5 (−19.5 to 2.5)	0.13
Subretinal tissue complex thickness at foveal centre (μm), mean (SE)	143.7 (10.4)	127.6 (26.3)	−20.7 (−77.6 to 36.2)	0.48	137.3 (10.3)	123.0 (25.2)	−18.1 (−72.8 to 36.7)	0.52
Change in retinal thickness at foveal centre from baseline (μm), mean (SE)	−68.3 (9.3)	−60.5 (23.3)	8.5 (−41.8 to 58.8)	0.74	−72.2 (10.8)	−37.6 (26.4)	36.9 (−20.4 to 94.1)	0.21
Change in SRF thickness at foveal centre from baseline (μm), mean (SE)	−11.8 (4.6)	−51.7 (11.5)	−41.9 (−66.7 to 17.0)	0.001	−14.3 (4.9)	−55.6 (12.1)	−43.3 (−69.5 to to 17.2)	0.001
Change in subretinal tissue complex thickness at foveal centre from baseline (μm), mean (SE)	−76.4 (12.1)	−157.9 (30.3)	−75.1 (−139.8 to to 10.4)	0.02	−77.4 (13.1)	−149.3 (32.0)	−67.0 (−135.4 to 1.4)	0.056
Visual acuity (letters): mean (SE)	68.0 (1.3)	65.3 (3.3)	−2.7 (−9.7 to 4.4)	0.46	66.6 (1.5)	62.5 (3.6)	−4.4 (−12.2 to 3.4)	0.27
Change in visual acuity from baseline (letters): mean (SE)	6.7 (1.0)	10.1 (2.6)	3.0 (−2.7 to 8.6)	0.30	5.1 (1.3)	7.2 (3.0)	1.6 (−5.0 to 8.2)	0.64

*ORs and differences are for participants taking versus not taking thiazolidinediones and adjusted by macular neovascularisation lesion type as a covariate in regression models.

IRF, intraretinal fluid; RPE, retinal pigment epithelium; SRF, subretinal fluid.